IN THE MATTER OF the *Patent Act*, R.S.C. 1985, c. P-4, as amended AND IN THE MATTER OF Horizon Pharma (the "Respondent") and the medicine Cysteamine Bitartrate sold by the Respondent under the trade name "Procysbi"

I, Howard Rosen, hereby certify that:

The attached report titled "Expert Report of Howard Rosen, Secretariat" dated October 6, 2020 and signed on October 6, 2020 is my testimony pursuant to Rule 8 of the Patented Medicine Prices Review Board Rules of Practice and Procedure.

Howard Rosen

October 6, 2020

SWORN BEFORE ME in the City of Toronto, in the Province of Ontario, on

October 6, 2020

(A Commissioner of Oaths)

Secretariat

PATENTED MEDICINE PRICES REVIEW BOARD

IN THE MATTER OF the *Patent Act*,
R.S.C., 1985, c. P-4, as amended

AND IN THE MATTER OF
Horizon Pharma (the "Respondent")
and the medicine Cysteamine Bitartrate sold by the Respondent
under the trade name PROCYSBI

Expert Report of Howard Rosen
Secretariat

October 6, 2020

Privileged & Confidential

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GLOSSARY

Term	Description
IRR	Internal rate of return
NC	Nephropathic cystinosis
NOC	Notice of Compliance
SKU	Stock keeping unit
SAP	Special Access Programme
OECD	Organization for Economic Co-operation and Development
IP	Intellectual property
UCSD	University of California at San Diego
FDA	US Food and Drug Administration
API	Active pharmaceutical ingredient
DEL	Drug Establishment License
R&D	Research and development
NPV	Net present value

1. INTRODUCTION

A. Assignment

1.1. I have been requested by Perley-Robertson, Hill & McDougall LLP ("Counsel"), on behalf of Board Staff of the Patented Medicine Prices Review Board ("Board Staff"), to review the report prepared by Dr. Joel Hay dated September 9, 2019 (the "Hay Report") and to provide the following:

a) My comments on the financial economic analysis of the net operating profits (i.e. cash flows) from sales of PROCYSBI in Canada detailed in the Hay Report;[1] and

b) My opinion of the impact, from a financial and economic perspective, of the Proposed Prices of PROCYSBI in Canada on Horizon's profits.

1.2. For the purposes of this report, I have also reviewed and considered the following:

a) The Affidavit of Andrew Harington dated December 13, 2019 (the "Harington Affidavit");

b) The Sur-Reply Affidavit of Andrew Harington dated January 10, 2020 (the "Harington Sur-Reply Affidavit");

c) The Joint Memorandum of Howard Rosen and Andrew Harington dated April 3, 2020 (the "Joint Experts Memo"); and

d) The Addendum to the Hay Report dated July 30, 2020 (the "Hay Addendum").

1.3. I understand that the Patented Medicine Prices Review Board (the "PMPRB"), through its investigation into the introductory price of PROCYSBI commenced on March 13, 2018,[2] found that HZNP Therapeutics Canada Limited ("HZNP Canada" or "Horizon Canada") has been selling PROCYSBI at an excessive price in Canada since its launch in 2017.[3] In particular, I understand that the PMPRB is seeking an order pursuant to section 83 of the *Patent Act*, R.S.C., 1985 (the "*Act*"):[4]

a) declaring that the price of PROCYSBI has been excessive since it was introduced in Canada on September 7, 2017;

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1 The details of the financial economic analysis in Appendix F of the Hay Report, and the schedules and exhibits to the analysis in Appendix G of the Hay Report.
2 Statement of Allegations, Paragraph 20.
3 Statement of Allegations, Paragraph 67.
4 Statement of Allegations, Paragraph 68.

b) requiring Horizon Canada to, among other things, reduce the price of PROCYSBI by approximately 71% to 98% of its current price (the "Proposed Prices"); and

c) requiring Horizon Canada to make a payment to offset the excess revenue it has received from September 7, 2017 to the date of payment.

B. Qualifications

1.4. I, Howard Rosen, am a Managing Director of Secretariat and have been involved exclusively in business valuation, damages quantification, and corporate finance related matters since 1981. I have acted as an advisor to private and public companies, regulatory bodies, and all levels of government on a wide variety of industries. My work experience covers assignments across North and South America, Europe, the Middle East, Africa, and Asia. I have been qualified as an expert witness in over 200 damages quantification and valuation matters in courts in Canada and the United States, and in international arbitration hearings in Canada, the United States, Europe, and Asia. I have acted as a court appointed administrator, monitor, and inspector, and sat as a member of an arbitral tribunal and as a sole arbitrator.

1.5. I am the co-author of two texts and a number of chapters and articles on the quantification of economic damages and business valuation, and I have lectured extensively to professional interest groups.

1.6. I have also acted as advisor on transactions in a wide variety of businesses, for both public and private equity investors, conducting strategic due diligence, valuations and deal structuring for both buyers and sellers. I have advised independent committees of boards of directors on non-arm's length transactions and have also acted as the chair of independent committees of boards of directors for non-arm's length transactions. My past board positions include a global agricultural commodities trading business as Vice-Chair and Lead Independent Director.

1.7. Prior to joining Secretariat, I was the Global Practice Leader of the international arbitration group at a large multinational professional services firm. I also previously practiced as a partner in specialty niche firms and as the Canadian partner in charge of the business valuation and damages quantification practice for another large multinational professional services firm.

1.8. My *curriculum vitae* is attached hereto as Appendix 1.

C. Independence

1.9. In preparing this report, I have been assisted by Secretariat staff working under my direction, supervision, and review.[5] The Secretariat professionals engaged on this assignment have acted independently and objectively in carrying out this assignment. None of the Secretariat professionals that were engaged on this assignment has owned, or currently owns, directly or indirectly, any of the shares of the parties involved, nor does Secretariat have any financial interest whatsoever in the outcome of this matter.

1.10. The fees payable to Secretariat related to the delivery of this report are not contingent on the conclusions reached or any action or event relating to this report, including the outcome of this matter. Secretariat's fees are based on time expended at hourly rates, plus disbursements related to the engagement and any taxes hereon.

1.11. Nothing in this report expresses an opinion on matters of law, which are outside my expertise.

D. Reporting Standards

1.12. This report has been prepared in conformity with the Practice Standards of the Canadian Institute of Chartered Business Valuators ("CICBV") of which I am a member in good standing. The relevant Practice Standards of the CICBV include those governing the preparation of Limited Critique Reports (CICBV Standards 410, 420, and 430) and Expert Reports (CICBV Standards 310, 320, and 330). I have prepared this report to be a Limited Critique Report and an Expert Report under Standards 410 and 310 (Report Disclosure Standards) of the CICBV Practice Standards. CICBV Standards 410 and 310 is appended hereto in Appendix 2.

1.13. All currency amounts contained in this report are stated in US dollars unless otherwise noted.

E. Restrictions

1.14. This report is not intended for general circulation or publication, nor is it to be reproduced, referred to, or used without my or Secretariat's written consent, for any purpose whatsoever other than for the purpose referred to above. Secretariat and I shall not assume any responsibility or liability for losses occasioned to any party as a result of the circulation, reproduction, reference to, or use of this report contrary to the provisions of this paragraph.

[5] As used herein, other than references to my education and experience, "I" and "We" shall mean either I personally or those personnel working under my supervision. Also, "My", "Our", and "Us" shall also refer to actions taken by me personally or by those personnel under my supervision.

1.15. I believe that the analyses in this report must be considered in its entirety and that selecting portions of the analyses, without considering all factors and analyses together, could result in the misinterpretation of the comments and analyses concerning the quantum of financial loss. The preparation of such a report is a complex process and the components cannot be viewed in isolation. Any attempt to do so could lead to undue emphasis on any particular factor or analysis.

1.16. I reserve the right, but am under no obligation, to review the analyses of this report, and if considered necessary by me, to revise the analyses in light of any information which becomes known after the date of this report.

F. Scope of Review

1.17. In the preparation of this report, I have relied on the documents set forth in Appendix 3.

G. Report Summary

1.18. In Sections 2 and 3 below, I provide an overview of the Parties and of the market for PROCYSBI.

1.19. In Section 4 below, I provide my understanding of the economic activities relating to the sale of PROCYSBI in Canada, based on the documents produced by Horizon to date. In the assessment of Horizon's profits related to the sales of PROCYSBI in Canada in this matter, it is important, in my view, to:

a) analyze from an economic perspective the form and the substance of the corporate setup of the multinational enterprise;

b) understand the transfer pricing arrangement within the Horizon Group related to PROCYSBI; and

c) assess the profits for both the Canadian entity and in the aggregate or at the global level.

1.20. In Section 5 below, I provide my comments on the Hay Report, where I provide my analysis of each component of the profits calculation (i.e. revenues less costs) with details of why I agreed or disagreed with Dr. Hay. As illustrated in Figure 2 below and detailed in Section 5E below, the most significant area of difference between Dr. Hay's and my profits calculation is the allocation of the Raptor Acquisition Cost. The figure below provides a summary of the areas of agreement and disagreement.

Figure 1: Areas of Agreement and Disagreement with Dr. Hay

Profit Component	Area of Agreement or Disagreement	Explanation
Revenue - Sales Volume and Prices	Agreement	As detailed in Section 5C below, for the purpose of my analysis of the impact, from a financial and economic perspective, of the Proposed Prices of PROCYSBI in Canada on Horizon's profits, I agree with the approach adopted by Dr. Hay to compute sales volume and prices for PROCYSBI in Canada. Therefore, I have adopted Dr. Hay's assumptions regarding sales volume and prices in my analysis and calculations.
Cost of Goods Sold	Disagreement	As detailed in Section 5D below, Dr. Hay used the standard cost of goods sold estimated by Horizon for 2019, and then from 2020 through [redacted] Based on my analysis of the historical data, [redacted] is not supported. Further, the Producer Price Index reported inflation of 3.16% from June 2018 to June 2019. Therefore, I have assumed the fully loaded standard cost of goods sold computed by Horizon from 2017 to 2020, and thereafter, assumed a rate of increase of 3% per annum up to [redacted].
Royalties	Agreement	As detailed in Section 5D below, based on the licensing agreement between Horizon and the Regents of the University of California, Horizon is required to pay royalties of 5.5% of net revenues from the sales of PROCYSBI to the University of California.
Sales and Marketing Expenses	Disagreement	As detailed in Section 5D below, [redacted] I agree with the approach adopted by Dr. Hay, except for the identified cost item that he included for 2017.

Profit Component	Area of Agreement or Disagreement	Explanation
Raptor Acquisition Cost and Ongoing R&D Expenses	Disagreement	As detailed in Section 5E below, in the Hay Report, the Raptor Acquisition Cost and [redacted] Subsequently, in the Hay Addendum, Dr. Hay was asked by counsel for Horizon to use [redacted] In my view, Dr. Hay's allocation approaches results in the over-allocation of these costs to PROCYSBI in Canada and are flawed because they ignore the sales prices at which Horizon sells PROCYSBI in different regions, especially in the US. Since almost all of the revenues earned by Horizon are generated from the US, these costs should be allocated on a pro-rata basis according to the revenues generated by each region.
Other Cost of Sales	Disagreement	As detailed in Section 5F below [redacted] appears to be unreasonably high. In the Addendum, [redacted] Both cost of goods sold and other cost of sales have been allocated based on sales units, which is consistent since both of these costs are driven by manufacturing activities.

Profit Component	Area of Agreement or Disagreement	Explanation
General and Administrative Expenses	Disagreement	As detailed in Section 5F below, the Hay Report states that [redacted] Horizon has not produced adequate information to identify and support the allocation of these costs towards the sale of PROCYSBI in Canada, and further, I understand that Innomar continues to receive and manage the flow of PROCYSBI products in Canada, and Horizon only maintains a sales and marketing team in Canada. Therefore, I have excluded certain category of costs, absent any documentary support. From the perspective of Horizon's business globally, I have only included certain category of costs that may be attributable to Horizon's day to day operations in Canada in my analysis, which I have allocated on the same basis as Dr. Hay.

1.21. The figure below is an illustration of the amount of difference for each profit component calculated in this report and in the Hay Addendum based on Horizon's ex-factory prices, and the percentage of the total difference that each represents.

Figure 2: Summary of Differences in Profit Components at Horizon's Ex-Factory Prices[6]

[redacted]

1.22. In Section 6 below, I provide my calculation and analysis of the expected net operating profits from the sale of PROCYSBI in Canada from the perspective of Horizon Canada and the Horizon Group. Based on the analysis and assumptions detailed in Section 5 and 6, my calculation of

[6] From Figure 3 and Figure 15 below.

the expected net operating profits to Horizon Canada and the Horizon Group from the sale of PROCYSBI in Canada for the period 2017 to [redacted] (Schedules 1 to 4) are summarized as follows.

Figure 3: Summary of Profits to Horizon Canada and the Horizon Group from the Sale of PROCYSBI in Canada

[redacted]

1.23. Based on my profits calculation, I also calculated the internal rate of return ("IRR") – representing the rate of return a project is expected to earn, which is generally used as a metric to assess the financial feasibility and viability of any project – under each of the pricing scenarios (Schedules 1 to 4), summarized as follows.

Figure 4: IRR from Sale of PROCYSBI in Canada Under Various Scenarios

[redacted]

1.24. While Dr. Hay has not provided his assessment of the expected rate of return (i.e. Dr. Hay has not calculated the IRR based on his profit analysis using ex-factory prices), I have used the components detailed in Section 6B below to compute the IRR implied by his profit analysis for

Horizon from the sale of PROCYSBI in Canada at ex-factory prices (Schedules 5 and 6), the results of which are presented as follows:

Figure 5: IRR from Sale of PROCYSBI in Canada at Ex-Factory Prices Computed Implied by Dr. Hay's Profit Analysis

[redacted]

1.25. As indicated above, Dr. Hay's profit analysis implies that Horizon would have expected to earn a return of between [redacted]

1.26. Based on my calculations of profits and IRR from the sale of PROCYSBI in Canada for the period 2017 to [redacted] I observe the following impacts of the pricing scenarios:

a) Based on my allocation of the Raptor Acquisition Cost and other expenses to Horizon Canada, and my calculation of profits and IRR thereon, the IRR for Horizon Canada and the Horizon Group at the current ex-factory price for the sale of PROCYSBI in Canada are [redacted]

b) At a 71% price reduction, Horizon Canada and the Horizon Group would [redacted], respectively, representing an IRR of [redacted] This level of IRR is higher than the IRR (ranging between [redacted] calculated at Section 6B below) implied by Dr. Hay's profit analysis that Horizon expects to earn through the sale of PROCYSBI in Canada based on ex-factory prices until [redacted]

c) At an 80% price reduction, Horizon Canada and the Horizon Group would [redacted] respectively, representing an IRR of [redacted] respectively. This level of IRR is comparable to the IRR (ranging between [redacted] calculated at Section 6B below) implied by Dr. Hay's profit analysis that Horizon expects to earn through the sale of PROCYSBI in Canada based on ex-factory prices until [redacted]

d) At a 96% price reduction, Horizon Canada and the Horizon Group would [redacted]

2. OVERVIEW OF THE PARTIES

A. The Parties

Horizon

2.1. Horizon Therapeutics Public Limited Company ("Horizon") is a biopharmaceutical company headquartered in Dublin, Ireland that focuses on researching, developing, and commercializing innovative medicines that address unmet treatment needs for rare and rheumatic diseases.[7] Horizon and its subsidiaries (collectively the "Horizon Group") markets eleven medicines through its orphan and rheumatology and inflammation reportable business segments, including PROCYSBI for the treatment of nephropathic cystinosis.

PMPRB[8]

2.2. The PMPRB is an independent quasi-judicial body established by Parliament in 1987 under the *Act*. The mandate of the PMPRB is to protect the interests of Canadian consumers by ensuring that the prices of patented medicines sold in Canada are not excessive. The PMPRB achieves this by reviewing the prices that patentees charge for each individual patented drug product in Canadian markets. If a price is found to be excessive, the PMPRB can hold public hearings and order price reductions and/or the offset of excess revenues.

2.3. The mandate of the PMPRB is also to report on trends in pharmaceutical sales and pricing for all medicines, and for reporting research and development spending by patentees.

[7] Response of Horizon Pharma, Paragraph 3.
[8] RR-1 – http://pmprb-cepmb.gc.ca/about-us/mandate-and-jurisdiction.

3. THE PRODUCT AND MARKET

A. Product and Market Overview[9]

3.1. PROCYSBI is indicated for nephropathic cystinosis ("NC"), a rare and life-threatening metabolic disorder. PROCYSBI capsules contain cysteamine bitartrate in the form of innovative microspheronized beads that are individually coated to create delayed and extended-release properties, allowing patients to maintain consistent therapeutic system drug levels over a twelve-hour dosing period.

3.2. PROCYSBI is differentiated by its ability to control cystine concentration continuously over twelve hours. Older therapies require administration of medicine every six hours. Other than PROCYSBI, there are currently two other pharmaceutical products approved to treat cystinosis, Cystagon and Cystaran.

3.3. Cystagon is PROCYSBI's primary competitor. It is an immediate-release cysteamine bitartrate capsule and is an older-generation systemic cystine-depleting therapy for cystinosis marketed by Mylan N.V. in the US, and by Orphan Europe SARL in markets outside of the US.

3.4. Cystaran is a cysteamine ophthalmic solution approved in the US for treatment of corneal crystal accumulation in patients with cystinosis, marketed by Leadiant Biosciences, Inc.

3.5. Horizon estimates that there are approximately 500 patients diagnosed with cystinosis living in the US. NC comprises 95% of known cases of cystinosis. In these patients, elevated cystine can lead to cellular dysfunction and death. Without treatment, the disease is usually fatal by the end of the first decade of life. Cystinosis is progressive, eventually causing irreversible tissue damage and multi-organ failure, including kidney failure, blindness, muscle wasting, and premature death. NC is usually diagnosed in infancy after children display symptoms to physicians. Management of cystinosis requires lifelong therapy.

3.6. Horizon's strategy for PROCYSBI is to drive conversion of patients from older-generation immediate-release capsules of cysteamine bitartrate; to increase the uptake of the medicine by diagnosed but untreated patients; to identify previously undiagnosed patients who are suitable for treatment; to position PROCYSBI as a first line of therapy; and to increase compliance rates.

[9] Information in this section was obtained from RR-10 – Horizon Therapeutics Public Limited Company Form 10-K for the fiscal year ended December 31, 2019.

B. The Market in Canada

3.7. Health Canada issued a Notice of Compliance ("NOC") for PROCYSBI on June 13, 2017, and the first sale of PROCYSBI in Canada was on September 7, 2017.[10] It was provided in two formats, 25 mg capsules and 75 mg capsules, at the introductory prices set out in the figure below, which have remained unchanged since introduction.

Figure 6: Introductory Price of PROCYSBI in Canada

Format	Price per capsule (CAD)	Price per mg (CAD)
25 mg capsule	$10.35	$0.414
75 mg capsule	$31.05	$0.414

3.8. Horizon sells two stock keeping units ("SKUs") of PROCYSBI in Canada:

a) Bottle with 60 capsules of 25 mg ("25MG Unit"), priced at [redacted] per unit;[11] and

b) Bottle with 250 capsules of 75 mg ("75MG Unit"), priced at [redacted] per unit.[12]

3.9. The ex-factory prices for PROCYSBI sold in the US (as of June 2019) are set out as follows:[13]

Figure 7: Ex-Factory Price of PROCYSBI in the US

Format	Price per capsule (CAD)	Price per mg (CAD)
25 mg capsule	$100.16	$4.006
75 mg capsule	$126.21	$1.683

3.10. Cystagon has been marketed internationally for many years and was approved for sale in the US in 1994. Cystagon is not approved or marketed in Canada, though it has been made available for sale in Canada for over two decades through the Special Access Programme ("SAP") maintained pursuant to C.08.010 and C.08.011 of the *Food and Drug Regulations*, C.R.C., c. 870.[14]

10 Statement of Allegations, Paragraph 4.
11 The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 7.
12 The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 7.
13 The Hay Report, Paragraph 66, Figure 4.
14 Statement of Allegations, Paragraph 9.

3.11. The total daily dose of cysteamine bitartrate for an adult patient taking it either in the form of Cystagon or PROCYSBI is the same, at 1,500 mg.[15] For a single adult patient with NC, the annual cost of cysteamine therapy in Canada is approximately $325,000 per year for PROCYSBI (based on its introductory price) or approximately $5,000 per year for Cystagon (price at the time of PROCYSBI's introduction).[16] In either case, cysteamine therapy must begin as soon as the condition is first diagnosed, often before the age of two, and continue for the entire life of the patient.[17]

3.12. Cystinosis affects approximately 100 people in Canada.[18] Horizon estimates that there are approximately 500 patients diagnosed with cystinosis living in the US.

15 Statement of Allegations, Paragraph 14.
16 Statement of Allegations, Paragraph 15.
17 Statement of Allegations, Paragraph 15.
18 RR-2 – House of Commons Canada – Report of the Standing Committee on Health – Canadians Affected by Rare Diseases and Disorders: Improving Access to Treatment, page 14.

4. ECONOMIC ACTIVITIES RELATING TO THE SALE OF PROCYSBI IN CANADA

4.1. The Organization for Economic Co-operation and Development ("OECD") – of which Canada, the United States, and Ireland, amongst other countries, are members – issues guidelines for multinational companies to follow in determining transaction prices between non-arm's length entities for tax purposes.[19] Transfer prices are "the prices at which an enterprise transfers physical goods and intangible property or provides services to associated enterprises."[20] OECD member countries have adopted the arm's length principle,[21] which is defined as:

"*Where conditions are made or imposed between the two associated enterprises in their commercial or financial relations which differ from those which would be made between independent enterprises, then any profits which would, but for those conditions, have accrued to one of the enterprises, but, by reason of those conditions, have not so accrued, may be included in the profits of that enterprise and taxed accordingly.*"[22]

4.2. In other words, when transfer pricing between associated enterprises does not reflect market forces, the tax liabilities of the associated enterprises (and the resulting tax revenues of the respective countries' tax authorities) may be distorted. Therefore, OECD member countries have agreed that, for tax purposes, the profits of associated enterprises may be adjusted accordingly, to correct any such distortions.[23]

4.3. It is not uncommon for multinational enterprises, especially for pharmaceutical companies, to set up corporate legal entities in different countries and tax jurisdictions, as well as various agreements which dictate the allocations of profits through transfer pricing, for reasons such as:

- Location of the original business setup;
- Allocation of risk between different aspects of the overall "value chain";
- Tax considerations; and
- Cash flow requirements of associated enterprises.

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19 RR-3 - OECD Transfer Pricing Guidelines for Multinational Enterprises and Tax Administrations, July 2017.
20 RR-3 - OECD Transfer Pricing Guidelines for Multinational Enterprises and Tax Administrations, July 2017, page 17.
21 RR-3 - OECD Transfer Pricing Guidelines for Multinational Enterprises and Tax Administrations, July 2017, page 16.
22 RR-3 - OECD Transfer Pricing Guidelines for Multinational Enterprises and Tax Administrations, July 2017, page 35.
23 RR-3 - OECD Transfer Pricing Guidelines for Multinational Enterprises and Tax Administrations, July 2017, page 34.

4.4. For example, a company may move its headquarters or transfer all its intellectual property ("IP") from a relatively higher tax jurisdiction, such as the United States or Canada, to a lower tax jurisdiction, such as Ireland. Then, through inter-corporate agreements, the company can set up transfer prices at which each entity transacts with another in order to allocate profits to each country/tax jurisdiction. For example, if the company's IP is held in Ireland, that entity may charge the US or Canadian entity an inter-corporate charge for the use of the IP. This will affect the cost and profits in each of the operating entities in the US and Canada.

4.5. In the assessment of Horizon's profits related to the sales of PROCYSBI in Canada in this matter, it is important to analyze from an economic perspective the form and the substance of the corporate setup of the multinational enterprise.

4.6. On one hand, the economic substance of the corporate setup is important because this dictates where and under which entities the actual economic activities take place and how the entities transact with each other.

4.7. On the other hand, the form of the corporate setup is also important because Horizon has chosen a specific corporate structure for income tax purposes in different countries and tax jurisdictions. Horizon has also chosen specific transfer pricing policies that dictate how profits are allocated between Horizon corporate legal entities.

4.8. Once corporate entities are set up for transfer pricing purposes, each entity is deemed to deal at arm's length and considered economically no different than unrelated parties such as third-party suppliers. Therefore, in the assessment of Horizon's profits related to PROCYSBI sales in Canada, it is important, in my view, to understand the transfer pricing arrangement within the Horizon Group related to PROCYSBI, and to assess the profits for both the Canadian entity and in the aggregate or at the global level.

4.9. In this section, I provide an overview of my understanding of the following, based on the documents produced by Horizon to date:

a) PROCYSBI's development and commercialization;

b) The Horizon Group's legal entity structure;

c) The economic activities relating to the sale of PROCYSBI in Canada; and

d) The financial performance of PROCYSBI.

A. PROCYSBI's Development and Commercialization

4.10. A summary of key events relating to PROCYSBI's development and commercialization is presented below.

1999	• The University of California at San Diego ("UCSD") began scientific research into Delay Release Cysteamine[24] ("DR Cysteamine" or "RP103" or "PROCYSBI"). • Encode Pharmaceuticals, Inc. ("Encode") entered into a licensing agreement with the UCSD to develop the product.[25] However, exact date of the agreement is not known.
2007	• Raptor Pharmaceuticals Corp.[26] ("Raptor Pharma") purchased clinical development and commercial rights to DR Cysteamine through a merger between Encode and Raptor Therapeutics, a subsidiary of Raptor Pharma. • Raptor Pharma issued 802,946 shares to Encode stockholders and recorded the intangible asset related to DR Cysteamine at $2.62 million in their financial statements for 2010.[27]
2013 to 2014	• Raptor Pharma received marketing approval for PROCYSBI from the US Food and Drug Administration ("FDA") on April 30, 2013, and from the European Commission on September 6, 2013. • Commercial sale of PROCYSBI began in the US in June 2013 and in Europe in April 2014.[28]
2016	<u>Raptor's Acquisition by Horizon</u> • Horizon completed acquisition of Raptor Pharma on October 25, 2016 by paying a consideration of $860.8 million, including goodwill valued at $189.1 million. • [redacted] • [redacted] • [redacted]

[24] DR Cysteamine was also referred to as RP103 by Raptor Pharma in its Form 10-Ks and is now sold as PROCYSBI.
[25] The Hay Report, Appendix E – Background: Commercialization of PROCYSBI, Paragraphs 1 and 2.
[26] Raptor Pharma (now known as Horizon Pharmaceutical LLC) was formed after a reverse merger with TorreyPines Therapeutics, Inc. in July 2009.
[27] RR-4 – Raptor Pharmaceutical Corp. Form 10-K for the fiscal year ended August 31, 2010.
[28] RR-5 – Raptor Pharmaceutical Corp. Form 10-K for the fiscal year ended December 31, 2014.
[29] (TOR0000001046.0002) KPMG - Valuation of Identifiable Subject Assets and Liabilities in Connection with the Acquisition of Raptor Pharmaceuticals Corp., dated October 24, 2016.
[30] RR-7 – Horizon Pharma Public Limited Company Form 10-K for the fiscal year ended December 31, 2016.

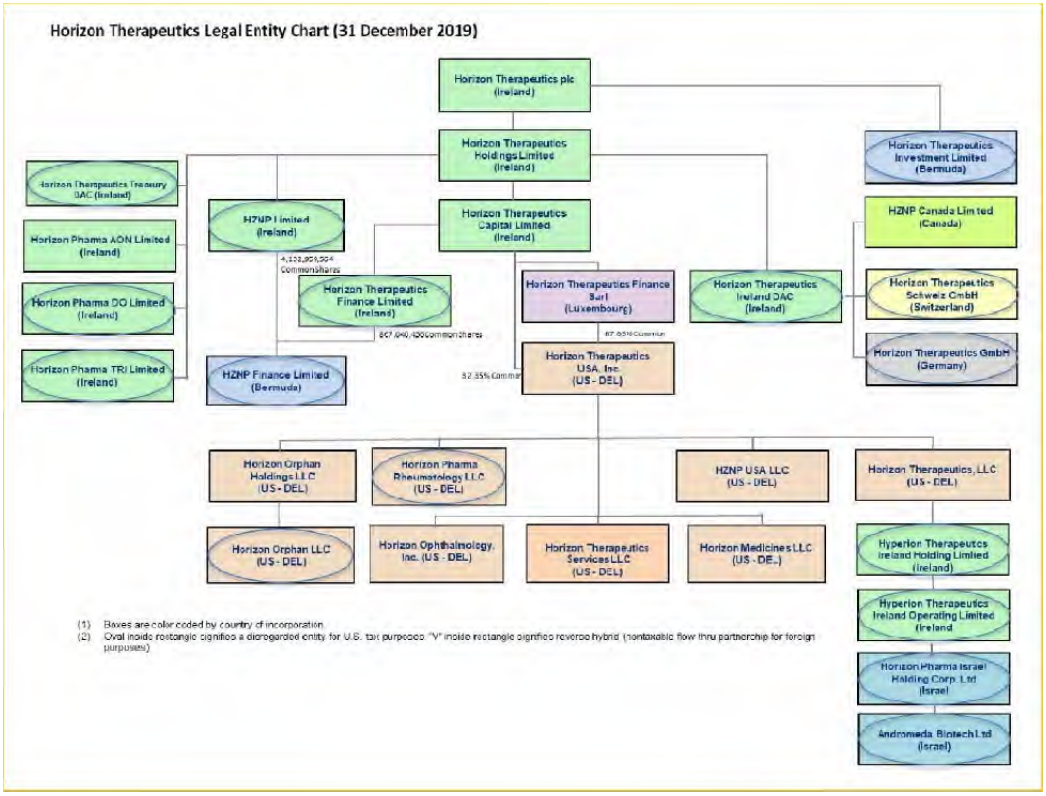
2017	<u>EMEA marketing rights divestiture</u> • On June 23, 2017, Horizon sold its European subsidiary that owned marketing rights to PROCYSBI and QUINSAIR in EMEA, [redacted] to Chiesi Farmaceuitici S.p.A. ("Chiesi") for $72.5 million. • Under the terms of the agreement, Horizon will continue to make royalty payments for sale of PROCYSBI and QUINSAIR in EMEA and Chiesi will reimburse the company for those payments.[32] <u>Regulatory approval and launch in Canada</u>[33] • On June 13, 2017, Health Canada granted a Notice of Compliance to market PROCYSBI in Canada. • Horizon made its first sale of PROCYSBI in Canada on September 7, 2017.
2018	• [redacted]

31 (TOR0000001046) "Impairment considerations of goodwill, IPR&D, long-live assets and going concern – Q1 2018", dated April 27, 2018.
32 RR-8 – Horizon Pharma Public Limited Company Form 10-K for the fiscal year ended December 31, 2017.
33 The Hay Report, Appendix E – Background: Commercialization of PROCYSBI, paragraph (5).
34 (TOR0000001046) "Impairment considerations of goodwill, IPR&D, long-live assets and going concern – Q1 2018", dated April 27, 2018.

B. Overview of the Horizon Group[35]

4.11. An overview of the Horizon Group legal entity structure is provided below.

Figure 8: Horizon Group Legal Entity Structure[36]



4.12. A summary of the Horizon group entities involved in the economic activities relating to the sale of PROCYSBI and their role is provided below.

Horizon Therapeutics Public Limited Company

4.13. Horizon is the ultimate parent company of the Horizon Group. Through its subsidiaries, Horizon markets eleven medicines through its orphan and rheumatology and inflammation reportable business segments, including PROCYSBI for the treatment of NC.

35 Information in this section was obtained from KPMG OECD Transfer Pricing Report dated July 6, 2020 (TOR0000001168).

36 (TOR0000001168) KPMG's OECD Transfer Pricing Report dated July 6, 2020, Page 13, Figure 1.

HZNP Limited

4.14. HZNP Limited ("HZNP") is an Ireland-based company that acquires and develops IP and manages development programs for new therapeutic uses for the drugs. HZNP also oversees and controls risks in relation to the exploitation of the IP, including IP relating to PROCYSBI.

Horizon Therapeutics Ireland DAC

4.15. Horizon Therapeutics Ireland DAC[37] ("HTI DAC" or "Horizon Ireland") is an Ireland-based specialty pharmaceutical company. During 2019, HTI DAC licensed IP from HZNP to commercialize various products across different regions, including PROCYSBI in ex-US and ex-EMEA region (which includes Brazil, Colombia, and Canada).

4.16. HTI DAC outsources the manufacturing of the licensed products to third parties. HTI DAC also performs quality control functions for its licensed products and tests the active pharmaceutical ingredient ("API") manufactured by the third-party contract manufacturers.

4.17. For PROCYSBI, HTI DAC has signed the following agreements to outsource manufacturing activities:

- API Supply Agreement with Cambrex Profarmaco Milano Srl ("Cambrex") for supply of Cysteamine Bitartrate;[38] and
- Manufacturing Services Agreement with Patheon Pharmaceuticals Inc., ("Patheon") to manufacture PROCYSBI 25MG Units and 75MG Units.[39]

4.18. For sales within the US and Canadian markets, HTI DAC sells product to a US or Canada based affiliate of Horizon, which in turn sells to third parties in the US or Canada. However, in the case of PROCYSBI to be sold in Canada, HTI DAC was initially selling the products to Innomar Strategies Inc. ("Innomar") directly until July 2019. Since August 2019, HTI DAC has been selling PROCYSBI products to Horizon Canada, which subsequently sells it to Innomar. The economic activities and product flow relating to the sale of PROCYSBI in Canada are detailed in the section below.

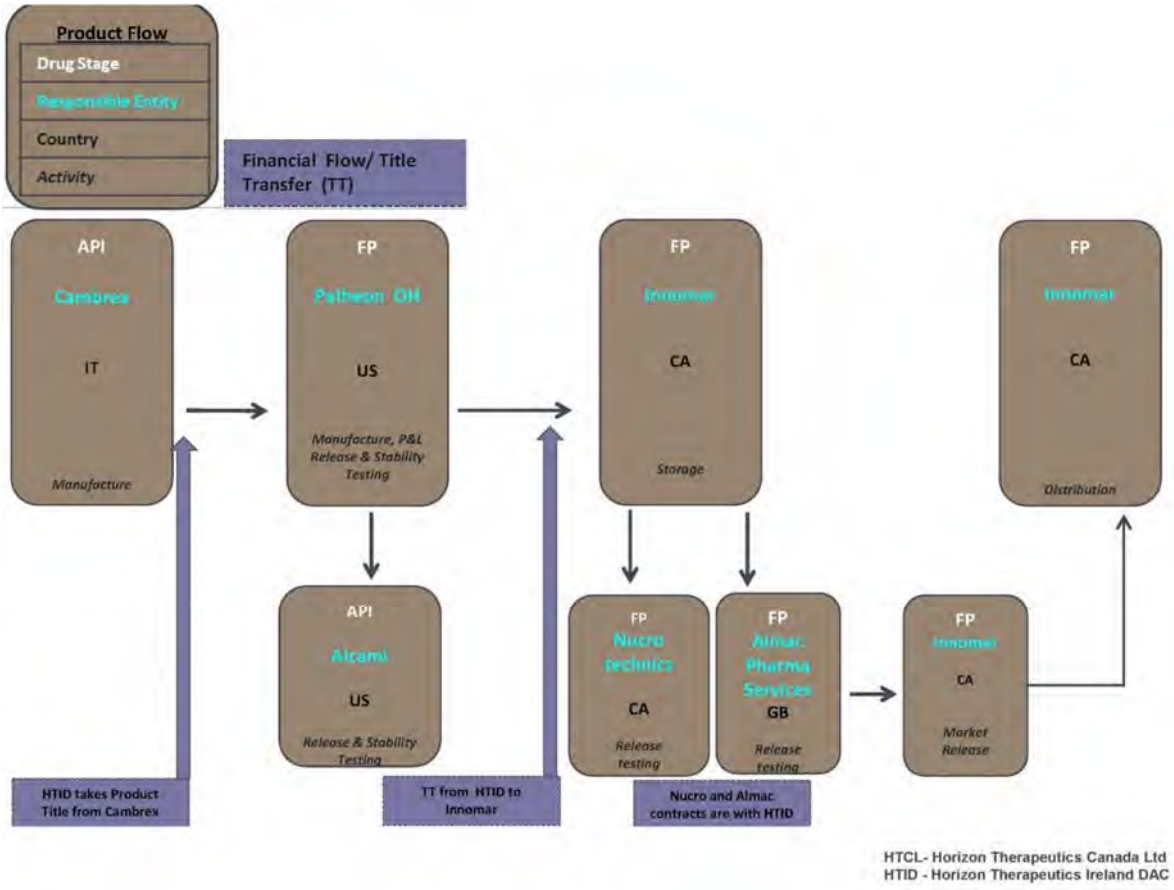
37 Horizon Therapeutics Ireland DAC was formerly known as Horizon Pharma Ireland Limited.
38 (TOR0000001148, TOR0000001150, TOR0000001134) API Supply Agreement and Amendments.
39 (TOR0000001154, TOR0000001152, TOR0000001153) Manufacturing Services Agreement and Amendments.

C. Economic Activities Relating to the Sale of PROCYSBI in Canada

4.19. All Canadian drug establishments are required to hold a Drug Establishment License ("DEL") in order to fabricate, package, label, distribute, import, wholesale, or test a drug. Horizon Canada obtained its DEL on May 18, 2019. Prior to July 2019, Innomar performed all warehousing and sales functions in Canada since Horizon Canada did not have its DEL. From July 2019 onward, Innomar performed only the distribution function. The economic activities relating to the sale of PROCYSBI in Canada before and after July 2019 are described below.

Before July 2019

Figure 9: Product Flow up to July 2019[40]



40 (TOR0000001146) PROCYSBI Canada product flow (Pre-DEL).

4.20. Before Horizon Canada received its DEL, HTI DAC sold PROCYSBI directly to Innomar, which performed all warehousing, importation, and distribution functions.[41] Horizon Canada conducted all other activities including sales, marketing, and medical functions in Canada.

4.21. Innomar distributed PROCYSBI to patients either directly through its warehouses located across various Canadian provinces, or through another intermediary, including partner pharmacies.

4.22. Prior to receiving its DEL, Horizon Canada's function was primarily to perform sales and marketing activities in Canada. HTI DAC had signed an Intercompany Services Agreement with Horizon Canada whereby the former would reimburse the latter for expenses incurred for the sale of PROCYSBI in Canada.[42]

Transition in July 2019

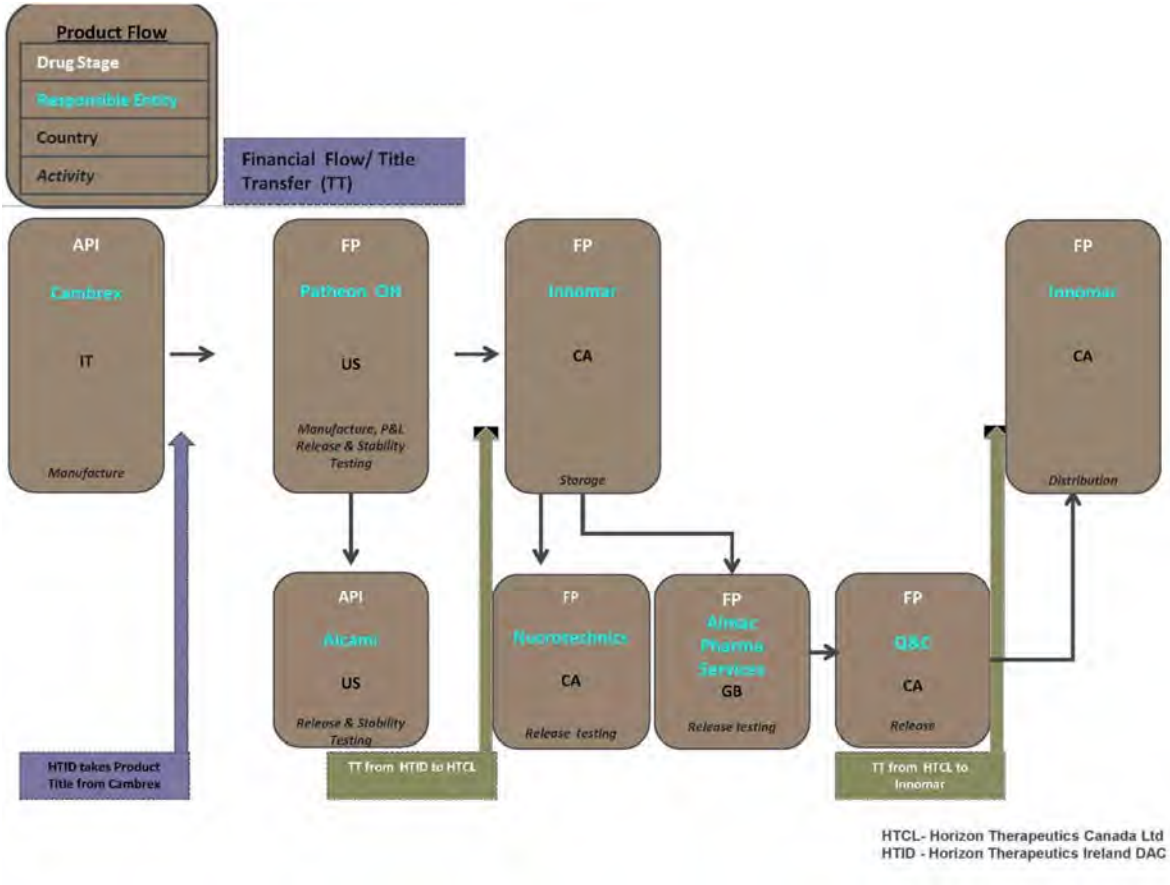
4.23. On May 18, 2019, Horizon Canada obtained its DEL. Horizon Canada acquired title to the inventory of PROCYSBI held by Innomar in Canada in August 2019.[43] As of this date, the scope of Innomar's services was restricted to the warehousing and distribution of PROCYSBI in Canada.

After July 2019

4.24. The product flow after July 2019 is summarized in the figure below.

41 (TOR0000001117, TOR0000001124, TOR0000001129) Commercial Outsourcing Services Agreement
42 (TOR0000001171) Intercompany Services Agreement between HTI DAC and HZNP Canada.
43 (TOR0000001127) Inventory Purchase Agreement.

Figure 10: Product Flow after July 2019[44]



4.25. Based on the Master Supply and Distribution Agreement effective July 31, 2019 (the "Master Agreement"), Horizon Canada acquires the title to PROCYSBI from HTI DAC after its manufacturing and packaging is completed in the USA by Patheon.[45] However, the physical product flow has effectively remained unchanged; Innomar continues to receive, store, and distribute PROCYSBI to patients either directly through its warehouses or through other healthcare professionals.[46]

44 (TOR0000001140) PROCYSBI CA Product Flow (Post-DEL). Differences from Figure 9 above highlighted in green.
45 (TOR0000001170) Master Supply and Distribution Agreement between HTI DAC and HZNP Canada.
46 (TOR0000001069) Commercial Outsourcing Services Agreement, (TOR0000001073) Wholesale Distribution Agreement.

4.26. Based on Exhibit B of the Master Agreement, Horizon Canada was to purchase PROCYSBI from HTI DAC at prices which would result in an operating profit of [redacted] of net revenue of PROCYSBI for Horizon Canada, plus [redacted] of sales and marketing internal costs incurred to perform the detailing activities.[47]

D. Financial Performance from the Sale of PROCYSBI

Horizon Canada

4.27. Since PROCYSBI's launch in 2017, Horizon Canada has sold [redacted] Units in Canada up to September 2019. A summary of sales volumes and revenues reported by Horizon Canada is provided below.

Figure 11: Summary of PROCYSBI Sales Volumes and Revenues in Canada[48]

[redacted]

[47] (TOR0000001170) Master Supply and Distribution Agreement, Exhibit B.
[48] (TOR0000001039) Horizon Canada PROCYSBI Revenue & Innomar Script Data.xlsx.

4.28. In its monthly business unit performance reports, Horizon Canada has deducted [redacted] (Schedule 8), which appears to be a provision created for the potential reduction of sales prices. For the purpose of my review of the actual financial results of PROCYSBI sold in Canada, I have excluded this deduction.

4.29. Horizon Canada tracks its sales and marketing expenses at the level of Horizon's overall [redacted] in its monthly business performance reports and management performance evaluation presentations. Further, I understand that it is [redacted]

4.30. Based on my analysis of the monthly business unit performance reports, Horizon Canada earned net profits of [redacted] between November 2017 and September 2019. A summary of the financial performance of Horizon Canada (Schedule 8) is provided below.

Figure 12: Summary of Financial Performance of Horizon Canada from November 2017 to September 2019[50]

[redacted]

[49] Joint Expert Memo, Part III - Requests that Remain in Dispute, Horizon's Position for Document Request #5 and #6.

[50] See Schedule 8 – Monthly Business Unit Performance Reports from November 2017 to September 2019.

Horizon Group

4.31. A summary of revenues reported by the Horizon Group from 2016 (when Horizon purchased the marketing rights to PROCYSBI) to 2019 from the sale of all products including PROCYSBI by year and by region (Schedule 7) is provided below.

Figure 13: Summary of Financial Performance of Horizon from 2016 to 2019

4.32. As shown in the figure above, PROCYSBI contributed approximately [redacted] of total net sales reported by the Horizon Group globally. Further, the contribution of net sales from the US to Horizon's total sales [redacted] in 2017 to [redacted] in 2019.

5. COMMENTS ON THE HAY REPORT

A. Summary of the Hay Report

Profits Earned by Horizon from sale of PROCYSBI in Canada

5.1. Dr. Hay calculated the net operating profits (i.e. revenues less costs) from the sales of PROCYSBI in Canada through to [redacted] to compute the cash flows that Horizon can expect over the product's life cycle.[52]

5.2. From the Harington Affidavit, I understand that the analysis and conclusions in the Hay Report are based on the aggregate profit generated by Horizon globally based on sales of PROCYSBI in Canada.[53]

5.3. Also, in Harington Sur-Reply Affidavit, Mr. Harington states that transfer pricing regulations require multinational corporations such as Horizon to share the total profits generated from operations among its group entities to reflect the value of each entity's economic contribution.[54] Accordingly, Horizon's profits would be shared among each Horizon entity, including:[55]

- The entity that manufactures the product;
- The entity that sells the product;
- The entity that facilitates the distribution of the product to Canada; and
- The entity(ies) that own(s) each aspect of the IP relating to the sales made in Canada.

5.4. Consequently, according to Mr. Harington, the [redacted]

[51] The Hay Report, Appendix F, Paragraph 1 states that June 2034 is the anticipated expiry date of Canadian Patent No. CA2914770 entitled "Delayed release cysteamine bead formulation, and methods of making and using same" (the "'770 Patent").
[52] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraphs 1 and 2.
[53] The Harington Affidavit, Paragraph 18i.
[54] The Harington Sur-Reply Affidavit, Paragraphs 5 to 8.
[55] The Harington Sur-Reply Affidavit, Paragraph 9.
[56] The Harington Sur-Reply Affidavit, Paragraphs 10 and 11.

5.5. Therefore, according to Mr. Harington, Dr. Hay has adopted a "conservative" approach to compute global net operating profits (or losses) generated from sale of PROCYSBI in Canada instead of computing net operating profits (or losses) earned by Horizon Canada.[57]

5.6. Dr. Hay's calculation of expected cash flow from Horizon's operations in Canada is primarily based on the actual performance reported by Horizon for 2017 and 2018, as well as contemporaneous forecasts prepared by Horizon for the period 2019 to [redacted] For the period [redacted] Dr. Hay has used different growth rates for sales volume and various cost items as summarized below.

Sales Volume and Price

5.7. Dr. Hay relied on actual unit sales (by SKU) of PROCYSBI in Canada from launch in September 2017 to December 2018. From 2019 to [redacted] Dr. Hay computed unit sales for PROCYSBI in Canada based on contemporaneous forecasts prepared by Horizon for the number of Canadian patients it expected to treat.[58]

5.8. Dr. Hay relied on his discussions with Horizon business representatives to assume that the company will continue selling PROCYSBI in Canada through to [redacted] at ex-factory prices at which it launched in September 2017.[59] As Horizon tracks its costs in USD$, Dr. Hay also converted gross sales computed in CAD$ to USD$ based on long term forecasts of the CAD$/USD$ exchange rate published by Deloitte.[60]

5.9. To derive net sales price, he relied on his discussions with Horizon business representatives and assumed that Horizon will [redacted]

5.10. In addition to using ex-factory prices, Dr. Hay has also computed expected cash flows for Horizon at the Proposed Prices.[62]

57 The Harington Sur-Reply Affidavit, Paragraph 13.
58 The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 3.
59 The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 7.
60 The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 8.
61 The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 10.
62 The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraphs 27 and 28.

Costs

5.11. Dr. Hay identified costs that Horizon incurs either in Canada or globally relating to the sale of PROCYSBI in Canada, including cost of goods sold, royalties, other cost of sales, sales and marketing, general and administrative, and research and development ("R&D") expenses.[63]

5.12. Cost of goods sold was determined based on the effective per unit costs paid to purchase units of 25MG Units and 75MG Units of PROCYSBI for sale in Canada in 2017 and 2018, and the standard costs estimated by Horizon for 2019. Thereafter, Dr. Hay assumed that [redacted]

5.13. Horizon is also required to pay royalties of 5.5% of net revenues from the sales of PROCYSBI to the University of California[65] in accordance with the terms of the licensing agreement between Horizon and the Regents of the University of California (the "License Agreement").[66]

5.14. To compute other cost items for each year during PROCYSBI's life cycle, Dr. Hay has used the following assumptions:[67]

a) [redacted]

b) [redacted]

c) [redacted]

5.15. Dr. Hay also noted that Horizon tracks its other cost items at [redacted]

63 The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 2.
64 The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 13, and Exhibit B.1.
65 Statement of Allegations, Paragraph 10 – The Regents of the University of California owns Canadian Patent No. CA2640531 entitled "Enterically coated cysteamine, cystamine and derivatives thereof" (the "'531 Patent"), which it licensed to Horizon.
66 The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 12.
67 The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraphs 15, 18, 20, 21, and 24.
68 The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraphs 16, 19, and 21.
69 Joint Expert Memo, Part III - Requests that Remain in Dispute, Horizon's Position for Document Request #5 and #6.

5.16. [redacted][70]

5.17. A summary of the profits from the sale of PROCYSBI in Canada under various scenarios as computed in the Hay Report (Schedule 9) and in the Hay Addendum (Schedule 10) is provided below.

Figure 14: Summary of Profits Computed in the Hay Report[71]

[redacted]

[70] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraphs 16, 19, 21, 23, and 24.
[71] The Hay Report, Appendix F – Details of Financial Economic Analysis, Schedule 1 to 3, and Exhibit G.

Figure 15: Summary of Profits Computed in the Hay Addendum[72]

B. Comments on the Hay Report

5.18. In his analysis, Dr. Hay has included two general categories of costs:

a) Incremental costs such as cost of goods sold, royalties, and sales and marketing expenses that Horizon Canada incurs to sell PROCYSBI in Canada; and

b) Allocation of other cost of sales, and fixed costs such as the cost of PROCYSBI development and commercialization, ongoing R&D costs, and general and administrative expenses that are incurred and tracked by Horizon on a global basis.

5.19. My comments on the Hay Report with respect to revenue and these two general categories of costs are detailed below.

[72] The Hay Addendum, Schedule 1S to 3S.
Please note that Dr. Hay did not provide the profits calculation at Horizon's ex-factory prices (Exhibit G of the Hay Report) in the Hay Addendum. Therefore, for illustrative purposes, I have calculated the profits at Horizon's ex-factory prices by updating the difference between the Hay Report and the Hay Addendum, i.e. the allocation of the Raptor Acquisition Cost and ongoing R&D expenses (see Schedule 10).

C. Analysis of Revenue

Sales Volume and Price

Dr. Hay's Approach and Assumptions

5.20. Dr. Hay relied on actual unit sales (by SKU) of PROCYSBI in Canada from launch in September 2017 to December 2018, as well as contemporaneous forecasts for the number of Canadian patients Horizon expected to treat from 2019 to [redacted][73]

5.21. From the patient forecasts, Dr. Hay estimated the total requirement of PROCYSBI in Canada from 2019 to [redacted] based on the following assumptions:[74]

a) Number of net new patients[75] that Horizon estimated to treat each year;

b) Age distribution of the patients; and

c) Daily dose of PROCYSBI required by patients.

5.22. The total sales in milligrams of PROCYSBI estimated by Dr. Hay [redacted]

5.23. [redacted]

[73] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 3.
[74] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraphs 3 to 5.
[75] Net new patients = New patients to be treated by PROCYSBI – Patients that discontinued PROCYSBI treatment.
[76] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 6, and Exhibit A.
[77] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 7.
[78] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 7.
[79] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 8.
[80] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 7.
[81] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 8.

5.24. In addition to using ex-factory prices, Dr. Hay has also computed cash flows that Horizon can expect over the product's patent period at the Proposed Prices.[82] A summary of sales prices assumed by Dr. Hay under various scenarios is presented below.[83]

Figure 16: Summary of Sales Prices Assumed by Dr. Hay

[redacted]

5.25. The Hay Report states that Horizon tracks its costs in USD$ globally. Therefore, to convert gross sales computed in CAD$ to USD$, Dr. Hay used long term forecasts of the CAD$/USD$ exchange rate published by Deloitte.[84]

5.26. To derive the net sales price, [redacted]

Our Assessment

5.27. For the purpose of my analysis of the impact, from a financial and economic perspective, of the Proposed Prices of PROCYSBI in Canada on Horizon's profits, I agree with the approach adopted by Dr. Hay to compute sales volume and prices for PROCYSBI in Canada. Therefore, I have adopted Dr. Hay's assumptions regarding sales volume and prices in my analysis and calculations provided in Section 6 below.

82 The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraphs 27 and 28.
83 The Hay Report, Paragraph 23.
84 The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 8.
85 The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 10.

D. Analysis of Incremental Costs

Cost of Goods Sold

Dr. Hay's Approach and Assumptions

5.28. For 2017 and 2018, [redacted]

5.29. For 2019, [redacted]

5.30. Dr. Hay estimated that Horizon would incur [redacted]

Our Assessment

5.31. Cost of goods sold relating to PROCYSBI includes two main components:

a) Cost of the API purchased from Cambrex; and

b) Cost of conversion to and packaging of PROCYSBI finished goods by Patheon.

5.32. To manufacture PROCYSBI 75MG Units and 25MG Units, [redacted] A summary of the per unit cost of API used to produce PROCYSBI to be sold in Canada between 2017 and 2020 (Schedule 17) is presented below.[94]

[86] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 14, and Exhibit B.2.
[87] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 14, and Exhibit B.1.
[88] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 13, and Exhibit B.1.
[89] The Hay Report, Appendix F – Details of Financial Economic Analysis, Schedule 1 to 3 and Exhibit G, Row [21].
[90] (TOR0000001141, TOR0000001142, TOR0000001143) PROCYSBI Canada Standard Cost Calculation (2018 to 2020).
[91] (TOR0000001148) API Supply Agreement, Exhibit 3.1.
[92] Article 1.9 of the API Supply Agreement (TOR0000001148) defines Inflation Index as the "*Annual average rate of change in the Harmonized Indices of Consumer Prices for the European Union published by Eurostat*".
[93] Article 3.1 of the API Supply Agreement (TOR0000001148) states that the adjustment for any year shall not increase or decrease the then-current Price by more than 3%.
[94] (TOR0000001145.0010, TOR0000001145.0009, TOR0000001145.0007, TOR0000001145.0008) Cambrex Invoices.

Figure 17: Per Unit API Cost Between 2017 and 2020

5.33. To manufacture PROCYSBI products, [redacted]

Figure 18: Per Unit Cost of PROCYSBI 25MG and 75MG Between 2017 and 2020[98]

5.34. Additionally, a summary by SKU and by year of fully loaded standard costs, which includes the cost of API, conversion, and packaging with inflation adjustment, computed by Horizon (Schedule 18) is provided below.

Figure 19: Standard Cost Per Unit From 2018 to 2020[99]

95 Article 4.2 (a) of the Manufacturing Services Agreement (TOR0000001154) defines Producer Price Index as the "*Pharmaceutical Preparation Manufacturing index published by the US Department of Labor, Bureau of Labor Statistics*". Also, see Schedule 18, and the PROCYSBI Canada Standard Cost Calculation from 2018 to 2020 (TOR0000001141, TOR0000001142, TOR0000001143) for Price Index values by month produced by Horizon.

96 (TOR0000001154) Manufacturing Services Agreement, Articles 4.1 and 4.2.

97 (TOR0000001145.0010, TOR0000001145.0009, TOR0000001145.0007, TOR0000001145.0008) Cambrex Invoices.

98 Inter-company invoices in CAD$ issued by Horizon Therapeutics Ireland DAC during 2019 and 2020 were converted to USD$ by using the same foreign exchange rates as Dr. Hay.

99 (TOR0000001141, TOR0000001142, TOR0000001143) PROCYSBI Canada Standard Cost Calculation from 2018 to 2020.

5.35. The per unit cost for PROCYSBI 75MG Units [redacted] As indicated in the figure above, Dr. Hay's assumption that cost of goods sold would [redacted] is not supported by historical data. Further, the Producer Price Index reported inflation of 3.16% from June 2018 to June 2019.[101]

5.36. As discussed in Section 4 above, Horizon's nature of operations relating to the sale of PROCYSBI in Canada changed in July 2019. Following this change, Horizon Canada signed the Master Agreement with HTI DAC, which owns the PROCYSBI intangible assets. Based on Exhibit B of the Master Agreement, Horizon Canada was to purchase PROCYSBI from HTI DAC at prices which would result in an operating profit of [redacted] of net revenue of PROCYSBI for Horizon Canada, plus [redacted] of sales and marketing internal costs incurred to perform the detailing activities.[102]

5.37. While the KPMG OECD Transfer Pricing Report dated July 6, 2020 concluded that Horizon Canada complies with the OECD transfer pricing regulations, details of the per unit price paid by Horizon Canada to HTI DAC during 2019 was not stated in the report. On comparison of the per unit price paid (Figure 18 above) and the standard costs estimated (Figure 19 above) during 2019 and 2020, it appears that Horizon Canada purchased PROCYSBI from HTI DAC at per unit prices determined based on the estimated standard costs instead of the transfer prices for the period.

5.38. Therefore, I have assumed the following for the purpose of my analysis (Schedule 11):

a) Fully loaded standard costs computed by Horizon from 2017 to 2020; and

b) [redacted]

100 (TOR0000001143.0001, TOR0000001143) PROCYSBI Canada Standard Cost Calculation for 2020, and Letter from Patheon regarding Price Adjustment for 2020 dated January 30, 2019.
101 (TOR0000001143), PROCYSBI Canada Standard Cost Calculation for 2020, Page 3.
102 (TOR0000001170) Master Supply and Distribution Agreement, Exhibit B.

Royalties

Dr. Hay's Approach and Assumptions

5.39. Horizon is required to pay royalties of 5.5% of net revenues from the sales of PROCYSBI to the University of California under the License Agreement.[103] Dr. Hay estimates that Horizon would incur between [redacted] as royalties under the various pricing scenarios.[104]

Figure 20: Royalties Payable from Sale of PROCYSBI in Canada Estimated by Dr. Hay

[redacted]

Our Assessment

5.40. Based on my review of the License Agreement,[105] I agree with the approach adopted by Dr. Hay to compute royalties for PROCYSBI Canada. Therefore, I have adopted Dr. Hay's assumptions regarding royalties in my analysis.

Sales and Marketing Expenses

Dr. Hay's Approach and Assumptions

5.41. Sales and marketing expenses include the cost of physician detailing (i.e. presentations to physicians by company salespersons), distribution fees paid to Innomar, and other promotional activities such as conferences and medical affairs presentations.[106] [redacted]

5.42. In the Hay Report, sales and marketing expenses for each year were computed as follows:[108]

a) [redacted]

b) [redacted]

[103] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 12.
[104] The Hay Report, Appendix F – Details of Financial Economic Analysis, Schedule 1 to 3 and Exhibit G, Row [21].
[105] (TOR0000001047, TOR0000001050) License Agreement and Amendment.
[106] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 17, and footnote 10.
[107] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 19.
[108] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 18.

c) [redacted]

5.43. Dr. Hay allocated [redacted]

5.44. Subsequently, Dr. Hay determined these [redacted]

5.45. Dr. Hay estimated that Horizon would incur between [redacted]

Figure 21: Sales and Marketing Expenses Relating to Sale of PROCYSBI in Canada Estimated by Dr. Hay

[redacted]

Our Assessment

5.46. As discussed in Section 4 above, Horizon's nature of operations relating to the sale of PROCYSBI in Canada changed in July 2019. Following this change, Horizon Canada signed the Master Agreement with HTI DAC, which owns the PROCYSBI intangible assets. Based on Exhibit B of the Master Agreement, Horizon Canada was to purchase PROCYSBI from HTI DAC at prices which would result in an operating profit of [redacted] of net revenue of PROCYSBI for

[109] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 18, and footnote 11.
[110] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 19.
[111] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraphs 29 and 30.
[112] The Hay Report, Appendix F – Details of Financial Economic Analysis, Schedule 1 to Schedule 3 – Row [23], Exhibit D, and Exhibit G.
[113] The Hay Report, Appendix F – Details of Financial Economic Analysis, Schedule 1 to Schedule 3 – Row [24], and Exhibit G – Row [23].

Horizon Canada, plus [redacted] of sales and marketing internal costs incurred to perform the detailing activities.[114]

5.47. While the KPMG OECD Transfer Pricing Report dated July 6, 2020 concluded that Horizon Canada complies with the OECD transfer pricing regulations, details of the mark-up charged by Horizon Canada to HTI DAC during 2019, if any, is not stated in the report. The documents produced by Horizon to date do not indicate that Horizon Canada has allocated this mark-up towards the sale of PROCYSBI in Canada.

5.48. Therefore, I agree with the approach adopted by Dr. Hay to compute and allocate sales and marketing expenses to PROCYSBI in Canada, except for the unidentified cost item that he included for 2017 as described below.

5.49. For 2017, PROCYSBI in Canada accounted for [redacted] of total Horizon net revenues in Canada. However, Dr. Hay has allocated [redacted] incurred towards sales and marketing expenses by Horizon Canada for 2017, including [redacted] that was identified Dr. Hay based on his discussions with business representatives of Horizon.[115]

5.50. Dr. Hay has not identified these expense items in his report. Horizon also has not produced any documents to support the allocation of these expenses. Therefore, I have excluded these cost items for the purpose of my analysis.

5.51. For 2017, I have allocated [redacted] which was computed as [redacted] of total sales and marketing expenses incurred by Horizon for its overall Canadian business, to PROCYSBI in Canada (Schedule 12).

[114] (TOR0000001170) Master Supply and Distribution Agreement, Exhibit B.
[115] The Hay Report, Exhibit D, footnote [17]-[19].

E. Analysis of Cost to Develop & Commercialize PROCYSBI and Ongoing R&D

Dr. Hay's Approach and Assumptions

5.52. The cost of PROCYSBI's development and commercialization includes $860.8 million paid by Horizon to acquire the worldwide marketing rights to PROCYSBI through its acquisition of Raptor Pharmaceutical Corp. ("Raptor Pharma") in October 2016 ("Raptor Acquisition Cost").[116]

5.53. Additionally, for ongoing R&D expenses (which include the cost of clinical trials, regulatory approvals, and quality checks)[117] incurred by Horizon after the Raptor Pharma acquisition, costs for each year were computed as follows:[118]

a) For 2017 and 2018, costs incurred by Horizon globally;

b) [redacted]

c) [redacted]

5.54. [redacted]

5.55. Subsequently, in the Hay Addendum, Dr. Hay was asked by counsel for Horizon to use a ratio based on the number of units sold in Canada to the [redacted][120]

[116] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 22.
[117] (TOR0000001137) Details of Expenses Line Items.
[118] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 24, and footnote 18.
[119] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 23 and 24.
[120] The Hay Addendum, Paragraph 3.

5.56. A summary of Dr. Hay's two approaches used to allocate the Raptor Acquisition Cost to PROCYSBI in Canada is below:[121]

Figure 22: Raptor Acquisition Cost Allocated to PROCYSBI in Canada

[redacted]

5.57. Further, Dr. Hay estimated that Horizon would incur [redacted]

Our Assessment

5.58. Section 85(3) of the *Act* states that:

"*In determining under section 83 whether a medicine is being or has been sold in any market in Canada at an excessive price, the Board shall not take into consideration research costs other than the Canadian portion of the world costs related to the research that led to the invention pertaining to that medicine or to the development and commercialization of that invention, calculated in proportion to the ratio of sales by the patentee in Canada of that medicine to total world sales.*" [123]

5.59. I disagree with Dr. Hay's allocation of the Raptor Acquisition Cost to PROCYSBI in Canada based on the following. At the time of acquiring Raptor Pharma in 2016, Horizon valued PROCYSBI's developed technology and global marketing rights [redacted]

[121] The Hay Report, Schedule 1, Row [27]; The Hay Addendum, Schedule 15, Row [27].
[122] The Hay Report, Appendix F – Details of Financial Economic Analysis, Schedule 1 to Schedule 3 – Row [26], and Exhibit G – Row [25].
[123] RR-11 – The *Patent Act*, R.S.C., 1985, Section 85(3).

[redacted]

5.60. Out of the total acquisition cost of $860.8 million, [redacted]

5.61. In my view, this value allocation approach is reasonable from a financial and economic perspective because independent and cash flow generating intangible assets such as marketing rights and patents are valued based on expected cash flows.[126] In this case, the US was and continues to be the highest revenue generating region for PROCYSBI, with the US contributing over 90% of revenues reported by Raptor Pharma until 2015,[127] and by Horizon in more recent years.[128]

5.62. By using the transaction value paid by Horizon to acquire worldwide marketing rights for PROCYSBI and allocating it [redacted] Dr. Hay has, in my view, over-allocated the amount of the Raptor Acquisition Cost to PROCYSBI in Canada.

5.63. In allocating the Raptor Acquisition Cost to PROCYSBI in Canada [redacted]

[124] (TOR0000001046.0002) KPMG - Valuation of Identifiable Subject Assets and Liabilities in Connection with the Acquisition of Raptor Pharmaceuticals Corp., dated October 24, 2016, (TOR0000001046) "Impairment considerations of goodwill, IPR&D, long-live assets and going concern – Q1 2018", dated April 27, 2018.

[125] (TOR0000001046.0002) KPMG - Valuation of Identifiable Subject Assets and Liabilities in Connection with the Acquisition of Raptor Pharmaceuticals Corp., dated October 24, 2016, (TOR0000001046) "Impairment considerations of goodwill, IPR&D, long-live assets and going concern – Q1 2018", dated April 27, 2018.

[126] RR-12 – The Value of Intangibles by Aswath Damodaran, available at http://people.stern.nyu.edu/adamodar/pdfiles/ovhds/dam2ed/intangibles.pdf

[127] RR-6 – Raptor Pharmaceutical Corp. Form 10-K for the fiscal year ended December 31, 2015.

[128] RR-10 – Horizon Therapeutics Public Limited Company Form 10-K for the fiscal year ended December 31, 2019.

5.64. Based on information available, cystinosis affects approximately 100 people in Canada,[129] 102 people in Brazil (as of 2010),[130] and 15 people in Colombia.[131] Accordingly, the Raptor Acquisition Cost to be allocated to PROCYSBI in Canada would be [redacted]

5.65. Further, the alternative approach introduced by Dr. Hay in the Hay Addendum is, in my view, flawed because it ignores the sales prices at which Horizon sells PROCYSBI in different regions. For instance, [redacted] contributed [redacted] of the sales volumes as opposed to [redacted] contributed by [redacted] during the fourth quarter of 2019.[132] However, as summarized in Section 3 above, PROCYSBI contributed to [redacted] of Horizon's global net sales, and Horizon earned [redacted] of its global revenues from [redacted] in 2019.[133]

5.66. Since almost all of the revenues earned by Horizon are generated from the US, the Raptor Acquisition Cost and ongoing R&D expenses should be allocated on a pro-rata basis according to the revenues generated by each region. In my view, this allocation method is reasonable from a financial and economic perspective and is consistent with section 85(3) of the *Act*.

5.67. For illustrative purposes, I have calculated Horizon's net sales and gross profits from the sale of PROCYSBI in the US at Schedule 7. After acquiring the global marketing rights to distribute PROCYSBI from Raptor Pharma in October 2016, Horizon has earned net revenues of [redacted][134] with gross profits[135] of [redacted] (or approximately [redacted] of the Raptor Acquisition Cost of $860.8 million as revenues from the US) between October 2016 and December 2019, with the marketing rights and patents being valid for another [redacted] years. In contrast, for sales of PROCYSBI in Canada, Dr. Hay has computed net revenues of [redacted] with gross profits of [redacted] up to December 2019 at ex-factory prices.

5.68. Accordingly, in my view, the Raptor Acquisition Cost and ongoing R&D expenses should be allocated to PROCYSBI in Canada based on the ratio of revenue reported by Horizon from the sale of PROCYSBI in Canada to the total revenue earned by Horizon from the sale of PROCYSBI

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129 RR-2 – House of Commons Canada – Report of the Standing Committee on Health – Canadians Affected by Rare Diseases and Disorders: Improving Access to Treatment, page 14.
130 RR-13 – Report of a Brazilian Multicenter Study on Nephropathic Cystinosis – PubMed.
131 RR-14 – Colombia National Public Health Surveillance System – 2019, page 4.
132 The Hay Addendum, Figure 1.
133 RR-10 – Horizon Therapeutics Public Limited Company Form 10-K for the fiscal year ended December 31, 2019.
134 Schedule 7 – The estimate of Horizon's net revenues from sale of PROCYSBI in the US is based on the limited information available to me at the time of writing this report.
135 Gross Profits = Net Sales - Cost of Goods Sold.

globally. However, disclosure in Horizon's financial statements do not provide the breakdown of revenues from the sale of PROCYSBI in Canada and across the rest of the world from 2016 to 2019.

5.69. Therefore, I have allocated the Raptor Acquisition Cost (Schedule 13) and ongoing R&D expenses (Schedule 14) to PROCYSBI in Canada on a pro-rata basis based on the average of revenues reported by Horizon from rest of the world relative to the total revenue earned by Horizon globally over the past four years.

$$Ratio\ of\ cost\ allocated\ to\ PROCYSBI\ Canada = Average\ of\ \left(\frac{Net\ Revenues\ from\ Rest\ of\ the\ World}{Net\ Revenues\ of\ Horizon\ Group}\right)\ from\ 2016\ to\ 2019$$

F. Analysis of Allocated Costs

Other Cost of Sales

Dr. Hay's Approach and Assumptions

5.70. Other cost of sales includes [redacted] The Hay Report also states that [redacted]

5.71. In the Hay Report, other cost of sales for each year was computed as follows:[138]

a) For 2017 and 2018, [redacted]

b) From [redacted]

c) [redacted]

5.72. Dr. Hay [redacted]

[136] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 15.
[137] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 16.
[138] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 15.
[139] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 15, and footnote 9.
[140] The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 16.

5.73. Dr. Hay estimated that Horizon [redacted]

Our Assessment

5.74. Other cost of sales includes costs incurred by Horizon globally relating to manufacturing operations, inventory adjustment, packaging, freight, and other supply chain related costs for PROCYSBI.[142] Horizon has not produced adequate information to identify and support the allocation of these costs to the sale of PROCYSBI in Canada. These costs were not included in the monthly business unit performance reports for Horizon Canada prepared by Horizon for its internal reviews and management presentations.[143]

5.75. In my view, for the analysis of Horizon Canada's profits from the sale of PROCYSBI in Canada, the other cost of sales should not be deducted [redacted]

5.76. For the analysis of the profits from the sale of PROCYSBI in Canada from the perspective of [redacted]

5.77. [redacted]

5.78. [redacted]

141 The Hay Report, Appendix F – Details of Financial Economic Analysis, Schedule 1 to Schedule 3 – Row [22], and Exhibit G – Row [22].
142 (TOR0000001137) Details of Expenses Line Items.
143 Schedule 8.
144 The Hay Report, Appendix F – Details of Financial Economic Analysis, Exhibit C – Row [3].
145 Dr. Hay notes that PROCYSBI is sold by Chiesi in EMEA and by Horizon and its subsidiaries in other regions.
146 The Hay Addendum, Paragraph 3.

General and Administrative Expenses

Dr. Hay's Approach and Assumptions

5.79. General and administrative expenses reflect managerial and business-services costs incurred in the day to day operation of pharmaceutical companies.[147] The Hay Report also states that [redacted].[148]

5.80. In the Hay Report, general and administrative expenses for each year were computed as follows:[149]

a) For 2017 and 2018, [redacted]

b) [redacted]

c) [redacted]

5.81. Dr. Hay [redacted]

5.82. Subsequently, Dr. Hay determined these allocated general and administrative expenses as [redacted]. For the computation of profits at the Proposed Prices, Dr. Hay assumed that Horizon would incur general and administrative expenses in the same ratio.[151] Therefore, general and administrative expenses under the alternative scenarios were determined as a percentage of net revenues earned at Proposed Prices.[152]

5.83. Dr. Hay estimated that Horizon would incur between [redacted] as general and administrative expenses under the various pricing scenarios. A summary of general and administrative expenses assumed by Dr. Hay under the various scenarios is presented below.[153]

147 The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 20.
148 The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 21.
149 The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraphs 20 and 21.
150 The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraph 21.
151 The Hay Report, Appendix F – Details of Financial Economic Analysis, Paragraphs 29 and 30.
152 The Hay Report, Appendix F – Details of Financial Economic Analysis, Schedule 1 to Schedule 3 – Row [25], and Exhibit G.
153 The Hay Report, Appendix F – Details of Financial Economic Analysis, Schedule 1 to Schedule 3 – Row [24], and Exhibit G – Row [23].

Figure 23: General and administrative Expenses Relating to Sale of PROCYSBI in Canada Estimated by Dr. Hay

Our Assessment

5.84. General and administrative expenses include costs incurred by Horizon on support functions such as human resources, finance, legal, business development, information technology, facilities, corporate security, communications, government affairs, public affairs, corporate development, and other incentives paid to employees globally.[154] A summary by year of general and administrative expenses incurred or estimated by Horizon (Schedule 19) is provided below.

Figure 24: Summary of General and Administrative Expenses by Cost Item and By Year

5.85. Horizon has not produced adequate information to identify and support the allocation of these costs towards sale of PROCYSBI in Canada. These costs were not included in the monthly business unit performance reports for Horizon Canada prepared by Horizon for its internal

[154] (TOR0000001130) Total Company Sales, General and Administrative Expenses.

reviews and management presentations.[155] Further, [redacted][156]

5.86. In my view, for the analysis of Horizon Canada's profits from the sale of PROCYSBI in Canada, general and administrative expenses should not be deducted since these costs were incurred by Horizon Ireland and not actually incurred by Horizon Canada.

5.87. As outlined in Section 4C above, Horizon Canada's business operations changed in July 2019, when Horizon Canada obtained the DEL. However, I understand that Innomar continues to receive and manage the flow of PROCYSBI products in Canada, with Horizon Canada continuing to have minimal involvement in the actual stocking and movement of goods. Horizon only maintains a sales and marketing team in Canada. Accordingly, in my view, many of the general and administrative expenses would not be attributable to the sale of PROCYSBI in Canada. Therefore, I have excluded the costs categorized under facilities, corporate security, communication, government affairs, public affairs, patient advocacy, corporate development, corporate management, and general and administrative incentives, absent any documentary support that any of these costs are directly attributable to the sale of PROCYSBI in Canada.

5.88. For the analysis of the profits from the sale of PROCYSBI in Canada from the perspective of Horizon's business globally, I have only included costs relating to human resources, finance, legal, business development, and information technology that may be attributable to Horizon's day to day operations in Canada in my analysis. For the allocation of these costs, I agree with the approach adopted by Dr. Hay of [redacted]

[155] Schedule 8.
[156] Joint Expert Memo, Part III - Requests that Remain in Dispute, Horizon's Position for Document Request #5 and #6.

6. CALCULATION AND ANALYSIS OF PROFITS

A. Calculation of Profits

6.1. In this section, I provide my calculation and analysis of the expected net operating profits from the sale of PROCYSBI in Canada from the perspective of Horizon Canada and the Horizon Group.

6.2. To compute the expected net operating profits for Horizon Canada from the sale of PROCYSBI in Canada during the period from 2017 to [redacted] (Schedules 1 to 4), I have made the following assumptions:

6.3. For sales volumes, gross and net sales prices, I have adopted the following assumptions used by Dr. Hay:

a) [redacted]

b) [redacted] Additionally, I have adopted the Proposed Prices used by Dr. Hay (Figure 16 above) to compute expected cash flows in the alternative scenarios; and

c) [redacted]

6.4. For cost of goods sold, I have assumed:

a) Fully loaded standard costs computed by Horizon from 2017 to 2020 (Figure 19 above); and

b) Thereafter, cost of goods sold increasing at the rate of 3% per annum up to [redacted]

6.5. For royalties, I have adopted Dr. Hay's assumption that Horizon would be required to pay 5.5% of net revenues to the University of California under the License Agreement.

6.6. I have also adopted Dr. Hay's estimates for sales and marketing expenses to be incurred by Horizon for its Canadian operations, except for the unidentified cost item that he included for 2017 as described in Section 5 above. Further, I have allocated sales and marketing expenses to PROCYSBI on a pro-rata basis according to its share of total Horizon net revenues in Canada from 2017 to [redacted]

6.7. For the cost of PROCYSBI's development and commercialization, I have adopted Dr. Hay's estimates of R&D expenses incurred by Horizon globally. However, I have allocated the Raptor Acquisition Cost and ongoing R&D expenses to PROCYSBI in Canada on a pro-rata basis based

on the average of revenues reported by Horizon from rest of the world relative to the total revenue earned by Horizon globally over the past four years.

6.8. I have excluded other cost of sales and general and administrative expenses when computing net operating profits for Horizon Canada. I have included these costs while computing profits from the sale of PROCYSBI in Canada from the perspective of Horizon's business globally.

6.9. For other cost of sales, I have adopted Dr. Hay's estimates, but these costs are allocated on a pro-rata basis according to the number of units sold in Canada to the number of units sold worldwide in the fourth quarter of 2019.

6.10. For general and administrative expenses, I have only deducted costs relating to key support functions such as human resources, finance, legal, business development, and information technology that may be attributed to Horizon's day to day operations in Canada. For allocating these cost items to PROCYSBI in Canada, I agree with the approach adopted by Dr. Hay of using a ratio of PROCYSBI Canada's share to total Horizon sales worldwide.

6.11. Based on the assumptions discussed above, my calculation of the expected net operating profits to Horizon Canada and the Horizon group from the sale of PROCYSBI in Canada for the period 2017 to [redacted] (Schedules 1 to 4) are summarized as follows.

Figure 25: Summary of Profits to Horizon Canada and the Horizon Group from the Sale of PROCYSBI in Canada

[redacted]

B. Calculation of Internal Rate of Return

6.12. In the Hay Report, Dr. Hay states that:[157]

"*From an economic perspective, a company is unlikely to invest in a project unless it expects to earn a return on investment that provides compensation for the risks involved, as well as for the time value of money. In deciding whether to undertake an investment, a company will consider the return that it will earn if the drug is successfully commercialized.*"

6.13. However, Dr. Hay has neither stated the rate of return that Horizon expects from PROCYSBI nor outlined any method to compute the expected returns for Horizon on PROCYSBI at the ex-factory price or at the Proposed Prices.

6.14. I agree with Dr. Hay that, from a financial and economic perspective, a company would expect to earn a rate of return on its investment on a project that would be commensurate with the risks involved, including the time value of money. In my experience, companies generally use an IRR as a metric to assess the financial feasibility and viability of any project, as well as net present value ("NPV") analysis to consider the time value of money – i.e. the concept that the value of a dollar today is worth more than the value of a dollar in the future due to inflation and the ability to invest today's money for future growth.

6.15. NPV discounts future cash flows to their present value at the expected rate of return and compares that to the initial investment. NPV is stated in dollars and does not determine the rate of return earned by a project. IRR is stated as an interest rate representing the profit potential of an investment at the point where NPV equals zero, so it determines the rate of return a project earns. Both NPV and IRR require the company to determine a rate of return to be used as the target return rate.[158]

6.16. The IRR for any investment is determined as follows:

"*IRR is the discounted rate (interest rate) point at which NPV equals zero i.e. the point at which the present value cash inflows equal the initial investment cost.*"[159]

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157 The Hay Report, Paragraph 38.
158 RR-15 – OpenStax Rice University, Principles of Accounting, Volume 2: Managerial Accounting. Chapter 11 Capital Budgeting Decisions, Page 586.
159 RR-15 – OpenStax Rice University, Principles of Accounting, Volume 2: Managerial Accounting. Chapter 11 Capital Budgeting Decisions, Page 591.

6.17. Accordingly, an IRR computation involves three key components:

a) initial cash outflow or investment;

b) expected cash flows over the project or product lifecycle; and

c) the terminal value.

6.18. While Dr. Hay has not provided his assessment of the expected rate of return (i.e. Dr. Hay has not calculated the IRR based on his profit analysis using ex-factory prices), I have used the above components to compute the IRR implied by his profit analysis for Horizon from the sale of PROCYSBI in Canada at ex-factory prices (Schedules 5 and 6, the results of which are presented as follows:

Figure 26: IRR from Sale of PROCYSBI in Canada at Ex-Factory Prices Computed Implied by Dr. Hay's Profit Analysis

[redacted]

6.19. As indicated above, Dr. Hay's profit analysis implies that Horizon would have expected to earn a return of between [redacted] (based on the Hay Addendum) to [redacted] (based on the Hay Report) through the sale of PROCYSBI in Canada based on ex-factory prices until [redacted]

C. Analysis of Impact of the Proposed Prices on Horizon's Profits

6.20. In the Hay Report, Dr. Hay concludes that:[160]

"*At Proposed Prices, Horizon would* [redacted]

6.21. As discussed in Section 5 above, in my view, Dr. Hay has over-allocated the amount of the Raptor Acquisition Cost (i.e. the portion of the investment) and other expenses incurred by Horizon globally [redacted][161] toward the sale of PROCYSBI in Canada. Further, in my view, the profits associated with the sale of PROCYSBI in Canada should be [redacted] Therefore, based on my comments and analysis in

[160] The Hay Report, Paragraph 101.

[161] Joint Expert Memo, Part III - Requests that Remain in Dispute, Horizon's Position for Document Request #5 and #6.

Section 5 above, and my calculation of the profits of Horizon Canada and the Horizon Group in Section 6A above, I have calculated the IRR under each of the pricing scenarios (Schedules 1 to 4), summarized as follows:

Figure 27: IRR from Sale of PROCYSBI in Canada Under Various Scenarios

[redacted]

6.22. Based on my calculations of profits and IRR from the sale of PROCYSBI in Canada for the period 2017 to [redacted], I observe the following impacts of the pricing scenarios:

a) Based on my allocation of the Raptor Acquisition Cost and other expenses to Horizon Canada, and my calculation of profits and IRR thereon, the IRR for Horizon Canada and the Horizon Group at the current ex-factory price for the sale of PROCYSBI in Canada are [redacted]

b) At a 71% price reduction, Horizon Canada and the Horizon Group would [redacted] representing an IRR of [redacted] respectively. This level of IRR is higher than the IRR (ranging between [redacted] calculated at Section 6B above) implied by Dr. Hay's profit analysis that Horizon expects to earn through the sale of PROCYSBI in Canada based on ex-factory prices until [redacted]

c) At an 80% price reduction, Horizon Canada and the Horizon Group would [redacted], respectively, representing an IRR of [redacted] respectively. This level of IRR is comparable to the IRR (ranging between [redacted] calculated at Section 6B above) implied by Dr. Hay's profit analysis that Horizon expects to earn through the sale of PROCYSBI in Canada based on ex-factory prices until [redacted]

d) At a 96% price reduction, Horizon Canada and the Horizon Group would [redacted] respectively.

7. EXPERT DECLARATION

7.1 I, Howard Rosen, resident of Toronto, in the province of Ontario, declare that:

a) I have been retained by Perley-Robertson, Hill & McDougall LLP to provide evidence in the matter of the *Patent Act*, R.S.C. 1985, c. P-4, as amended and in the matter of Horizon Pharma (the "Respondent") and the medicine Cysteamine Bitartrate sold by the Respondent under the trade name PROCYSBI;

b) It is my duty to provide evidence in relation to this proceeding as follows:

i) to provide opinion evidence that is impartial;

ii) to provide opinion evidence that is related only to matters that are within my area of expertise; and

iii) to provide any additional assistance that the Board may reasonably require to determine a matter at issue.

c) I acknowledge that the duties referred to above take precedence over any obligation which I may owe to any party by whom or on whose behalf I am engaged.

Dated at Toronto, Ontario this 6th day of October, 2020.

Howard Rosen

Managing Director

Secretariat

APPENDIX 1 – CURRICULUM VITAE OF HOWARD ROSEN

Curriculum Vitae

Contact Details
hrosen@secretariat-intl.com
Office: +1.647.846.1944
Mobile: +1.416.567.9930

Professional History
- Secretariat (2018-Present)
- FTI Consulting (2009-2018)
- LECG (2004-2009)
- LRTS (1998-2004)
- Arthur Andersen (1992-1998)
- Berenblut & Rosen (1981-1992)
- Coopers & Lybrand (1979-1981)

Education
- Certified Fraud Examiner, 1992
- Accredited Senior Appraiser, 1988
- Chartered Business Valuator, 1984
- Chartered Accountant, 1981
- Bachelor of Business Administration, 1979

Professional Associations
- Swiss Arbitration Association
- Arbitrators Institute of Canada
- Canadian Institute of Chartered Accountants
- Canadian Institute of Chartered Business Valuators
- Institute of Chartered Accountants of Ontario
- National Association of Certified Fraud Examiners
- London Court of International Arbitration

Certifications
- Chartered Professional Accountant/Chartered Accountant, 1981
- Chartered Business Valuator, 1984

Languages
- English

Howard Rosen

Managing Director

Professional Experience

Howard Rosen has over 38 years' experience of advising on all aspects of business valuations, damages quantification, and corporate finance related matters. He has acted as an advisor to private and public companies, regulatory bodies, and all levels of government on a wide variety of industries. His work experience covers assignments across North and South America, Europe, the Middle East, Africa, and Asia. Howard has testified in damages quantification and valuation matters on over 200 occasions.

Howard has acted as court appointed administrator, monitor and inspector and sat as a member of an Arbitral Tribunal and sole Arbitrator. He is the co-author of two texts, a number of chapters and articles on the quantification of economic damages and has lectured extensively to professional interest groups. Howard has acted as instructor at the NITA and FIAA Expert Witness Trial Practice Programs, the MIDS Program at the University of Geneva, and as an MBA instructor at York University's Schulich School of Business in Toronto. Howard has been listed as one of the leading valuations and damages experts in Canada by Lexpert, and Internationally by Who's Who Legal as one of the top experts in international commercial arbitration worldwide, every year since the inception of the list in 2011.

Howard is recognized consistently by Who's Who Legal annually in a number of key listings, most recently including:

Thought Leader
- » *Thought Leaders Global Elite 2020 – Arbitration Expert Witnesses*
- » *Thought Leaders Global Elite 2020 – Quantum of Damages*
- » *Thought Leaders – Arbitration*

Global Leader
- » *Arbitration Expert Witness 2020 – Global Elite Thought Leader;*
- » *Energy Experts 2019 – Recommended*
- » *Experts – Financial Advisory and Valuation – Quantum of Damages 2019 – Global Elite Thought Leader*
- » *Mining Experts – Global Elite Thought Leader*

National Leader
- » *Canada - Arbitration Expert Witnesses 2019 - Recommended*

Howard has also acted as advisor on transactions in a wide variety of businesses, for both public and private equity investors, conducting strategic due diligence, valuations and deal structuring for both buyers and sellers. Howard has advised independent committees of boards of directors on non-arm's length transactions and has also acted as the chair of independent committees of boards of directors for non-arm's length transactions.

Howard's corporate finance experience extends to private equity investments, and managing investments through liquidity transactions, including sale to strategic buyers and IPO. Howard currently sits on the advisory committee of an institutional investor. Howard's past board positions have included a global Agriculture trading business (Vice-Chair and Lead Independent Director), a Junior resource company (Gas and Mining), a Medical Software and Devices company where he served as Chair of the Audit Committee, as well as a Specialty Manufacturer.

Howard is also a Qualified Valuator under the Canadian CIMVAL standards.

Pharmaceutical and Intellectual Property Experience

» Recent cases related to the pharmaceutical industry and intellectual property that Howard has worked on as the testifying expert or signatory of a valuation opinion include the following:

» Expert reports in connection with patent infringement cases in Canada – Expert opinion reports providing quantification of damages and/or accounting of profits relating to the alleged patent infringement of certain pharmaceutical drugs.

» Reply reports providing comments on reports prepared by other experts and quantifying the impact of different issues on lost profits calculated by other experts.

» Reports also provided financial analysis on the impact of generic entry into the market; commentary on transfer pricing issues; addressing the appropriateness of expenses and deductions in an accounting of profits; analysis of the costs and profitability of manufacturing an active pharmaceutical ingredient and finished drug product using a non-infringing process; addressing pre-judgment interest and appropriate measures of the return realized on the funds retained from infringing profits.

» Reports have been filed in connection with the following cases in the Federal Court of Canada:
  - AstraZeneca Canada Inc., Aktiebolaget Hässle, and AstraZeneca AB v Apotex Inc. (T-1409-04 and T-1890-11) relating to Omeprazole (Oral expert evidence provided at trial in February 2017)
  - ADIR and Servier Canada Inc. v Apotex Inc. and Apotex Pharmachem Inc. (T-1548-06) relating to Perindopril (Oral expert evidence provided at trial in November 2014)
  - H. Lundbeck A/S v Apotex Inc. (T-1407-09) relating to Escitalopram (Oral expert evidence provided at trial in December 2012)
  - Sanofi-Aventis Canada Inc. et al v Apotex Inc. (T-161-07) relating to Ramipril (Oral expert evidence provided at trial in February 2009)
  - Merck & Co. et al v Apotex Inc. et al (T-1272-97) relating to Lovastatin
  - GlaxoSmithKline Inc. et al v Apotex Inc. (T-14-09) relating to Valacyclovir
  - Merck & Co., AstraZeneca UK Limited et al v Apotex Inc. (T-2792-96) relating to Lisinopril

» Expert reports in connection with Section 8 damages proceedings under the Patented Medicines (Notice of Compliance) Regulations – Expert opinion reports providing quantification of damages as a result of commencements of proceedings pursuant to Canadian Patent Regulations which sought prohibition orders to prevent the Minister of Health of Canada from issuing Notices of Compliance for certain pharmaceutical drugs.

» Reply reports providing comments on reports prepared by other experts and quantifying the impact of different issues on lost profits calculated by other experts.

» Reports have been filed in connection with the following cases in the Federal Court of Canada:
  - Apotex Inc. v AstraZeneca Canada Inc. (T-389-11) relating to Esomeprazole (Oral expert evidence provided at trial in May 2017)
  - Apotex Inc. v AstraZeneca Canada Inc. (T-2300-05) relating to Omeprazole (Oral expert evidence provided at trial in February 2017)
  - Apotex Inc. v Merck Frosst Canada (T-1144-05) relating to Alendronate (Oral expert evidence provided at trial in September 2012)
  - Apotex Inc. v Pfizer Canada Inc. (T-825-06) relating to Azithromycin
  - Apotex Inc. v Abbott Laboratories, Limited (T-1396-07) relating to Clarithromycin
  - Apotex Inc. v Merck Frosst Canada (T-411-01) relating to Norfloxacin
  - Apotex Inc. v Ferring Inc. (T-1954-08 and T-165-07) relating to Desmopressin
  - Apotex Inc. v Servier Canada Inc. (T-1783-08) relating to Gliclazide

» Expert report in connection with a dispute under NAFTA – Expert opinion report providing a quantification of damages of a Canadian generic pharmaceutical company as a result of the alleged violations under NAFTA by the U.S. Government and the alleged actions of the U.S. Food and Drug Administration.

» Affidavit in connection with an application for leave to appeal to the Supreme Court of Canada – In connection with a Section 8 damages proceeding under the Patented Medicines (Notice of Compliance) Regulations, which was being appealed to the Supreme Court of Canada. Affidavit providing comments on the concept of "loss" (past losses and future losses) in the context of quantifying damages, and how the concept of "loss" accords with generally accepted accounting principles and business valuation. The affidavit also provided comments on the specific issues regarding damages sought in the claim for lost sales and permanent market share under the Regulations.

» Affidavit in connection with an application for leave to appeal to the Supreme Court of Canada – In connection with a Section 8 damages proceeding under the Patented Medicines (Notice of Compliance) Regulations, which is being appealed to the Supreme Court of Canada. Affidavit providing a calculation of the profits earned during a period when there was no generic competition compared to profits that would have been earned in the presence of generic competition and to Section 8 damages amounts.

» Expert report in connection with a pharmaceutical drug supply agreement dispute under the Ontario Superior Court of Justice – Preparation of an expert opinion report providing a quantification of damages based on analysis of historical sales and market share related to a pharmaceutical drug under a supply agreement.

» Expert report in connection with a pharmaceutical drug supply agreement dispute under the Arbitrations Act, Ontario, Canada – Expert opinion report providing a quantification of damages based on lost market share related to a pharmaceutical drug under a supply agreement.

» Expert report in connection with a dispute under the International Centre for Dispute Resolution of the American Arbitration Association – Preparation of an expert opinion report with respect to the net present value of a branded drug product related to a contract dispute between two pharmaceutical companies based in the U.S.A. and Japan, respectively, for a drug expected in Japan.

» Advisor to a Claimant in connection with an arbitration in Israel – Provided advisory services related to damages issues, critique of the opposing expert reports, and development of questions for cross-examination. This matter related to a contract dispute between two pharmaceutical companies based in Israel.

» Advisor to a pharmaceutical distribution and services company in Canada – Provided advisory services for the purpose of assisting in the assessment of potential claims between a major pharmaceutical distribution and services company and a pharmacy chain in respect to their prime vendor relationship in Canada.

» Expert report in connection with a failed initial public offering case in Canada – Expert report with an analysis of damages relating to the loss of goodwill to a parent company resulting from an alleged conspiracy causing failure of an IPO. The case relates to a national mail order pharmacy.

» Valuation report for corporate reorganization – Valuation of a company which manufactures soft gel capsules, provides encapsulation services, and manufactures pharmaceutical packaging (including bottling and blister packing). The company is based in Canada and services customers worldwide.

» Valuation report for corporate reorganization – Valuation of the intangible assets of a company which markets and distributes sports nutrition, weight loss, and health nutrition supplement products. The company is based in Canada and distributes products worldwide.

Current Position

Managing Director, Secretariat

Other Positions Held

FTI Consulting, Senior Managing Director, Global Practice Leader - International Arbitration and Head of Economic and Financial Consulting for North America and Asia
LECG, Managing Director, 2004 - 2009
Low Rosen Taylor Soriano, Principal, 1998-2004
Arthur Andersen & Company, Partner, 1992-1998
Berenblut & Rosen, Partner, 1982-1992
Coopers & Lybrand 1979-1981

Publications (Last Five Years)

- Co-author, "Making Effective Use of Experts", Austrian Yearbook on International Arbitration, 2020.
- Co-author, "Evaluating Your Business: What Is It Really Worth?", 2019.
- Featured expert article for the King & Spalding Quantum Quarterly Damages Newsletter, 2019.
- Co-author, "Restoring Faith in the Party-Appointed Expert**",** NYSBA Dispute Resolution Lawyer, 2019.
- Co-author, "Expert Evidence" the Guide to Energy Arbitrations, 2018
- Co-author, "Expert Evidence" the Guide to Energy Arbitrations, 2015.
- Co-author, "Trends in International Arbitration", FTI Journal, 2015.
- Co-author, "Trends in International Arbitration", The European, Middle Eastern and Africa Arbitration Review 2015.
- Co-author, "Going Concern versus Liquidation Valuations, the Impact on Value Maximization in Insolvency Situations", Evergreening and the transfer of patent value", The Asia-Pacific Arbitration Review 2015.
- Author, "How Useful are Party-Appointed Experts in International Arbitration", International Council for Commercial Arbitration (ICCA) Paper, 2014.
- Co-author, "The Valuation of Minority Interests in Forced Takings", The Arbitration Review of the Americas 2014.

Professional Presentations and Speaking Engagements, Seminars and Training (Last Five Years)

- **Prospectors & Developers Association of Canada (PDAC) Annual Conference.** Technical Program speaker on the topic, "Valuation of Damages in International Arbitration Cases". (2019)

- **Vienna International Arbitration Days.** Panelist on the topic, "Juggling the Numbers: Mathematics and Economics in Arbitration". (2019)

- **2018 Summit on Global Dispute Resolution** hosted by Cravath, Swaine & Moore LLP in conjunction with Fordham University, Centre for International Commercial and Investment Arbitration, Georgetown Law, NYU Law and the Engelberg Center on Innovation Law & Policy. Co-presenter on topic of Data Trends in International Disputes. (2018)

- **MCIA: The Changing Landscape of Arbitration in India.** Panelist on the topic, "Role of Experts in Arbitration". (2017)

- **Foundation for International Arbitration Advocacy (FIAA) (2012-2017).** FTI Consulting lead in coordinating our participation in the FIAA workshops. Authored materials conducted workshops and acted as an expert witness and instructor in three-day mock trial in a program that draws counsel from all over the world.

- **Northwind's 2016 Mining Invitational Forum, Modern Management for 21st Century Resource Companies.** Panelist on the topic, "International Arbitration: Its Effects on the Mining Industry and What Can We Do About It". (2016)

- **GAR Live Energy Disputes.** Panelist on the topic, "Recent BIT Cases and the Damages Fog". (2015)

- **Fourth Annual Damages in International Arbitration Conference.** Participant in Mock Arbitration – "Should country Risk Premiums be Included in Determining a Discount Rate? Shades of Gold Reserve v. Venezuela and Exxon Mobil v. Venezuela". (2015)

APPENDIX 2 – CICBV STANDARD 410 AND 310

PRACTICE STANDARD NO. 410

LIMITED CRITIQUE REPORTS

REPORT DISCLOSURE STANDARDS AND RECOMMENDATIONS

1. Chartered Business Valuators may be retained as independent experts to provide comments on another report that contains a conclusion as to the value of shares, assets, or an interest in a business, or a conclusion as to the quantum of financial gain/loss, but where a conclusion is not provided by the reviewing Valuator. In these circumstances, reports arising from such engagements are termed "Limited Critique Reports".

2. A Limited Critique Report is defined as **"any written communication containing comments on a report that was prepared by a Member or non-Member containing a conclusion as to the value of shares, assets or an interest in a business, or a conclusion as to the quantum of financial gain/loss, or any conclusion of a financial nature in the context of litigation or a dispute (the "Original Report"), prepared by a Valuator (the "Reviewer") that does not itself contain a valuation conclusion or conclusion as to the quantum of financial gain/loss, or any conclusion of a financial nature in the context of litigation or dispute."** A Limited Critique Report does not include work product that is in the process of being completed that is provided to a client or knowledgeable third party in circumstances where each of the following conditions are met: (i) the work product is clearly marked as being in draft form and subject to change; (ii) the work product is issued for the purpose of obtaining comment, instruction, confirmation or other information required to complete the Limited Critique Report; (iii) the Reviewer knows, or reasonably ought to know, that the intended reader(s) does not intend to rely on the work product or distribute the work product to a third party who may in turn rely on such work product; and (iv) the Reviewer has a reasonable expectation at the time the work product is provided that a Limited Critique Report will be completed and issued in due course.

3. At a minimum, a Limited Critique Report shall contain the following information, which is set out herein in bold characters. "*Recommendations*" are not mandatory but encouraged. "*Explanatory comments*" provide additional guidance in applying the specific provisions of the Standard.

4. **Report Introduction**

4.1 The Limited Critique Report shall have an introduction that includes the following information:

A. **To whom the Limited Critique Report is being provided;**

B. **A statement of the nature of the mandate, including the purpose of the Limited Critique Report and the identification of the Original Report being reviewed;** (*Explanatory comment*: this is to emphasize that the Limited Critique Report is addressed to specific readers in specific circumstances and having specific needs and knowledge)

C. **A description of the shares, assets or interests being valued, or a description of the dispute and the events giving rise to the quantum of financial gain/loss in the Original Report, and the valuation or quantification date in the Original Report;** (*Recommendation*: the description may simply refer to the Original Report where the Reviewer is reasonably satisfied that the Original Report is available to whom the Limited Critique Report is being provided)

D. **The date when pertinent information (including discussions with management or outsiders) was last obtained and analyzed;**

E. **If the Reviewer has previously issued a Valuation, Advisory and/or an Expert Report containing a valuation conclusion of shares, assets or an interest in a business, or a conclusion as to the quantum of financial gain/loss (the "Initial Report") dealing with the same subject matter as the Original Report now being reviewed, the identification of the Initial Report and a summary of its conclusions;**

F. **The name of the firm responsible for preparing the Limited Critique Report, as well as the name of the Reviewer when the Limited Critique Report is prepared for litigation purposes.** (*Explanatory comment*: this information may be disclosed elsewhere in the Limited Critique Report, such as in the letterhead and/or on the signature page)

G. **A statement that the Limited Critique Report was prepared by the Reviewer acting independently and objectively;** (*Explanatory comment*: in circumstances where a firm is responsible for preparing the Limited Critique Report, this statement is in respect of the independence and objectivity of the person(s) who prepared the Limited Critique Report and any assistants)

H. **A statement that the Reviewer's compensation is not contingent on an action or event resulting from the use of the Limited Critique Report;** and

I. **A statement that the Limited Critique Report has been prepared in conformity with the Practice Standards of The Canadian Institute of Chartered Business Valuators.**

5. Report Definitions

5.1 The Limited Critique Report shall contain definitions of the terms of value used in the Limited Critique Report (such as "fair market value", "market value", etc.) to the extent they are different from the Original Report, or a statement that the terms of value are the same as in the Original Report. (Recommendation: unless self-evident, other terms and phrases with technical meaning should be defined or explained as they appear in the body of the Limited Critique Report, or refer to the definitions in the Original Report if the same definitions are assumed.)

6. Report Scope of Review

6.1 The Limited Critique Report shall contain a scope of review, including a clear summary of the specific information which was reviewed and relied upon. (*Explanatory comment*: a Limited Critique Report may not have the same scope as the Original Report, such as being limited to a review of the Original Report itself and certain other documents.)

7. Report Disclosure

7.1 At a minimum, all Limited Critique Reports shall include a statement of the key assumptions made in making the Limited Critique Report comments to the extent they differ from those in the Original Report. (*Recommendation*: the Reviewer should consider restating all key assumptions, even those that do not differ from those in the Original Report, and state whether the facts stated in the Original Report are being assumed to be complete or correct unless otherwise note.)

7.2 It is recommended that Limited Critique Reports also include the following information:

A. Comments on the approach and techniques used in the Original Report, as appropriate;

B. Comments on the strengths and weaknesses of differing positions on subjective matters, as appropriate;

C. Comments on the calculations contained in the Original Report, and statement of directional impact of differing calculations or assumptions on the Original Report's conclusion, as appropriate; and

D. Comments on whether the opinion and analysis in the Original Report are suitable for the purpose at hand, with reasons and alternatives, as appropriate.

8. Report Restrictions and Qualifications

8.1 **All Limited Critique Reports shall disclose any restrictions that affect the Reviewer's comments, as noted below:**

A. Where the Reviewer was limited in the scope of review or where information provided to the Reviewer was substantially incomplete, disclosure should be made of the limitation and of the incomplete information, the reasons given and the potential impact on the comments. (*Recommendation*: the Reviewer should assess whether the lack of access to relevant information is so significant as to limit his or her ability to issue the Limited Critique Report.)

B. The Limited Critique Report shall caution the reader that it does not contain a conclusion as to the value of shares, assets or an interest in a business, or a conclusion as to the quantum of financial gain/loss and does not contain all the adjustments, if any, the Reviewer may have found necessary to arrive at a conclusion on value or quantum of financial gain/loss. (*Explanatory comment*: a report containing, or that may reasonably be considered to contain, a

conclusion as to the value of shares, assets or an interest in a business or a conclusion as to the quantum of financial gain/loss should be prepared according to Standards 110, 210 or 310, as appropriate.)

8.2 It is recommended that Limited Critique Reports also disclose any restrictions that affect the Reviewer's comments, as noted below:

A. A statement restricting the use of the Limited Critique Report to the persons for whom it was prepared and only for the stated purpose;

B. A statement disclaiming responsibility for losses resulting from unauthorized or improper use of the Limited Critique Report;

C. A statement giving the Reviewer the right to make revisions and/or further support the comments under specified circumstances, such as when facts existing at the Limited Critique Report date become apparent to the Reviewer after the Limited Critique Report is issued; and

D. A statement cautioning the reader that selecting portions of the analysis, without considering all factors and analysis in the Limited Critique Report together, could result in the misinterpretation of comments and analysis concerning value, or the quantum of financial gain/loss. (*Explanatory comment*: the preparation of a Limited Critique Report is a complex process and components cannot be viewed in isolation.)

October 7, 2010

PRACTICE STANDARD NO. 310

EXPERT REPORTS

REPORT DISCLOSURE STANDARDS AND RECOMMENDATIONS

1. Chartered Business Valuators may be retained as experts to provide their professional opinion as to the quantum of financial gain/loss or any conclusion of a financial nature in the context of litigation or a dispute. Such expert opinion is often requested in respect of claims arising from financial disputes such as corporate commercial matters, shareholder matters, securities litigation, personal injury matters, breach of contract, intellectual property infringement and income determination for family law purposes or other similar claims.

2. An Expert Report is defined as **"any written communication other than a Valuation Report, containing a conclusion as to the quantum of financial gain/loss, or any conclusion of a financial nature in the context of litigation or a dispute, prepared by an Expert acting independently."** An Expert Report does not include work product that is in the process of being completed that is provided to a client or knowledgeable third party in circumstances where each of the following conditions are met: (i) the work product is clearly marked as being in draft form and subject to change; (ii) the work product is issued for the purpose of obtaining comment, instruction, confirmation or other information required to complete the Expert Report; (iii) the Expert knows, or reasonably ought to know, that the intended reader(s) does not intend to rely on the work product or distribute the work product to a third party who may in turn rely on such work product; and (iv) the Expert has a reasonable expectation at the time the work product is provided that an Expert Report will be completed and issued in due course.

3. A summary of an Expert Report shall be exempt from the following standards and/or recommendations provided that the summary clearly refers to the Expert Report.

4. Where a Valuation Report forms part of an Expert Report that Valuation Report shall conform to Standards 110, 120 and 130.

5. At a minimum, all Expert Reports shall contain the following information, which is set out herein in bold characters. "Recommendations" are not mandatory but encouraged. "Explanatory comments" provide additional guidance in applying the specific provisions of the Standard.

6. **Report Introduction**

6.1 The Expert Report shall have an introduction that includes the following information:

A. **To whom the Expert Report is being provided**; (*Explanatory comment*: if not readily apparent from the addressee, the name of the party(ies) who engaged the Expert should be disclosed)

B. **A statement of the nature of the mandate;**

C. **The effective date or time period of the Expert Report calculation(s);**

D. **The date of the Expert Report;** (*Explanatory comment*: the Expert Report should be dated at the time when pertinent information was last obtained and analyzed, including information obtained from discussions with lawyers, client or other parties)

E. **The purpose for which the Expert Report is being prepared;** (*Explanatory comment:* the Expert may want to emphasize that the Expert Report is addressed to specific readers in specific circumstances, having specific needs and/or knowledge)

F. **The name and firm of the Expert responsible for preparing the Expert Report;** (*Explanatory comment*: this information may be disclosed elsewhere in the Expert Report, such as in the letterhead and/or on the signature page)

G. **A statement that the Expert Report was prepared by the Expert acting independently and objectively;** (*Explanatory comment*: in circumstances where a firm is responsible for preparing the Expert Report, this statement is in respect of the independence and objectivity of the person(s) who prepared the Expert Report and any assistants)

H. **A statement that the Expert's compensation is not contingent on an action or event resulting from the use of the Expert Report;** and

I. **A statement that the Expert Report has been prepared in conformity with the Practice Standards of The Canadian Institute of Chartered Business Valuators**.

7. Report Definitions

7.1 The Expert Report shall contain a definition(s) for the quantum of financial gain/loss, or any conclusion of a financial nature in the context of litigation or a dispute.

8. Report Scope of Review

8.1 **The Expert Report shall contain a detailed scope of review that clearly identifies the specific information upon which the Expert relied to arrive at a conclusion.** (*Explanatory comment*: such information might consist of the documents reviewed, the individuals interviewed, the facilities visited, other expert reports (including future-care cost studies, Valuation Reports, management consulting studies, etc.), management representations concerning budgets, projections and interim financial statements)

8.2 **Where the conclusion is qualified by a scope limitation, the limitation shall be explained, setting out the reasons for the limitation and disclosure of the potential impact on the Expert's conclusion.** (*Explanatory comment*: to the extent that the scope of review has been significantly restricted, or information provided is substantially incomplete, the Expert shall determine if an unqualified conclusion can be provided. If the Expert Report is qualified because of a scope limitation, the details shall be fully disclosed)

9. Report Disclosure

9.1 **The Expert Report should provide sufficient information to allow the reader to understand how the Expert arrived at the conclusion expressed.** (*Explanatory comment*: the amount of information included is a matter of professional judgment, based on the scope of review, the purpose for which the Expert Report is intended)

9.2 **At a minimum, all Expert Reports that will (or likely will) be disclosed publicly (e.g. in open court, in a prospectus, etc.) shall include the following information:** (*Explanatory comment*: when the Expert has been assured in writing that the Expert Report is to be restricted to review only by well-informed parties to the dispute or their counsel and the Expert is of the opinion that the omission of one or more of the following would not render the Expert Report misleading, then the following points should be considered as recommendations which should be followed)

A. **A description of the nature of the dispute and the events giving rise to the claim;** (*Explanatory comment*: this would include a narrative description of the business/employment activities, a brief history of relevant events and a discussion of factors influencing the Expert Report calculation(s))

B. Where applicable, **a description of the economic context and industry outlook bearing on the individual(s) and/or business(es) central to the Expert Report calculation(s)**, taking account of the past and foreseeable future as well as of the present;

C. **A statement of the approach taken and techniques used**, explaining the rationale for selecting a particular analytical technique and summarizing the key areas considered when selecting the analytical approach and determining financial gain/loss or any conclusion of a financial nature; (*Recommendation*: the basic mechanics of the techniques should be outlined and appropriate definitions should be provided)

D. **A description of the financial gain/loss, or other calculations relating to any conclusion of a financial nature,** explaining how each of the significant factors in the calculation(s) was developed and the rationale for each;

E. **Assumptions used and the procedures followed to determine the reasonableness and appropriateness of key assumptions;** (Explanatory comments: the Expert should classify the assumptions used as: (i) those assumptions that the Expert is directed to take, that are not within his/her area of expertise; (ii) those assumptions made by the Expert, within his/her area of expertise and based on scope of work executed by him/her; and (iii) those assumptions that the Expert is directed to take on matters that are within his/her area of expertise, but where the Expert was not provided opportunity to execute a scope of work appropriate to add assurance to the assumption)

F. **Financial information.** (*Explanatory comments*: comprising the most current (as close as possible to the effective date of the Expert Report calculation(s)) balance sheets, income/cash-flow statements or a summary thereof, tax returns and/or any other financial information central to the Expert Report calculation(s))

10. Report Restrictions and Qualifications

10.1 The Expert Report shall disclose any restrictions and qualifications that affect the Expert's conclusion as follows:

A. **A statement restricting the use of the Expert Report by the persons for whom the Report was prepared and only for the stated purpose**;

B. **A statement denying responsibility for losses resulting from any unauthorized or improper use of the Expert Report;** and

C. **A statement giving the Expert the right to make revisions and/or further support the conclusion under specified circumstances, such as when facts existing at the effective date become apparent to the Expert after the report is issued.**
(*Explanatory comment*: to the extent that the scope has been significantly restricted or information provided is incomplete, then the Expert must determine if an unqualified conclusion can be provided)

11. Conclusion

11.1 **The Expert Report shall contain a conclusion as to the quantum of financial gain/loss or conclusion of a financial nature. The conclusion shall include a reference to the scope of review, key assumptions, any restrictions and/or qualifications in the Expert Report.**

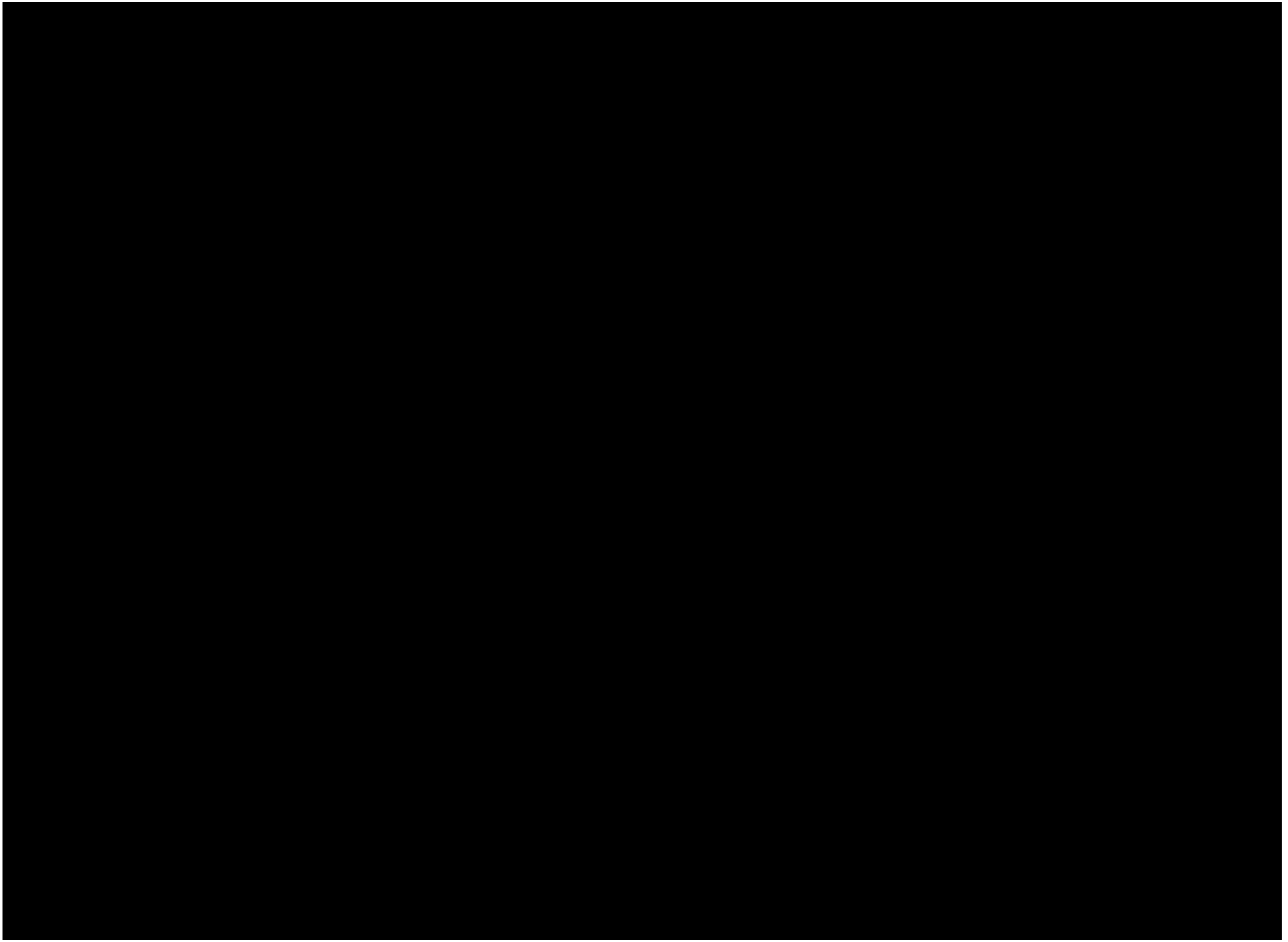
June 17, 2009

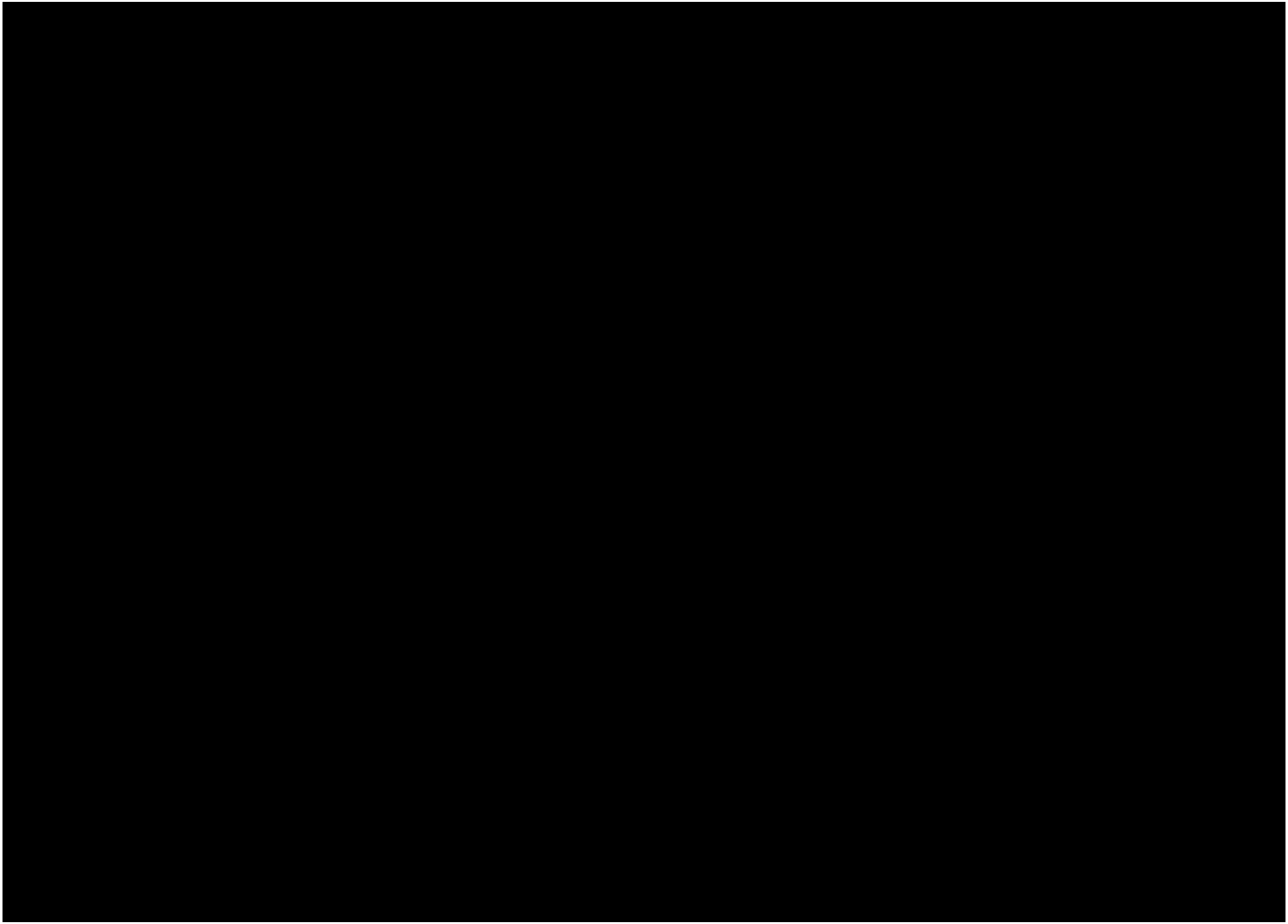
APPENDIX 3 – SCOPE OF REVIEW

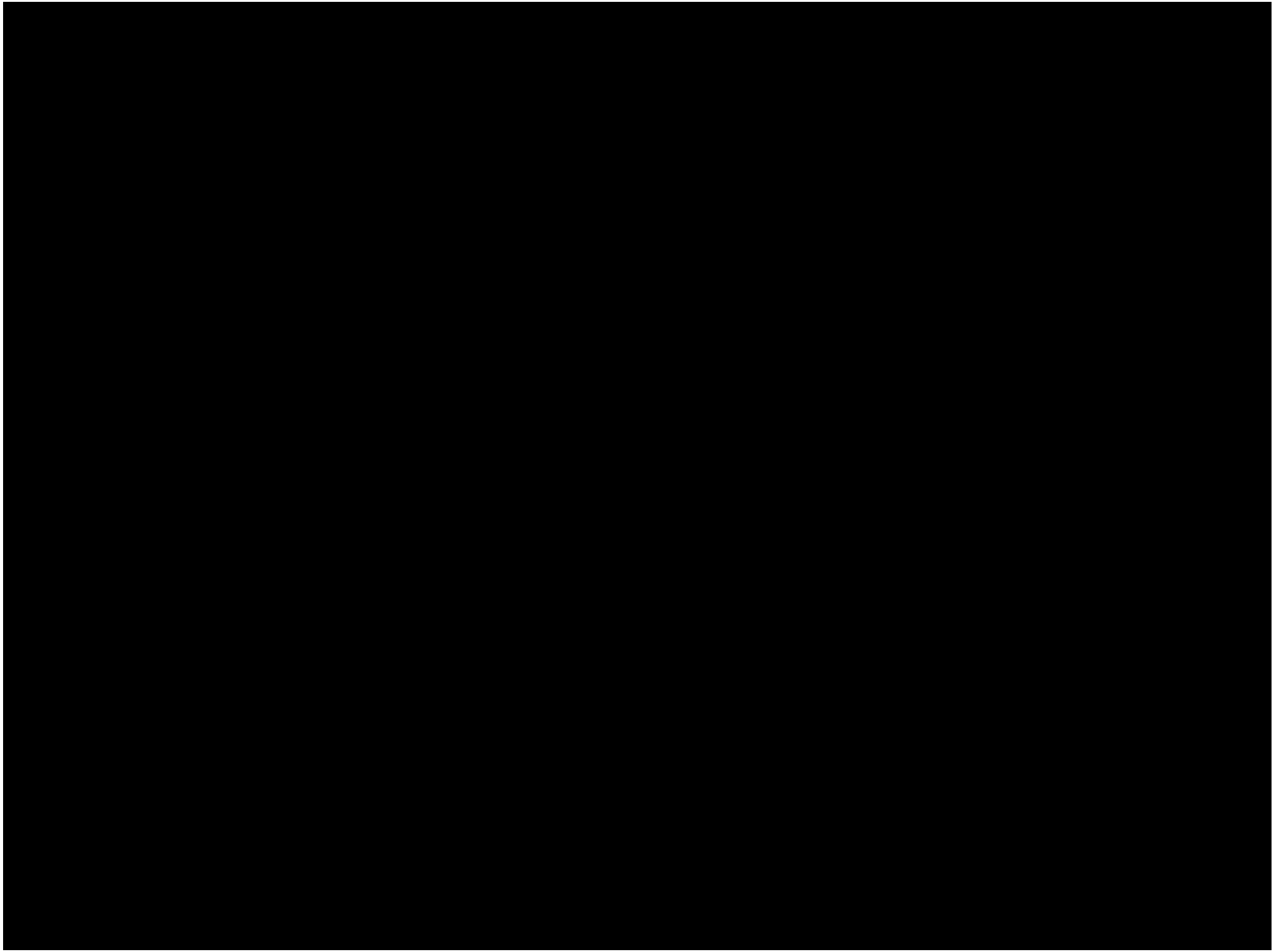
Reference Number	Description
Filings with the PMPRB	
	The Expert Report of Dr. Joel Hay dated September 9, 2019
	The Affidavit of Andrew Harington dated December 13, 2019
	The Sur-Reply Affidavit of Andrew Harington dated January 10, 2020
	The Joint Memorandum of Howard Rosen and Andrew Harington dated April 3, 2020
	Statement of Allegations of Board Staff dated January 16, 2019
	Response of Horizon Pharma dated February 18, 2019
Rosen Report Exhibits	
RR-1	http://pmprb-cepmb.gc.ca/about-us/mandate-and-jurisdiction
RR-2	House of Commons Canada – Report of the Standing Committee on Health – Canadians Affected by Rare Diseases and Disorders: Improving Access to Treatment
RR-3	OECD Transfer Pricing Guidelines for Multinational Enterprises and Tax Administrations, July 2017
RR-4	Raptor Pharmaceutical Corp. Form 10-K for the fiscal year ended August 31, 2010
RR-5	Raptor Pharmaceutical Corp. Form 10-K for the fiscal year ended December 31, 2014
RR-6	Raptor Pharmaceutical Corp. Form 10-K for the fiscal year ended December 31, 2015
RR-7	Horizon Pharma Public Limited Company Form 10-K for the fiscal year ended December 31, 2016
RR-8	Horizon Pharma Public Limited Company Form 10-K for the fiscal year ended December 31, 2017
RR-9	Horizon Pharma Public Limited Company Form 10-K for the fiscal year ended December 31, 2018
RR-10	Horizon Therapeutics Public Limited Company Form 10-K for the fiscal year ended December 31, 2019
RR-11	The *Patent Act*, R.S.C., 1985
RR-12	The Value of Intangibles, Aswath Damodaran
RR-13	Report of a Brazilian Multicenter Study on Nephropathic Cystinosis - PubMed
RR-14	Colombia National Public Health Surveillance System - 2019
RR-15	OpenStax Rice University, Principles of Accounting, Volume 2: Managerial Accounting. Chapter 11 Capital Budgeting Decisions
Documents Produced by Horizon	
TOR0000001013	Canada BU Perf_December_2017.xlsx
TOR0000001014	Canada BU Perf_November_2017.xlsx
TOR0000001015	Canada BU Perf_April_2018.xlsx
TOR0000001016	Canada BU Perf_August_2018.xlsx
TOR0000001017	Canada BU Perf_December_2018.xlsx
TOR0000001018	Canada BU Perf_February_2018.xlsx
TOR0000001019	Canada BU Perf_January_2018.xlsx
TOR0000001020	Canada BU Perf_July_2018.xlsx
TOR0000001021	Canada BU Perf_June_2018.xlsx
TOR0000001022	Canada BU Perf_March_2018.xlsx

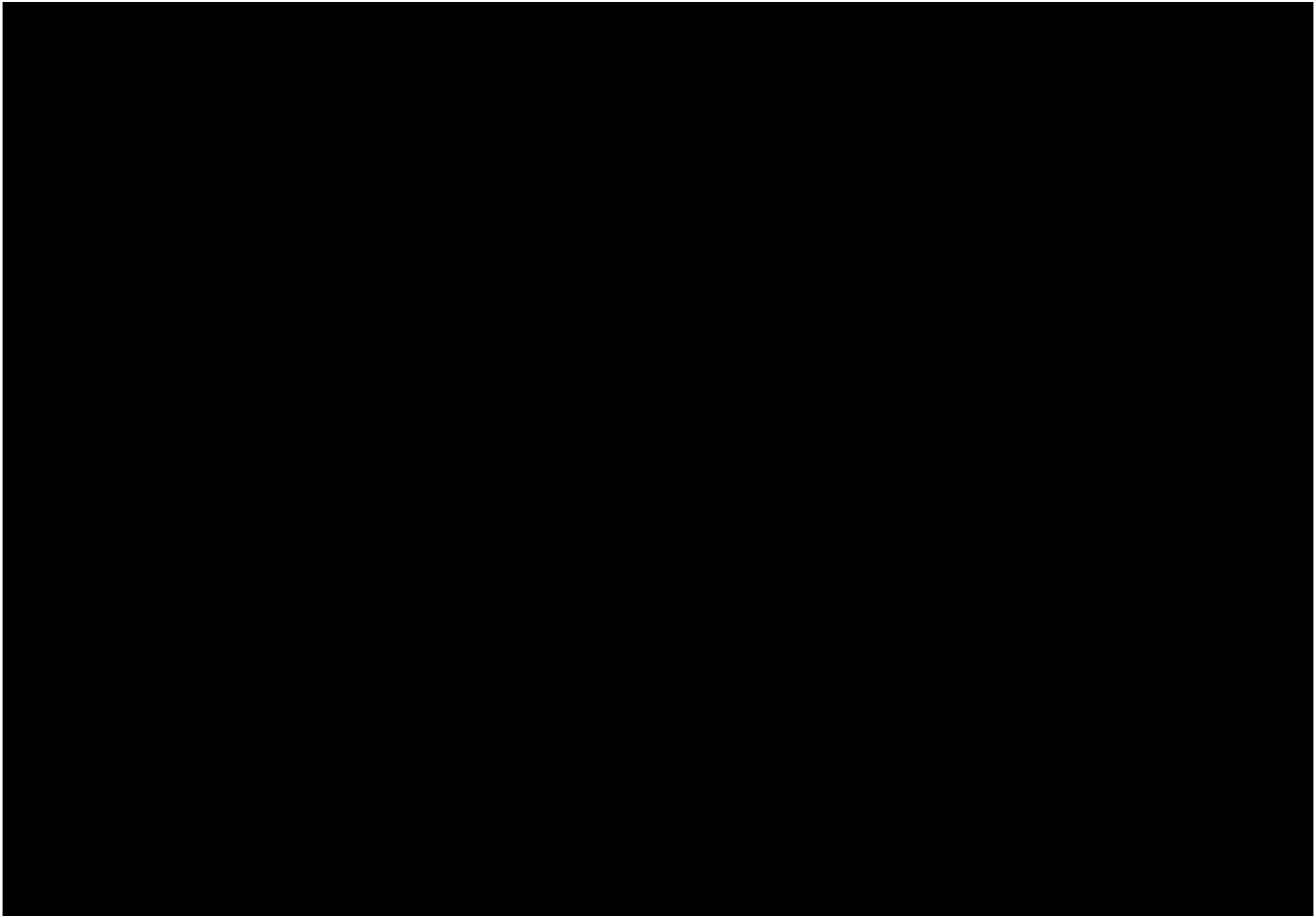
Reference Number	Description
TOR0000001023	Canada BU Perf_May_2018.xlsx
TOR0000001024	Canada BU Perf_November_2018.xlsx
TOR0000001025	Canada BU Perf_October_2018.xlsx
TOR0000001026	Canada BU Perf_September_2018.xlsx
TOR0000001027	Canada BU Perf_April_2019.xlsx
TOR0000001028	Canada BU Perf_August_2019.xlsx
TOR0000001030	Canada BU Perf_February_2019.xlsx
TOR0000001031	Canada BU Perf_January_2019.xlsx
TOR0000001032	Canada BU Perf_July_2019.xlsx
TOR0000001033	Canada BU Perf_June_2019.xlsx
TOR0000001034	Canada BU Perf_March_2019.xlsx
TOR0000001035	Canada BU Perf_May_2019.xlsx
TOR0000001038	Canada BU Perf_September_2019.xlsx
TOR0000001039	Horizon Canada PROCSYBI Revenue & Innomar Script Data.xlsx
TOR0000001046.0002	Valuation of Identifiable Subject Assets and Liabilities in Connection with the Acquisition of Raptor Pharmaceuticals Corp.
TOR0000001046.0007	Valuation of Certain Subject Asset and Liability of Raptor CV
TOR0000001046	Final Q1 2018 Impairment analysis memo MWM Comments 05031802_29245520_1.DOCX
TOR0000001047	1. Horizon Orphan_University of California San Diego (UCSD) - Amended an_29245321_1.PDF
TOR0000001050	4. FE Amendment No 1 to AmRstd License Horizon UCSD_29245324_1.PDF
TOR0000001057	Copy of Copy of HNZP -- Proposed Redactions.xlsx
TOR0000001069	COSA Final Innomar Signed.pdf
TOR0000001071	SOW-Innomar.pdf
TOR0000001073	WDA Final Innomar Signed.pdf
TOR0000001080	Canada PROCYSBI S&M Opex Detail_08.07.19.XLSX
TOR0000001081	Innomar Invoice Listing.XLSX
TOR0000001105	2019+PVA+Innomar-HZNP+V3.0 (1).pdf
TOR0000001108	Copy_of_Horizon-Innomar_PVA_V20.pdf
TOR0000001114	Innomar+-++Quality+Agreement+-+Canada+(18+MAR+2016).pdf
TOR0000001117	Innomar+Strategies+inc++-+Commercial+Outsourcing+Services+Agreement+-+MSA+(13MAY2016).pdf
TOR0000001124	Innomar_HPIL_First+Amendment_COSA_12.16.2016_signed.pdf
TOR0000001127	IPA+Final+Innomar+Signed (1).pdf
TOR0000001129	Second+Amendment+to+COSA+Innomar+HPIL+HZNP+5+OCT+2017.pdf
TOR0000001130	Total Company SG&A (GAAP and Non-GAAP).XLSX
TOR0000001134	Cambrex Profarmaco Milano - HPIL Amendment No 2 17 January 2017.pdf
TOR0000001135	Cambrex Quality Agreement executed.pdf
TOR0000001137	Expense Line Item Detail C6_ C7_C8_C9_C14.xlsx
TOR0000001138	NucroTechnics Inc - MSA Master Services Agreement (01APR2015).pdf
TOR0000001140	PROCYSBI Canada Product Flow_post DEL.pdf
TOR0000001141	2018 PROCYSBI CA std cost calculation_02.24.20.xlsx
TOR0000001142	2019 PROCYSBI CA std cost calculation_02.24.2020.xlsx

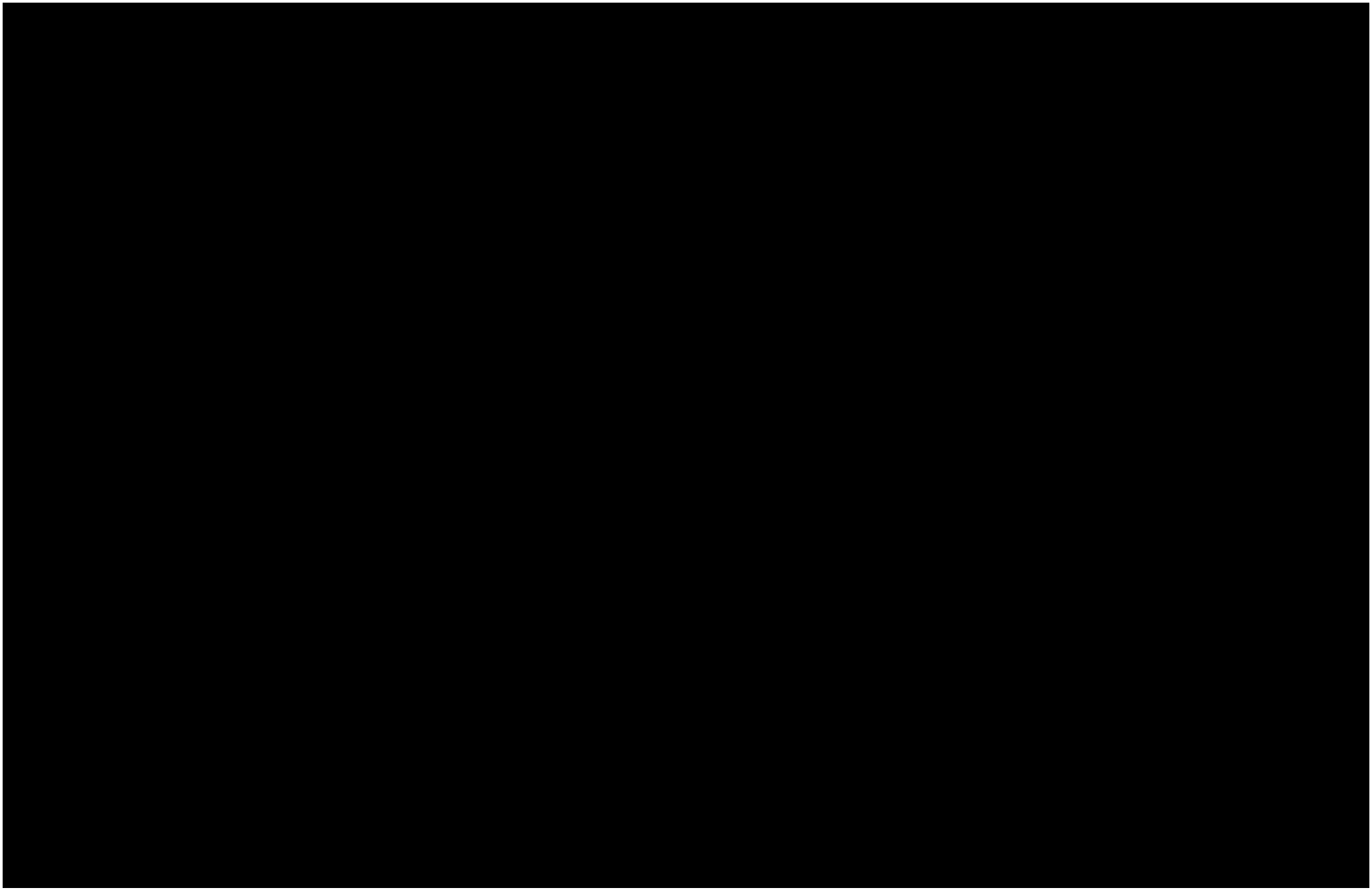
Reference Number	Description
TOR0000001142.0001	Procysbi (RP103) - 2018 Annual Pricing Proposal for Horizon Orphan LLC - C-CRC-18464-R9
TOR0000001143	2020 PROCYSBI CA std cost calculation_02.24.2020.xlsx
TOR0000001143.0001	Letter from Thermo Fisher Scientific to Horizon Pharma re Master Manufacturing Services Agreement - November 15, 2010 - Price Adjustment dated January 30, 2019.
TOR0000001145	Canada PO and Invoices 02.24.2020.xlsx
TOR0000001145.0001	Patheon Invoice 97018755
TOR0000001145.0002	Patheon Invoice 90706622
TOR0000001145.0003	Patheon Invoice 97020801
TOR0000001145.0004	Patheon Invoice 90707114
TOR0000001145.0005	Patheon Invoice 90707812
TOR0000001145.0006	Patheon Invoice 97021929
TOR0000001145.0007	Cambrex Invoice 1000000953
TOR0000001145.0008	Cambrex Invoice 1000000835
TOR0000001145.0009	Cambrex Invoice 1000000711
TOR0000001145.0010	Cambrex Invoice 37/0126
TOR0000001146	PROCYSBI Canada Pre DEL product flow.pdf
TOR0000001148	Cambrex API SUPPLY AGREEMENT 2010-11-3.pdf
TOR0000001150	Cambrex API Supply Agreement Amendment Executed (09APR2013).PDF
TOR0000001152	Patheon - MSA Amendment - Schedule B revisions (05APR2012) OCR (2).pdf
TOR0000001153	Patheon - MSA Amendment 2 - Schedule B Revision and BV Addition (21JUL2013) OCR (2).pdf
TOR0000001154	Patheon - MSA Manufacturing Services Agreement (15NOV2010) OCR (2) (6).pdf
TOR0000001155	Horizon_Innomar_Q&C_ECQTA_02Aug2019.pdf
TOR0000001168	FY19 HZNP Canada Report FINAL_20200706.pdf
TOR0000001170	HZNP Canada Sup_30281929_1.pdf
TOR0000001171	Intercompany se_30281927_1.pdf
TOR0000001172	FYE 2017 Horizon Pharma Inc. TP Report FINAL 10082018.pdf
TOR0000001173	FYE 2018 Horizon US-OECD TP Report FINAL 10082019.pdf
TOR0000001174	91000356 assignment 61-319.pdf
TOR0000001175	91000399 assignment 61-364.pdf
TOR0000001176	91000402 assignment 61-367.pdf
TOR0000001177	91000425 assignment 61-389.pdf
TOR0000001178	91000457 assignment 61-418.pdf
TOR0000001179	InterCo. PO - 61xxx319 - 75MG.pdf
TOR0000001180	InterCo. PO - 61xxx364 - 75MG.pdf
TOR0000001181	InterCo. PO - 61xxx367 - 25MG.pdf
TOR0000001182	InterCo. PO - 61xxx389 - 75MG.pdf
TOR0000001183	InterCo. PO - 61xxx418 - 75MG.pdf
TOR0000001184	PO - 42xxx479 - 75-25MG Split.pdf
TOR0000001185	PO - 42xxx482 - 75MG.pdf
TOR0000001186	PO - 42xxx484 - 75MG.pdf

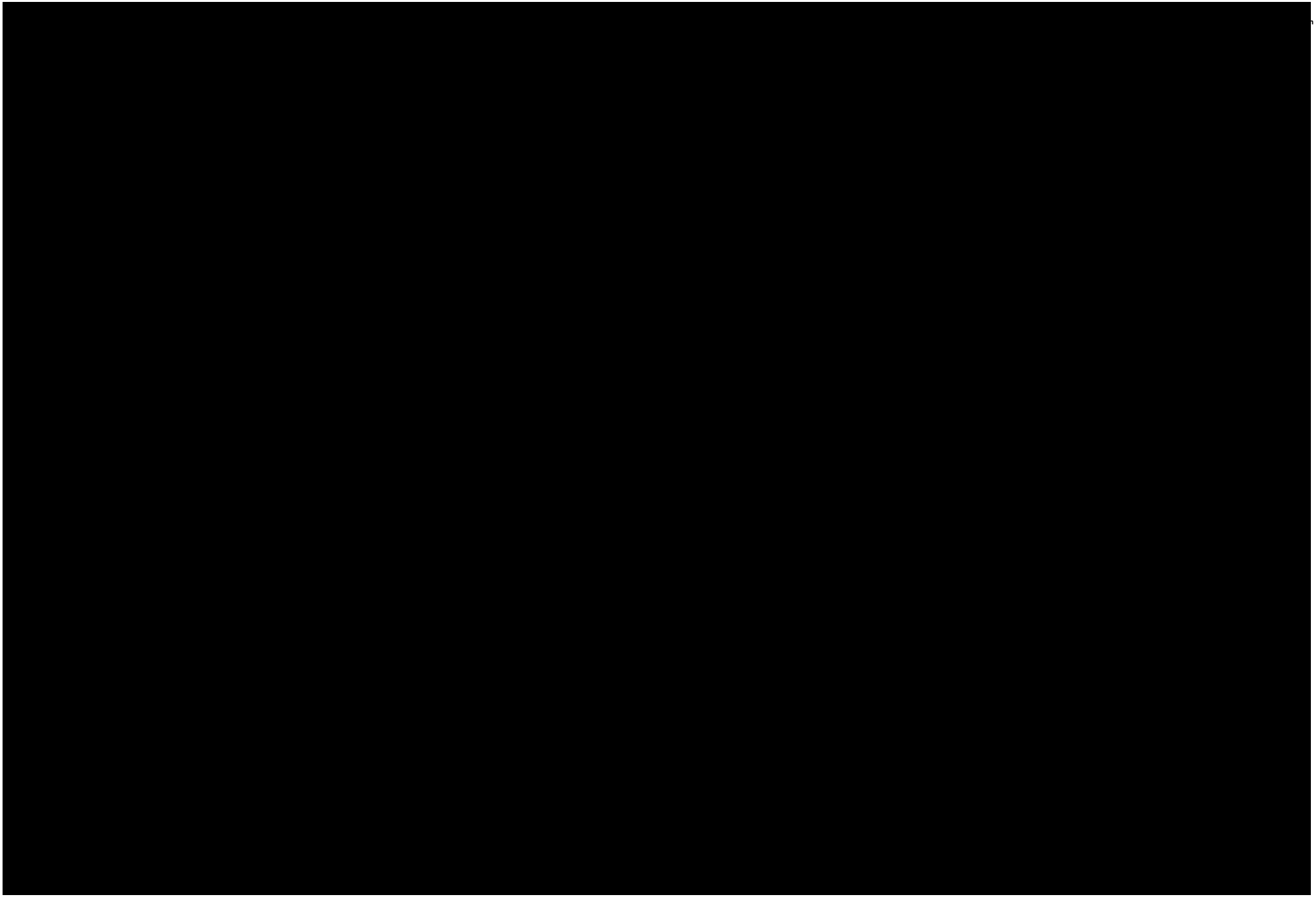


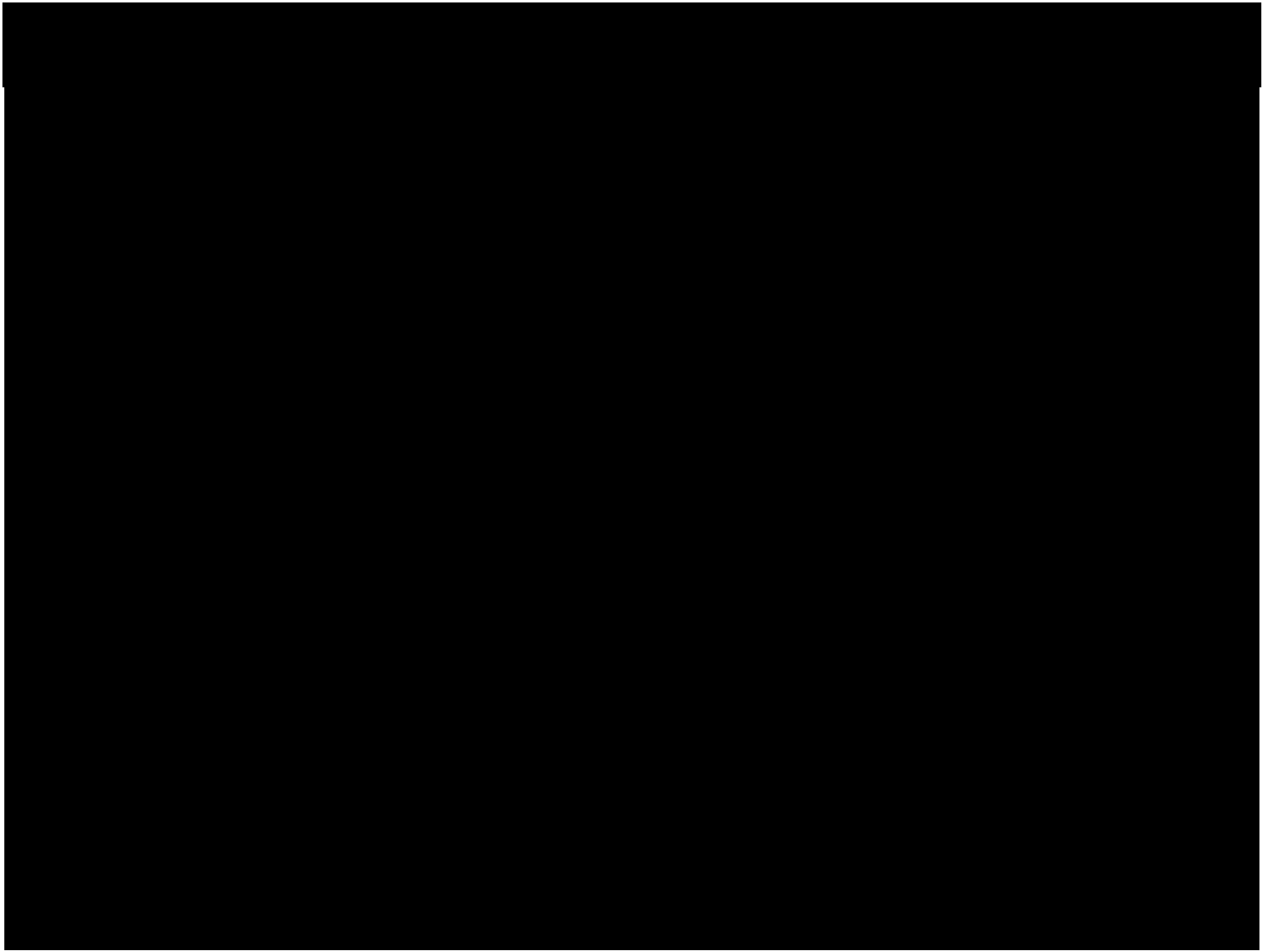


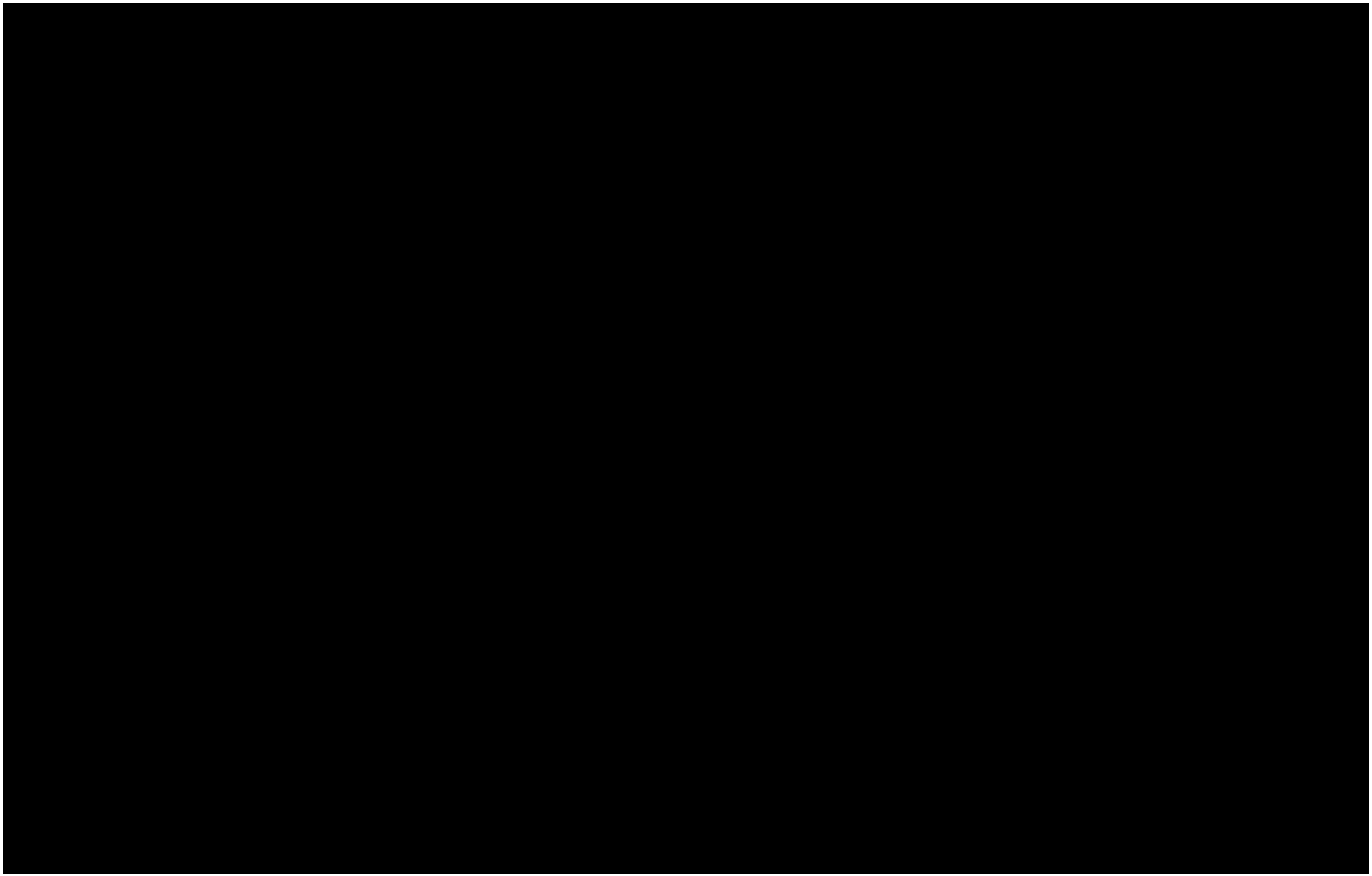


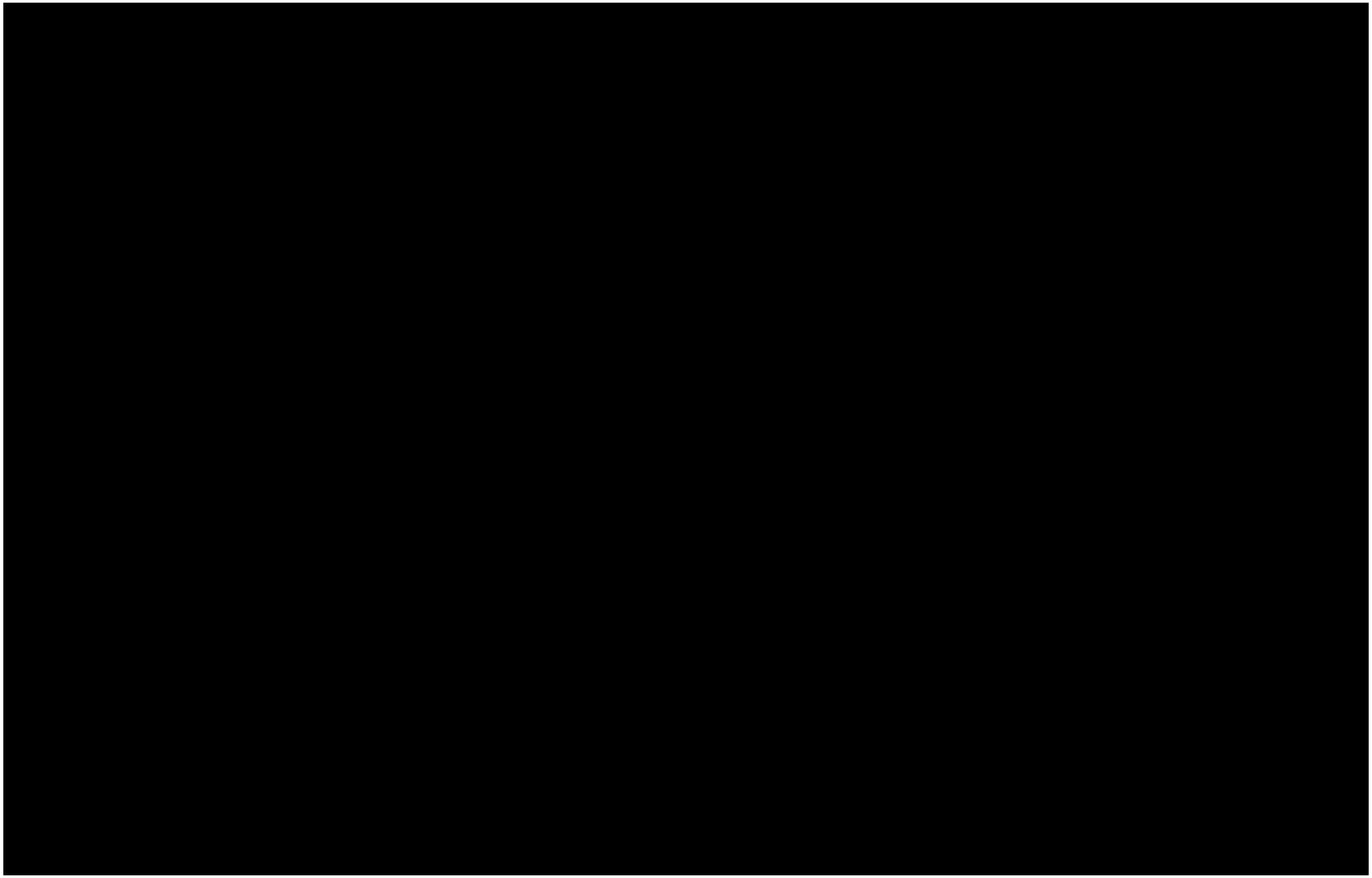


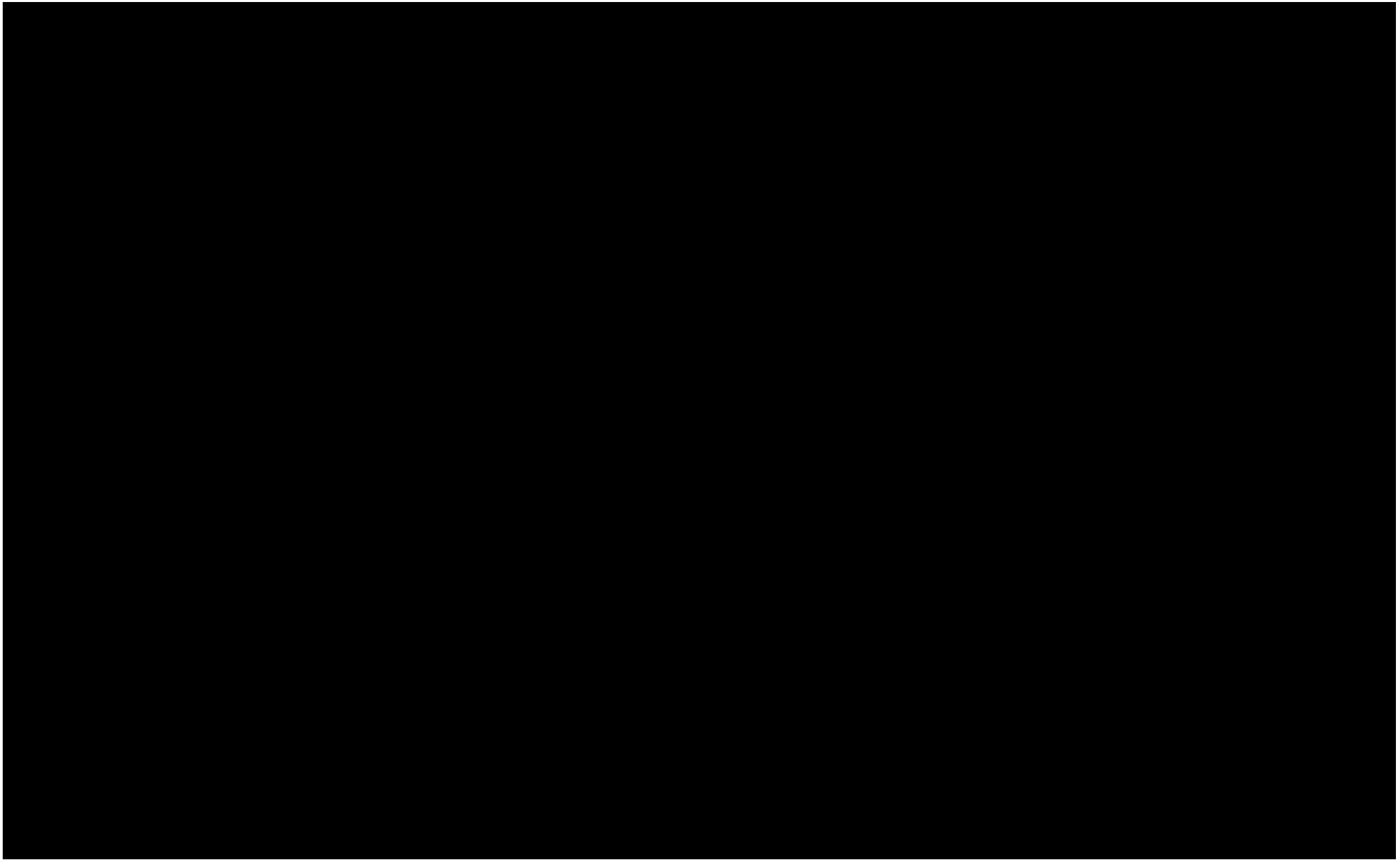












Mandate and Jurisdiction

The Patented Medicine Prices Review Board (PMPRB) is an independent quasi-judicial body established by Parliament in 1987 under the *Patent Act* (Act). The Minister of Health is responsible for the pharmaceutical provisions of the Act, as set out in sections 79 to 103.

The PMPRB (Patented Medicine Prices Review Board) protects the interests of Canadian consumers by ensuring that the prices of patented medicines sold in Canada are not excessive. It does this by reviewing the prices that patentees charge for each individual patented drug product in Canadian markets. If a price is found to be excessive, the Board can hold public hearings and order price reductions and/or the offset of excess revenues. The PMPRB (Patented Medicine Prices Review Board) regulates the "factory gate" prices and does not have jurisdiction over prices charged by wholesalers or pharmacies, or over pharmacists' professional fees.

The PMPRB (Patented Medicine Prices Review Board) is also responsible for reporting on trends in pharmaceutical sales and pricing for all medicines and for reporting research and development spending by patentees.

Although the PMPRB (Patented Medicine Prices Review Board) is part of the Health Portfolio (http://www.hc-sc.gc.ca/ahc-asc/minist/portfolio/index-eng.php), it carries out its mandate at arms-length from the Minister of Health. It also operates independently of other bodies such as Health Canada, which approves drugs for safety and efficacy, and public drug plans, which approve the listing of drugs on their respective formularies for reimbursement purposes.

Raison d’être

The PMPRB (Patented Medicine Prices Review Board) protects and informs Canadians by ensuring that the prices of patented medicines sold in Canada are not excessive and by reporting on pharmaceutical trends.

Mandate

The PMPRB (Patented Medicine Prices Review Board) has a dual role:

Regulatory – To ensure that prices charged by patentees for patented medicines sold in Canada are not excessive;

Reporting – To report on pharmaceutical trends of all medicines and on R&D spending by pharmaceutical patentees.

Jurisdiction

Regulatory – The PMPRB (Patented Medicine Prices Review Board) is responsible for regulating the prices that patentees charge, the factory-gate price, for prescription and non-prescription patented drugs sold in Canada, to wholesalers, hospitals or pharmacies, for human and veterinary use to ensure that they are not excessive. The PMPRB (Patented Medicine Prices Review Board) regulates the price of each patented drug product, including each strength of each dosage form of each patented medicine sold in Canada. This is normally the level at which Health Canada assigns a Drug Identification Number (DIN).

In Canada, Health Canada assesses new medicines to ensure that they conform with the Food and Drugs Act and Regulations. Formal authorization to market or distribute a medicine is granted through a Notice of Compliance (NOC). A medicine may be temporarily distributed with specified restrictions before receiving a NOC, as an Investigational New Drug or under the Special Access Programme.

The PMPRB (Patented Medicine Prices Review Board) has no authority to regulate the prices of non-patented drugs, including generic drugs sold under compulsory licenses, and does not have jurisdiction over prices charged by wholesalers or retailers nor over pharmacists' professional fees. Also, matters such as distribution and prescribing are outside the purview of the PMPRB (Patented Medicine Prices Review Board).

Under the Patented Medicines Regulations, patentees are required to file price and sales information twice a year for each strength of each dosage form of each patented medicine sold in Canada for price regulation purposes. Patentees are also required to file R&D expenditures once a year for reporting purposes.

Patentees are also required to inform the PMPRB (Patented Medicine Prices Review Board) of their intention to sell a patented medicine but are not required to obtain approval of the price before they do so.

Patentees are required to comply with the Patent Act to ensure that prices of patented medicines sold in Canada are not excessive. In the event that the Board finds, after a public hearing, that a price is excessive in any market it may order the patentee to reduce the price and take measures to offset any excess revenues it may have received.

Reporting – The PMPRB (Patented Medicine Prices Review Board) reports annually to Parliament through the Minister of Health. The Annual Report, which covers each calendar year, includes a review of the PMPRB (Patented Medicine Prices Review Board)'s major activities, analyses of the prices of patented medicines and of the price trends of all drugs, and reports on the R&D expenditures as reported by patent-holding drug manufacturers. In addition, the PMPRB (Patented Medicine Prices Review Board) reports through its quarterly NEWSletter and various studies.

Pursuant to an agreement by the Federal/Provincial/Territorial Ministers of Health and at the request of the federal Minister of Health, the PMPRB (Patented Medicine Prices Review Board) reports on its research studies conducted under the National Prescription Drug Utilization Information System (NPDUIS) on the utilization and management of pharmaceutical products in Canada.

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2018-04-18

HOUSE OF COMMONS
CHAMBRE DES COMMUNES
CANADA

CANADIANS AFFECTED BY RARE DISEASES AND DISORDERS: IMPROVING ACCESS TO TREATMENT

Report of the Standing Committee on Health

Bill Casey, Chair

FEBRUARY 2019
42nd PARLIAMENT, 1st SESSION

CANADIANS AFFECTED BY RARE DISEASES AND DISORDERS: IMPROVING ACCESS TO TREATMENT

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Bill Casey
Chair

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NOTICE TO READER

Reports from committee presented to the House of Commons

Presenting a report to the House is the way a committee makes public its findings and recommendations on a particular topic. Substantive reports on a subject-matter study usually contain a synopsis of the testimony heard, the recommendations made by the committee, as well as the reasons for those recommendations.

Ms. Erin Little, President of Liv-A-Little Foundation, appeared before the House of Commons Standing Committee on Health on 30 November 2018, advocating for better access to treatment for her daughter Olivia (on the left of photo). Olivia has cystinosis, a rare incurable metabolic disease.

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THE STANDING COMMITTEE ON HEALTH

has the honour to present its

TWENTY-SECOND REPORT

Pursuant to its mandate under Standing Order 108(2), the Committee has studied Barriers to Access to Treatment and Drugs for Canadians Affected by Rare Diseases and Disorders and has agreed to report the following:

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SUMMARY

According to Health Canada, rare diseases are life-threatening, debilitating or serious and chronic conditions that affect a small number of individuals. Approximately one million Canadians are affected by rare diseases. These diseases often appear at birth or emerge in early childhood. One-third of children with rare diseases die before their fifth birthday. For 94% of these conditions, there is no treatment available.

On 18 April 2018, the House of Commons Standing Committee on Health ("the Committee") agreed to conduct a study on the barriers that Canadians with rare diseases face in accessing treatments, and examine how the federal government, in partnership with the provinces and territories, could help remove these barriers.

The Committee held five meetings and heard from 24 witnesses, including government officials, physicians, researchers, industry representatives and patient groups, and received 10 written submissions. These witnesses outlined key challenges Canadians face in accessing treatment for rare diseases in the following areas: regulatory approval of drugs for rare diseases for sale; pricing; reimbursement for drug costs through provincial and territorial drug coverage plans; and access to diagnostics for these diseases.

Witnesses told the Committee that there is a lack of coordination between federal regulatory approval processes for the sale of drugs for rare diseases and provincial and territorial processes that make reimbursement decisions about these drugs. This lack of coordination leads to delays in treatment for patients. Health Canada also needs to do a better job of communicating its regulatory decisions to physicians and patients.

The biggest barrier limiting patients' access to these drugs is their affordability. Drugs for rare diseases can cost between $0.5 million to $4.9 million per person per year.

With more and more of these drugs coming to market, governments may not be able to cover the costs of the drugs without sacrificing other health care priorities. Governments also face difficulties justifying spending funds on the reimbursement of these drugs when there is limited evidence showing that they offer significant health benefits. At the same time, drug manufacturers must continue to have incentives to invest in the development of treatments in this area and to seek market authorization for the sale of these drugs in Canada.

The Committee agrees with witnesses that it is time to change Canada's approach towards drugs for rare diseases. The Committee makes 19 recommendations in this report that focus on:

- establishing coordinated processes for the approval and reimbursement of drugs for rare diseases in Canada;
- implementing the proposed amendments to the *Patented Medicines Regulations* that will lead to lower drug prices;
- short- and long-term options for covering the costs of drugs for rare diseases; and
- supporting research that examines the real-world benefits and risks of drugs for rare diseases.

LIST OF RECOMMENDATIONS

As a result of their deliberations committees may make recommendations which they include in their reports for the consideration of the House of Commons or the Government. Recommendations related to this study are listed below.

Health Canada's Market Authorization of Drugs for Rare Diseases

Recommendation 1

That the Government of Canada, in collaboration with the provinces and territories, develop a coordinated process for the market authorization and reimbursement of drugs for rare diseases. 33

Recommendation 2

That the Government of Canada work to ensure greater transparency and information sharing throughout the life cycle of drugs for rare diseases to ensure timely access for key decision-makers, including health care providers, health technology assessors and patients. 33

Recommendation 3

That the Government of Canada in collaboration with the provinces and territories develop a national, independent, expert review panel to provide recommendations and guidance on the regulatory review, pricing and reimbursement of drugs for rare diseases in Canada, including instructions on how to streamline these processes; and report publicly on its findings. 33

Recommendation 4

That Health Canada and the Canadian Agency for Drugs and Technologies in Health undertake their respective scientific evidence review processes of drugs for rare diseases in tandem as a standard practice. 33

Recommendation 5

That Health Canada, in collaboration with the Canadian Agency for Drugs and Technologies in Health, provide guidance and advice to drug manufacturers in the design of clinical trials to ensure that they meet the requirements of both market authorization and reimbursement processes in Canada. 33

CANADIANS AFFECTED BY RARE DISEASES AND DISORDERS: IMPROVING ACCESS TO TREATMENT

INTRODUCTION

On 18 April 2018, the House of Commons Standing Committee on Health ("the Committee") adopted the following motion:

> That, pursuant to Standing Order 108(2), the Committee undertake a study on the barriers to access to treatment and drugs for Canadians affected by rare diseases and disorders, including the Special Access Program, in order to develop recommendations on actions that the federal government can take, in partnership with the provinces and territories, to remove these barriers; that the Committee report its findings and recommendations to the House.[1]

As part of its study, the Committee held five meetings and heard from 24 witnesses, including government officials, physicians, researchers, pharmaceutical industry representatives and patient groups, and received 10 written submissions. Drawing on this testimony, the report begins with an overview of rare diseases in Canada and then examines the key challenges Canadians face in accessing treatment for these conditions in the following areas: regulatory approval of drugs for rare diseases; drug pricing; drug cost reimbursement through provincial and territorial drug coverage plans; and access to diagnostics. It concludes with the Committee's observations and recommendations on how the federal government can address these challenges in collaboration with the provinces and territories.

OVERVIEW OF RARE DISEASES IN CANADA

In her appearance before the Committee, Ms. Catherine Parker (Director General, Biologics and Genetic Therapies Directorate, Health Products and Food Branch, Health Canada) explained that "rare diseases are life-threatening, debilitating or serious and chronic conditions affecting a small number of patients."[2] Ms. Parker explained that

1 House of Commons Standing Committee on Health (HESA), *Minutes of Proceedings*, 1st Session, 42nd Parliament, 18 April 2018.

2 HESA, *Evidence*, 27 September 2018, 0900 (Ms. Catherine Parker, Director General, Biologics and Genetic Therapies Directorate, Health Products and Food Branch, Department of Health).

there is no international standard definition of a rare disease. Definitions that do exist focus on determining whether the disease is rare based upon its prevalence, the proportion of a population that has the disease, or its incidence, which refers to the number of new cases of the disease that are diagnosed per year.[3] According to Ms. Parker, Health Canada has adopted a definition of a rare disease being one that affects fewer than 5 in 10,000 Canadians, which is similar to the definition adopted by the European Union. She also explained that within this definition, there are also conditions that are considered "ultra-rare," which may affect fewer than 10 Canadians overall. In his appearance before the Committee, Dr. Joel Lexchin (professor emeritus, School of Health Policy and Management, York University) further noted that any definition of a rare disease should take into consideration not just the frequency or rarity of the disease, but also its severity or the extent to which it is debilitating.[4]

The Committee learned that approximately 80% of rare diseases are genetically based, which means that they are caused by changes or mutations in one or a few of the 20,000 genes that make up the human genome.[5] These conditions often appear at birth or in early childhood.[6] Dr. Alex MacKenzie (Clinician Scientist, Children's Hospital of Eastern Ontario) explained that estimates suggest that there are approximately 7,000 rare diseases that have been identified to date and for approximately 94% of these diseases, no therapy or treatment is available.[7]

In terms of the impact of rare diseases on the Canadian population, witnesses provided the Committee with various figures. According to the Canadian Organization for Rare Disorders (CORD), 3 million or 1 in 12 Canadians live with a rare disease.[8] However, other witnesses including Dr. Mackenzie, Dr. Lexchin and Dr. Doug Coyle, professor, School of Epidemiology, Public Health and Preventative Medicine, University of Ottawa, suggested that this number is an over-estimation of the prevalence of rare diseases in Canada.[9]

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3 Ibid.

4 HESA, *Evidence*, 25 October 2018, 0835 (Dr. Joel Lexchin, professor emeritus, School of Health Policy and Management, York University, as an Individual).

5 Ibid., 0830 (Dr. Michael Brudno, professor and Scientific Director for Computational Medicine, Hospital for Sick Children).

6 HESA, *Evidence*, 27 September 2018, 0900 (Parker).

7 HESA, *Evidence*, 25 October 2018, 0835 (Dr. Alex MacKenzie, Clinician Scientist, Children's Hospital of Eastern Ontario (CHEO)).

8 HESA, *Evidence*, 27 September 2018, 0945 (Dr. Durhane Wong-Rieger, President and Chief Executive Officer, Canadian Organization for Rare Disorders).

9 HESA, *Evidence*, 25 October 2018, 0835 (Lexchin, Mackenzie) and HESA, *Evidence*, 4 October 2018, 1005 (Dr. Doug Coyle, professor, School of Epidemiology, Public Health and Preventative Medicine, University of Ottawa, as an Individual).

Dr. Mackenzie explained that evidence suggests that approximately one million Canadians or 2% to 3% of the population are affected by rare diseases.[10]

Dr. Mackenzie further articulated that children are disproportionately affected by rare diseases.[11] Approximately, 50% of Canadians with rare diseases are children. In addition, children with rare diseases make up one third of hospital pædiatric patients. One third of deaths in the first year of life are caused by rare diseases and one third of children with rare diseases will die before their fifth birthday. Consequently, rare diseases have a disproportionate impact in terms of years of lives lost[12] in the general population in comparison to other diseases in Canada:

> Perhaps the most telling statistic is that when you look at the proportion of general years of life lost for rare diseases, it's around 4.6%. That's years of life lost in Canadian society. For infectious diseases, the number is around 1.4% or 1.6%. For diabetes, it's only 2.6%. It's really dramatic. I think the reason for this is that it takes life early on, so that carries a disproportionate impact.[13]

Finally, Dr. Mackenzie explained that approximately 50% of Canadians with a rare disease do not have a diagnosis for their condition.[14]

BARRIERS IN ACCESSING TREATMENT FOR RARE DISEASES IN CANADA: WHAT THE COMMITTEE HEARD

Witnesses appearing before the Committee identified four main areas where there are barriers to accessing treatments for rare diseases: market authorization; pricing of drugs for rare diseases; reimbursement of costs for drugs for rare diseases through provincial and territorial drug coverage plans; and access to diagnostic tests for rare diseases. An overview of key challenges in these areas and possible ways that the federal government could help address these issues is provided in the sections below.

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10 Ibid., 0835 (MacKenzie).

11 Ibid.

12 Years of lives lost (YLL) measures the number of years of life lost to a cause as a proportion of the total YLL lost in the population due to premature mortality. YLL is calculated by multiplying the number of deaths by a standard life expectancy at the age at which death occurs. By taking into account the age at which death occurs, this indicator give greater weight to diseases that result in loss of life at an early age. WHO, Years of lives lost (percentage of total).

13 Ibid.

14 Ibid.

Market Authorization of Drugs for Rare Diseases

Health Canada is authorized under the *Food and Drugs Act*[15] and Part C, Division 8 of the *Food and Drug Regulations*[16] to regulate the safety, efficacy and quality of drugs, including drugs for rare diseases in Canada. Ms. Catherine Parker (Health Canada) explained to the Committee that this regulation involves overseeing the testing of new drugs in Canada through clinical trials.[17] In addition, the Department is responsible for issuing market authorizations for the sale of a new drug, once it has undertaken an assessment of both the benefits and risks of the drug to determine its quality, safety and efficacy. Finally, the Department is also responsible for monitoring the safety of these drugs once they are on the market, which is referred to as post-market surveillance. Within the context of rare diseases, Ms. Parker explained to the Committee that there are three main regulatory avenues that support Canadians' access to drugs for rare diseases: accelerated or priority status drug approval; the Special Access Programme and clinical trials.[18]

Priority Status Drug Approval for Drugs for Rare Diseases

Ms. Parker (Health Canada) explained that the Department accelerates the approval of drugs that are intended to treat serious or life-threatening diseases, including rare diseases.[19] The Department gives them priority status or conditional approval so that patients have earlier access to them. The Committee heard that 30% to 40% of all new drugs now approved in Canada are drugs to treat rare diseases.[20] In 2017, 16 of the 36 brand name drugs approved by Health Canada are classified as orphan drugs (or drugs for rare diseases) in Europe or the United States.[21] She explained that most of these drugs were reviewed and approved using accelerated pathways. She also explained that the Department has harmonized its regulatory requirements for drug approval with those in other jurisdictions so that drug companies can file one dossier to all regulators. Health Canada and the U.S. Food and Drug Administration (FDA) now have a common portal allowing companies to file for drug approval simultaneously in both

15 *Food and Drugs Act*, R.S.C., 1985, c. F-27.

16 *Food and Drug Regulations*, C.R.C., c. 870.

17 HESA, *Evidence*, 27 September 2018, 0900 (Parker).

18 Ibid.

19 Ibid.

20 Ibid.

21 Ibid.

jurisdictions.[22] As a result, recent research from the Patented Medicine Prices Review Board indicates that 9 of the 10 top-selling orphan drugs in the United States are available for sale in Canada.[23] However, Ms. Parker also noted that the Department recognized the need to do more and is undertaking a review of its regulatory approval of prescription drugs, including drugs for rare diseases, to identify ways to improve its efficiency and meet patient and health care system needs.[24]

Though some witnesses[25] appearing before the Committee were generally supportive of Health Canada's accelerated approach towards the approval of drugs for rare diseases, they also identified ways in which the Department could improve its regulatory approval process for these drugs. Dr. Craig Campbell (Pædiatric Nephrologist, Children's Hospital, London Health Sciences Centre) articulated that regulatory agencies need to undertake a more comprehensive and flexible review of scientific evidence in their approval process for drugs for rare diseases.[26] He explained that Canadian regulatory agencies do not take into consideration all the different types of data available to evaluate the efficacy of drugs for rare diseases, such as quality-of-life data, impact on daily living, cost-analysis and meta-analysis data:

> In almost every single interaction I've had with Canadian regulatory agencies that I've been a participant in, regulatory personnel have claimed that reviews for rare disease drug files can and will be done with more flexibility and be more considerate of the context and totality of the data. Further, they often claim that the existing approval processes and evidence review pathways are adaptable to rare disease drugs. However, when the final decisions are made, this rarely seems to be the case.[27]

The Committee heard that a flexible and broader approach to the review of scientific evidence for drugs for rare diseases is necessary because of the challenges associated with conducting standard clinical trials for treatments for patients with rare diseases, including the limited number of individuals who can participate in trials because of the rarity of conditions; the absence of control groups; and limited knowledge about rare

22 Ibid., 0940.

23 Ibid., 0905.

24 Ibid.

25 Please see for example, HESA, *Evidence*, 27 September 2018, 0945 (Wong-Rieger) and HESA, *Evidence*, 4 October 2018, 0905 (Mr. Andrew McFadyen, Executive Director, the Isaac Foundation).

26 HESA, *Evidence*, 4 October 2018, 0915 (Dr. Craig Campbell, Pædiatric Nephrologist, Children's Hospital, London Health Sciences Centre).

27 Ibid.

diseases themselves.[28] To address this issue, Dr. Campbell recommended that Canadian regulatory bodies adopt the Canadian GRADE guidelines, which grade the quality and strength of scientific evidence and treatment recommendations.[29] He further recommended the establishment of an independent rare disease review committee that would, "help inform any regulatory agency at any level when they're confronted with a rare disease drug review."[30]

Given the challenges associated with the research and development (R&D) of drugs for rare diseases, other witnesses, such as representatives of the Canadian Organization for Rare Disorders (CORD), Janssen Pharmaceutical Companies, Horizon Therapeutics Canada and the Canadian Forum for Rare Disease Innovators (RAREi), recommended that Health Canada develop a specific regulatory pathway for these drugs, which has been done in other jurisdictions, such as the United States and European Union.[31] A specific regulatory framework for rare disease treatments could include incentives to develop and commercialize drugs for rare diseases in Canada, an orphan drug designation process,

> **"[T]hey often claim that the existing approval processes and evidence review pathways are adaptable to rare disease drugs. However, when the final decisions are made, this rarely seems to be the case."**
>
> *Dr. Craig Campbell,*
> *Pædiatric Nephrologist, Children's Hospital,*
> *London Health Sciences Centre*

28 HESA, *Evidence*, 27 September 2018, 0915 (Dr. John Patrick Stewart, Director General, Therapeutic Products Directorate, Department of Health) and The Canadian Forum for Rare Disease Innovators (RAREi), "Unique approach needed: Addressing barriers to accessing rare disease treatments," written submission to HESA, 20 November 2018.

29 HESA, *Evidence*, 4 October 2018, 0915 (Campbell).

30 Ibid., 0920.

31 HESA, *Evidence*, 27 September 2018, 0945 (Wong-Rieger); (RAREi), "Unique approach needed: Addressing barriers to accessing rare disease treatments," written submission to HESA, 20 November 2018; Horizon Therapeutics Canada, "Barriers to Access Treatment and Drugs for Canadians Affected by Rare Diseases and Disorders," written submission, October 2018; Janssen Pharmaceutical Companies, "Janssen submission to the House of Commons Standing Committee on Health's consultations on barriers to access to treatment and drugs for Canadians affected by rare diseases and disorders," written submission, 25 October 2018.

additional market exclusivity, research promotion funds, tax incentives and regulatory submission fee reductions.[32]

However, in his appearance before the Committee, Dr. Joel Lexchin explained that if a specific regulatory pathway for drugs for rare diseases were developed by Health Canada, it would not need to include monetary or tax incentives for the development of drugs for rare diseases, as they currently represent 37% of drugs being approved in the United States.[33] Instead, investments in research should be made for these diseases. Further, he suggested that orphan drug designations should be limited to truly unique drugs that treat only one disease rather than drugs that can be used more broadly to treat disease subsets or other diseases with similar genetic underpinnings. In addition, Health Canada should demand a high degree of rigour in clinical trials for drugs for rare diseases despite the small patient populations involved. The Department should also require post-market clinical trials for these drugs, where the evidence of their clinical benefits is not clear.[34] As noted above, Dr. Lexchin also recommended that the definition of a rare disease adopted by Health Canada include a reference to both the disease's frequency and severity.

Special Access Programme

The Committee heard from Health Canada officials that the Special Access Programme (SAP) is another important avenue that provides patients with access to drugs for rare diseases.[35] According to Ms. Parker, Health Canada's SAP provides access to unapproved medications on an exceptional case-by-case basis for patients with serious or life-threatening conditions when conventional treatments have failed, are unsuitable or unavailable.[36] To obtain access to drugs through this program, Dr. John Patrick Stewart (Director General, Therapeutic Products Directorate, Health Canada) explained that a physician must make a request to the program and "explain why this therapy is the best choice for the particular patient in front of them, why it's a serious and life-threatening condition, why other therapies, if they exist have been considered and are not suitable, and evidence that supports its use."[37] He further noted that because these requests are

32 RAREi, "Unique approach needed: Addressing barriers to accessing rare disease treatments," written submission to HESA, 20 November 2018.

33 HESA, *Evidence*, 25 October 2018, 0840 (Lexchin).

34 Ibid.

35 HESA, *Evidence*, 27 September 2018, 0900 (Parker).

36 Ibid.

37 HESA, *Evidence*, 30 October 2018, 1025 (Stewart).

made only under exceptional circumstances and the drugs themselves do not go through the regular scrutiny of evidence regarding the quality, safety and efficacy of their use, they are not authorized for long periods of time, typically between three to six months. The Committee heard that approximately 30% of the drugs requested through this program are drugs for rare diseases.[38]

Witnesses appearing before the Committee saw the SAP as an important avenue for obtaining access to treatments for rare diseases.[39] However, they outlined several challenges associated with the administration of this program, which were illustrated by the problems experienced by physicians and patients who sought access to a drug to treat cystinosis in 2017. The Committee learned that cystinosis is a rare incurable, metabolic disease which effects between 75 and 100 Canadian children and young adults.[40] Without treatment, the disease results in end-stage renal failure by the time a patient reaches the average age of nine years old.[41] According to Dr. Julian Midgley, a pædiatric nephrologist, the primary treatment for cystinosis is a drug called Cystagon, which was approved by the U.S. FDA in 1994.[42] The manufacturer has never sought market authorization in Canada and consequently, patients have obtained access to this drug through the SAP for the past 20 years.

The Committee heard that in June 2017, Health Canada granted Notice of Compliance or regulatory market authorization for another drug to treat cystinosis, Procysbi.[43] Dr. Midgley explained that the new drug has the same active ingredient as Cystagon but a longer lasting formulation which improves adherence to treatment in adolescents and adults. However, he explained that there are no long-term studies of the effectiveness of the drug, which meant that many families wanted to continue to use the treatment that they knew worked for them. In addition, the cost of Procysbi is significantly higher than Cystagon at $35.05 for a 75 milligram capsule (list price), amounting to $400,000 per year in comparison to $10,000 per year for Cystagon. Once Procysbi was approved in Canada, the Committee heard from Dr. Midgely that the Department gave physicians the

38 HESA, *Evidence*, 27 September 2018, 0900 (Parker).

39 Ibid., 0945 (Wong-Rieger); RAREi, "Unique approach needed: Addressing barriers to accessing rare disease treatments," written submission to HESA, 20 November 2018; and Horizon Therapeutics Canada, "Barriers to Access Treatment and Drugs for Canadians Affected by Rare Diseases and Disorders," written submission, October 2018.

40 HESA, *Evidence*, 4 October 2018, 0845 (Dr. Julian Midgley, Pediatric Nephrologist, As an Individual).

41 HESA, *Evidence*, 30 October 2018, 0910 (Ms. Erin Little, President, Liv-A-Little Foundation).

42 HESA, *Evidence*, 4 October 2018, 0850 (Midgley).

43 Ibid.

impression that Cystagon would no longer be available through the SAP.[44] However, once concerns were raised about the cost of Procysbi, Health Canada did continue to approve requests for Cystagon based upon medical need but did not indicate under what criteria the drug would continue to be made available through the program.[45] Furthermore, any access granted through the program has been for only three or four months, rather than the previous six months, at a time.

Ms. Erin Little, President, Liv-A-Little Foundation explained to the Committee that the uncertainty surrounding continued access to Cystagon has caused physicians, patients and their families significant duress:

> When Procysbi was approved and Cystagon was so abruptly removed from Canada, and our letter of cancellation was issued, our doctor was shocked, because she had not been informed about the approval of Procysbi, and did not necessarily feel it was the best choice for her patients. When our nephrologist spoke with someone from Health Canada, giving verbal medical reasoning for Olivia to remain on her current treatment, she was denied that choice, leaving us terrified about what to do next. We were stunned that someone, however highly educated, sitting in an office, who did not know cystinosis or our child, was able to make a decision overruling our child's physician. As Olivia's primary caregiver and someone who trusts our doctors and medical system, I was disgusted that our physician was not trusted to make the most important decision for her patient.[46]

In a subsequent follow-up letter to the Committee received in January 2019, the Minister of Health provided further clarification regarding the Department's response to providing access to Cystagon through the SAP once Procysbi became available as a marketed drug in Canada. According to the letter, Health Canada initially cancelled existing requests for Cystagon through the SAP. They then followed up with a letter to each physician who had requested Cystagon through the SAP, requesting that they provide a medical rationale as to why their patient still required the drug instead of the approved and marketed drug Procysbi. Physicians were also directly contacted by a health care professional from the SAP, who explained that they could resubmit their request through the SAP for Cycstagon instead of Procysbi, if they had a medical rationale. The letter further noted that over 60 patients have been provided access to Cystagon through the Special Access Programme since the marketing of Procysbi.

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44 Ibid.

45 Ibid.

46 HESA, *Evidence*, 30 October 2018, 0910 (Little).

To address situations of these types, the Committee heard that Health Canada needs to be more proactive in their communications with physicians regarding the medical need criteria of the SAP and ensuring patients have access to drugs through this program for longer periods of time before requiring re-application.[47] In addition, patients and physicians felt that the Department needs to make a greater effort to account for patient and health care system needs in their decision-making process, such as the potential costs of medications.[48] Finally, witnesses articulated that the Cystagon case highlights the need for Health Canada to develop incentives for drug manufacturers who provide drugs through the SAP to apply for market authorization in Canada through the standard regulatory approval process.[49]

> **"We were stunned that someone, however highly educated, sitting in an office, who did not know cystinosis or our child, was able to make a decision overruling our child's physician. As Olivia's primary caregiver and someone who trusts our doctors and medical system, I was disgusted that our physician was not trusted to make the most important decision for her patient."**
>
> *Ms. Erin Little,*
> *President,*
> *Liv-A-Little Foundation*

47 HESA, *Evidence*, 4 October 2018, 0850 (Midgley) and RAREi, "Unique approach needed: Addressing barriers to accessing rare disease treatments," written submission to HESA, 20 November 2018.

48 HESA, *Evidence*, 4 October 2018, 0850 (Midgley) and HESA, Evidence, 30 October 2018, 0910 (Little).

49 HESA, *Evidence*, 27 September 2018, 0940 (Parker and Stewart).

Accessing Drugs for Rare Diseases Through Clinical Trials

According to Ms. Parker (Health Canada), clinical trials conducted by drug manufacturers and authorized by Health Canada also represent another opportunity for patients with rare diseases to access new treatments.[50] The Department provides drug manufacturers with advice on the design of clinical trials in small patient populations and has a clinical trial database that helps patients and primary care providers find suitable clinical trials in which to participate. While clinical trials represent an opportunity for accessing new treatments, the Committee heard that often patients face barriers in having continued access to a treatment once a clinical trial ends.[51] For example, Ms. Tammy Moore (Chief Executive Officer, Amyotrophic Lateral Sclerosis Society of Canada) told the story of Norm who had access to a drug with no adverse events through a clinical trial. While the manufacturer was willing to continue to provide the drug to him after the trial concluded, it needed to apply to Health Canada for an open-label extension to have access to the drug after the clinical trial had been completed, which can take up to six weeks. Ms. Moore explained that this time gap has negative health consequences for patients:

> **"Unfortunately for Norm, during this gap in treatment his disease progressed with a loss of function. It directly resulted in two significant falls. The resulting injuries required hospitalization, including epidurals, to deal with the pain from the back injury."**
>
> *Ms. Tammy Moore, Chief Executive Officer, Amyotrophic Lateral Sclerosis Society of Canada*

> Unfortunately for Norm, during this gap in treatment his disease progressed with a loss of function. It directly resulted in two significant falls. The resulting injuries required hospitalization, including epidurals, to deal with the pain from the back injury.[52]

To address this issue, Ms. Moore recommended that Health Canada automatically grant an open-label extension at the conclusion of a trial, as long as there were no safety

50 Ibid., 0900 (Parker).

51 Ibid., 1005 (Ms. Tammy Moore, Chief Executive Officer, Amyotrophic Lateral Sclerosis Society of Canada).

52 Ibid.

concerns during the trial, an approach that is currently taken by the FDA in the United States.

Prices Of Drugs for Rare Diseases

The Committee heard that the federal government is also responsible for regulating the prices of patented medicines, including drugs for rare diseases, through the Patented Medicine Prices Review Board (PMPRB). Mr. Douglas Clark (Executive Director, PMPRB) explained to the Committee that his organization was created in 1987 under the *Patent Act* through a set of reforms that aimed to encourage greater investment in pharmaceutical R&D in Canada through stronger patent protection for pharmaceuticals.[53] According to Mr. Clark:

> PMPRB is a quasi-judicial body with a regulatory mandate to ensure that patentees do not abuse their patent rights by charging consumers excessive prices during the statutory monopoly period. Its creation arose out of concern that stronger patent protection for medicines might cause prices to rise unacceptably so as to become unaffordable to consumers.[54]

Mr. Clark explained that the PMPRB determines whether or not patented drug prices are excessive through an assessment that includes an evaluation of the therapeutic benefit they provide relative to existing medicines on the market. Once completed, PMPRB limits increases in the price of existing patented drugs to the rate of general inflation, and the sale price of the same drug in other seven jurisdictions, including France, Germany, Italy, Sweden, Switzerland, the United Kingdom and the United States which are referred to as the "PMPRB7".[55] The Committee heard that the PMPRB process takes approximately three months.[56] If a price is found to be excessive, the Board can then hold public hearings and order price reductions and/or the payback of excess revenues.

Despite the price ceilings set by the PMPRB, the Committee heard from witnesses that one of the main challenges in terms of accessing drugs for rare diseases is their high prices, which threaten the financial sustainability of public and private drug coverage

53 HESA, *Evidence*, 6 November 2018, 0850 (Mr. Douglas Clark, Executive Director, Patented Medicine Prices Review Board (PMPRB)).

54 Ibid.

55 Ibid and PMPRB, Annual Report, 2017.

56 HESA, *Evidence*, 6 November 2018, 0940 (Clark).

plans.[57] In their written submission to the Committee, the pan-Canadian Pharmaceutical Alliance (pCPA), which negotiates drug prices with drug manufacturers on behalf of federal, provincial and territorial public drug plans, explained that current list prices for drugs for rare diseases range from $0.5 million to $4.9 million per person per year.[58] As these conditions are chronic in nature, treating one patient for 10 years can cost from $1 million to $49 million.[59] In its submission to the Committee, the RAREi further explained that though these drugs have a high cost per patient, their overall budgetary impact is comparatively low, representing 3.3% to 5.6% of total pharmaceutical expenditures between 2007 and 2013.[60] In addition, they are expected to remain below 6% of total pharmaceutical expenditures up to 2018. However, the Committee also heard that these drugs are expected to make up an increasing proportion of budgets of public and private drugs coverage plans in the future, as 50% of new patented medicines under the PMPRB's jurisdiction obtained orphan drug designation in the United States or the European Union.[61] As a result, Mr. Clark explained that they pose a significant risk to the financial sustainability of the health care system:

> While our system can absorb one, two or maybe even dozens of high-cost drugs, it will collapse under the weight of hundreds, no matter how good they are. At the end of the day, the single most important determinant of access is affordability. The best drug in the world won't bring value to society if no one can afford it, or if the effect of paying for it for the fortunate few is to deprive effective health care to the multitudes.[62]

According to RAREi, manufacturers of these drugs charge high prices because of the risks and costs associated with their R&D. These risks include a lack of knowledge of rare diseases which lead to a high failure rate of treatments in clinical trials and the need to find alternative approaches to develop clinical trial data for these treatments due to small patient populations affected by the disease.[63] Most significantly, the organization

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57 Ibid and pan-Canadian Pharmaceutical Alliance (pCPA), "Brief to House of Commons Standing Committee on Health: Barriers to Access Treatment and Drugs for Canadians Affected by Rare Diseases and Disorders," written submission to HESA, 7 December 2018.

58 pCPA, "Brief to House of Commons Standing Committee on Health: Barriers to Access Treatment and Drugs for Canadians Affected by Rare Diseases and Disorders," written submission to HESA, 7 December 2018, p. 4.

59 Ibid.

60 RAREi, "Unique approach needed: Addressing barriers to accessing rare disease treatments," written submission to HESA, 20 November 2018.

61 HESA, *Evidence*, 6 November 2018, 0850 (Clark).

62 Ibid., 0855 (Clark).

63 RAREi, "Unique approach needed: Addressing barriers to accessing rare disease treatments," written submission to HESA, 20 November 2018, pp. 3-6.

explained that high prices for these drugs are necessary because they are able to recover their research and development costs from a small market due to the rarity of the condition that the drugs are treating.[64]

> **"The best drug in the world won't bring value to society if no one can afford it, or if the effect of paying for it for the fortunate few is to deprive effective health care to the multitudes."**
>
> *Mr. Douglas Clark,*
> *Executive Director,*
> *Patented Medicine Prices*
> *Review Board (PMPRB)*

However, the Committee heard from other witnesses, such as Drs. Lexchin, Midgley, and Coyle[65] and the pCPA, that it is also necessary for manufacturers of drugs for rare diseases to be more transparent in demonstrating the costs associated with the R&D of these drugs to justify their high prices. In its submission to the Committee, pCPA indicated that in contrast to claims made by drug manufacturers, published evidence suggests that there is considerable profit for manufacturers in the rare disease drug market. For example, a 2016 study found that orphan drugs are five times more profitable than non-orphan drugs for manufacturers.[66] Furthermore, despite the pCPA's repeated requests for drug manufacturers to justify "their extremely high pricing, there has been no transparent justification provided to date."[67] The organization explained that without transparent justification, payers and the public are left "with the conclusion that the prices are set based on profit maximization objectives rather than R&D recovery."[68]

To address the high prices associated with drugs for rare diseases and other complex drugs, the Committee heard from some witnesses that is necessary to adopt a new framework for the regulation of patented drug prices through proposed amendments to the *Patented Medicines Regulations* that were tabled in the Canada Gazette on

64 Ibid., p. 6.

65 HESA, *Evidence*, 4 October 2018 (Midgley, Coyle); HESA, *Evidence*, 25 October 2018, 0840 (Lexchin); and pCPA, "Brief to House of Commons Standing Committee on Health: Barriers to Access Treatment and Drugs for Canadians Affected by Rare Diseases and Disorders," written submission to HESA, 7 December 2018.

66 pCPA, "Brief to House of Commons Standing Committee on Health: Barriers to Access Treatment and Drugs for Canadians Affected by Rare Diseases and Disorders," written submission to HESA, 7 December 2018.

67 Ibid., p. 5.

68 Ibid.

2 December 2017.[69] Mr. Clark explained that there are three main types of changes being considered by the federal government through these proposed regulatory amendments.[70] First, the basket of countries used for price comparison would be expanded to include countries that have drug prices that are closer to the OECD average and health care systems and economies that are similar to Canada's. The proposed schedule lists Australia, Belgium, France, Germany, Italy, Japan, the Netherlands, Norway, South Korea, Spain, Sweden and the United Kingdom as the new PMPRB12.[71] Second, proposed amendments would introduce new factors to determine whether a price is excessive, including the value of the drug in terms of increase in length or quality of life and potential market share of the new drug relative to Gross Domestic Product.[72] Third, manufacturers would be compelled to provide the PMPRB with information regarding confidential price rebates that they offer to public and private drug coverage payers to have a true understanding of the prices of drugs on the market.[73]

The Committee heard that drug manufacturers are opposed to these proposed regulatory changes.[74] In its submission, RAREi explained that these changes would disproportionately affect drugs for rare diseases, resulting in price reductions of between 70-90%. Furthermore, the organization explained that the proposed approach for determining the value of the drug or cost-effectiveness of a drug does not take into account limitations associated with developing scientific evidence for drugs for rare diseases, as noted above. RAREi indicated that these changes would create barriers for manufacturers seeking market approval in Canada, causing delays and/or limiting access to treatments for patients altogether by no longer launching products in the Canadian market. It therefore recommended that the federal government reconsider this regulatory proposal.[75]

Mr. Clark explained to the Committee that the PMPRB is aware of concerns that the proposed changes to the PMPRB regulatory framework might delay or compromise

69 Ibid and HESA, *Evidence*, 4 October 2018, 0900 (Coyle) and HESA, *Evidence*, 6 November 2018, 0850 (Clark).

70 HESA, *Evidence*, 6 November 2018, 0930 (Clark).

71 Canada Gazette, "Regulations Amending the Patented Medicines Regulations," Vol. 151, No.48-December 2, 2017.

72 HESA, *Evidence*, 6 November 2018, 0930 (Clark).

73 Ibid.

74 RAREi, "Unique approach needed: Addressing barriers to accessing rare disease treatments," written submission to HESA, 20 November 2018, p. 7.

75 Ibid.

Canadians' access to the very latest patented drugs.[76] However, he cautioned the Committee that there is little evidence to support the argument that lower prices result in less access. According to Mr. Clark, "the reality is that many countries with similar health care systems and economies to Canada's pay less for drugs yet enjoy the same or better access. The same is true of research and development investment."[77]

The Committee heard that Canada currently pays the third-highest price for patented medicines in the world, and yet the ratio of research and development to sales in Canada pales in comparison to the PMPRB7 countries. [78] According to Mr. Clark:

> [T]he original composition of that group of countries was based upon the assumption that if we emulated the intellectual property regimes in those countries and priced in line with them, we would come to enjoy a similar level of R and D to sales as in those countries. Obviously, that assumption has not been borne out over time. Currently, we are at an historical low in our ratio of R and D to sales.… It currently stands at about 4.4%, versus over 20% R and D to sales in the countries we compare ourselves to on average under the PMPRB7.[79]

According to Mr. Clark, the PMPRB is "not doing a very good job" of protecting Canadians from excessive pricing with the tools currently at its disposal and it is for this reason that the PMPRB is seeking to move forward with ambitious reforms to its pricing guidelines.[80] First announced in June of 2016, these changes were set to take effect on 1 January 2019 but they have now been postponed indefinitely.[81]

76 HESA, *Evidence*, 6 November 2018, 0855 (Clark).

77 Ibid.

78 Ibid.

79 Ibid., 0905.

80 Ibid., 0925.

81 *The Globe and Mail*, "Canada's drug-pricing regulator brings rare allegation of excessive pricing against Horizon Pharma," 18 January 2019.

Reimbursement of Rare Disease Drug Costs Through Federal Provincial and Territorial Public Drug Coverage Plans

The Committee heard that provinces and territories are responsible for determining which drugs will be reimbursed through their respective public drug coverage plans, including drugs for rare diseases.[82] In addition, the federal government offers or facilitates public drug coverage for some groups of people, including members of the military, veterans, First Nations and Inuit, federal inmates, and certain classes of refugees.[83] In its submission to the Committee on behalf of public drug plans in Canada, the pCPA explained that each plan aims to deliver coverage that is accessible, appropriate, affordable and responsive to population health needs.[84] These plans are also responsible for funding other aspects of the health care system, including medical devices and supplies as well as pharmacy services. Finally, they are also publicly accountable for the use of tax payer funds and must make trade-offs in terms of which drugs and services will be funded within health care systems that have a significant number of competing health priorities but limited budgets.

> **“ Obviously, that assumption has not been borne out over time. Currently, we are at an historical low in our ratio of R and D to sales…. It currently stands at about 4.4%, versus over 20% R and D to sales in the countries we compare ourselves to on average under the PMPRB7.**
>
> *Mr. Douglas Clark,*
> *Executive Director,*
> *Patented Medicine Prices*
> *Review Board (PMPRB)*

In its submission, pCPA explained that federal, provincial and territorial public drug coverage plans rely on national and pan-Canadian processes to support their decision-making, including the Canadian Agency for Drugs and Technologies in Health (CADTH) and the pan-Canadian Pharmaceutical Alliance (pCPA) (see Figure 1).[85] The aim of both CADTH and the pCPA is to establish consistency in pricing and reimbursement decisions

82 pCPA, “Brief to House of Commons Standing Committee on Health: Barriers to Access Treatment and Drugs for Canadians Affected by Rare Diseases and Disorders,” written submission to HESA, 7 December 2018.

83 Ibid.

84 Ibid.

85 Ibid.

for drugs across the country.[86] CADTH is an independent not-for-profit corporation that was established by federal, provincial and territorial governments (except Quebec)[87] in 1989 to provide them with advice and guidance to determine which drugs and medical technologies should be reimbursed through public health care plans.[88] Ms. Heather Logan (Acting Vice-President, Pharmaceutical Reviews, CADTH) explained to the Committee that once a drug has been authorized for sale by Health Canada, CADTH then provides advice and recommendations to public drug coverage plans by undertaking a health technology assessment (HTA), which is an evidence-based review of both the clinical- and cost-effectiveness of drugs.[89] Evaluating the cost-effectiveness of a drug involves looking at the clinical benefit of a drug in terms of health outcomes, such as quality of life, morbidity, and mortality, in comparison to its cost to determine whether it represents value for money. HTAs also examine the cost-effectiveness of a drug in comparison to other treatments available. They also identify specific patient and clinical circumstances when the drug works best.[90] Through the Common Drug Review, CADTH provides recommendations for drug coverage decisions for 18 of the 19 publicly funded drug coverage plans in Canada, including federal programs. CADTH has a similar but separate process for making recommendations for oncology drugs through the pan-Canadian oncology drug review.[91]

86 Ibid.

87 Quebec has its own separate HTA process conducted by the Institut national d'excellence en santé et en services sociaux.

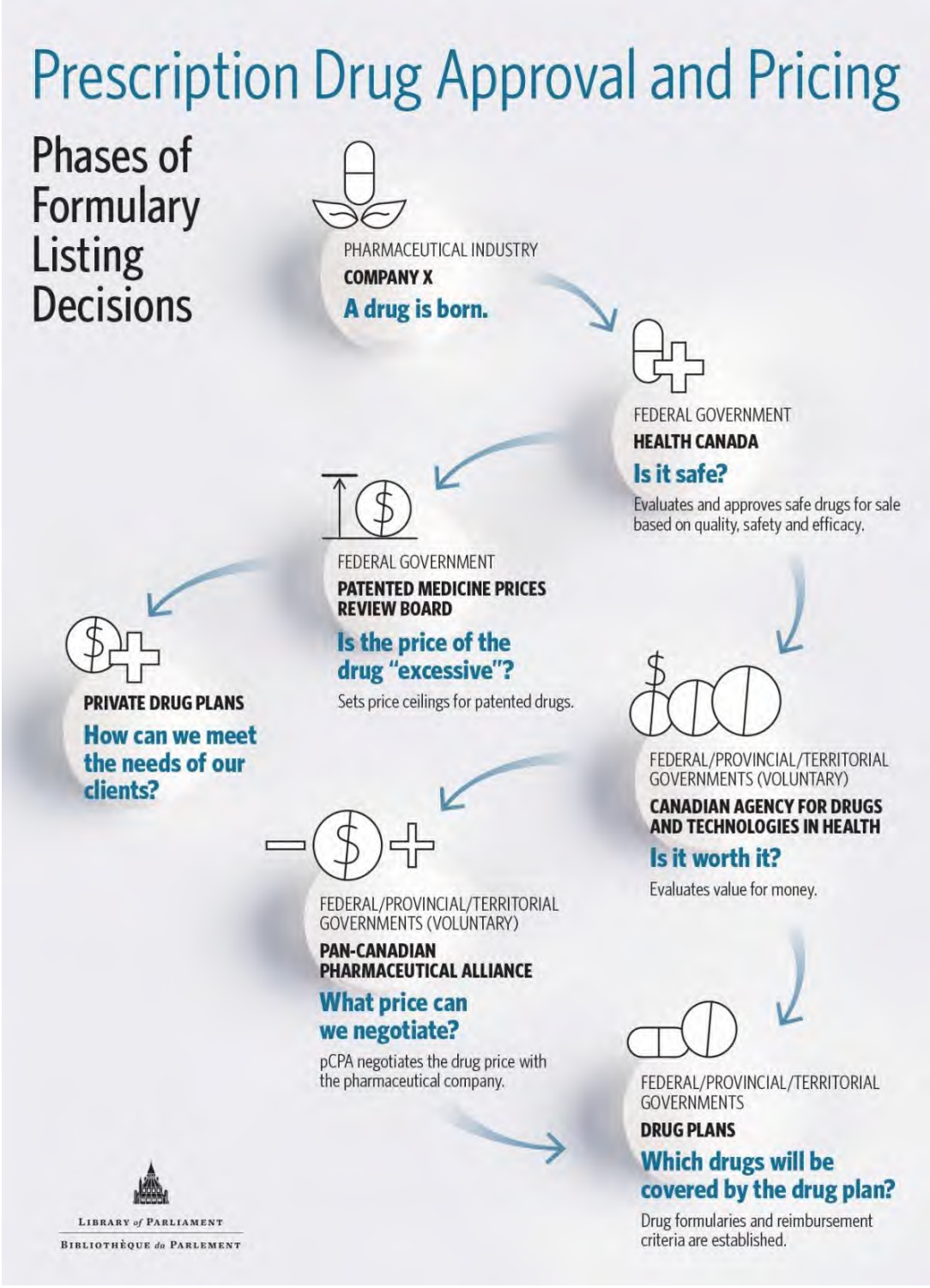
88 HESA, *Evidence*, 6 November 2018, 0855 (Ms. Heather Logan, Acting Vice-President, Pharmaceutical Reviews, Canadian Agency for Drugs and Technologies in Health).

89 Ibid.

90 pCPA, "Brief to House of Commons Standing Committee on Health: Barriers to Access Treatment and Drugs for Canadians Affected by Rare Diseases and Disorders," written submission to HESA, 7 December 2018.

91 HESA, *Evidence*, 6 November 2018, 0855 (Logan).

Figure 1


Prescription Drug Approval and Pricing
Phases of Formulary Listing Decisions
PHARMACEUTICAL INDUSTRY
COMPANY X
A drug is born.
FEDERAL GOVERNMENT
HEALTH CANADA
Is it safe?
Evaluates and approves safe drugs for sale based on quality, safety and efficacy.
FEDERAL GOVERNMENT
PATENTED MEDICINE PRICES REVIEW BOARD
Is the price of the drug "excessive"?
Sets price ceilings for patented drugs.
PRIVATE DRUG PLANS
How can we meet the needs of our clients?
FEDERAL/PROVINCIAL/TERRITORIAL GOVERNMENTS (VOLUNTARY)
CANADIAN AGENCY FOR DRUGS AND TECHNOLOGIES IN HEALTH
Is it worth it?
Evaluates value for money.
FEDERAL/PROVINCIAL/TERRITORIAL GOVERNMENTS (VOLUNTARY)
PAN-CANADIAN PHARMACEUTICAL ALLIANCE
What price can we negotiate?
pCPA negotiates the drug price with the pharmaceutical company.
FEDERAL/PROVINCIAL/TERRITORIAL GOVERNMENTS
DRUG PLANS
Which drugs will be covered by the drug plan?
Drug formularies and reimbursement criteria are established.
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Once a drug has undergone CADTH's assessment process and received a positive recommendation, the pCPA, on behalf of provincial, territorial and federal drug coverage plans, negotiates with drug manufacturers to obtain price reductions and other conditions for the listing of a drug on public drug coverage plans.[92] Once these negotiations are complete, jurisdictions then enter into their own respective product listing agreements with drug manufacturers. As of 30 September 2018, the pCPA had completed 200 negotiations for both brand-name and generic medicines, realizing a savings of $1.98 billion.[93] As of 26 November 2018, the organization had completed nine negotiations for drugs for rare diseases.[94]

The Committee heard that both CADTH and the pCPA face difficulties in making drug coverage recommendations and undertaking price negotiations for drugs for rare diseases because of the limited clinical data for these drugs. As the target population for these drugs is small, it is difficult to conduct a standard clinical trial.[95] When less than robust clinical trial data for these drugs exist, there is a high degree of uncertainty around the clinical benefit and long-term safety, efficacy and cost-effectiveness of the treatment. Further, the clinical data for these drugs use surrogate end-points such as changes to biomarkers or biological processes, which may correlate with improvements in health outcomes, such as quality of life or reduction in mortality, but are not proven to result in better health outcomes.[96]

Finally, pCPA, in its brief, also explained that when Health Canada approves a drug for sale with conditions, such as the need to collect more evidence to support its efficacy, there are limited consequences for pharmaceutical companies who do not fulfil these obligations.[97] Consequently, when these drugs are later assessed by CADTH and the pCPA, they are unable to evaluate the efficacy of a drug because this data is missing or limited. The unclear evidence regarding the clinical benefits or harms of drugs for rare diseases coupled with their high costs therefore makes it difficult for public drug plans to justify their reimbursement. The pCPA explained that there are some drugs for rare diseases that have adequately demonstrated their clinical efficacy sufficiently to support

92 pCPA, "Brief to House of Commons Standing Committee on Health: Barriers to Access Treatment and Drugs for Canadians Affected by Rare Diseases and Disorders," written submission to HESA, 7 December 2018.

93 Ibid.

94 Ibid.

95 HESA, *Evidence*, 6 November 2018, 0855 (Logan).

96 Ibid.

97 pCPA, "Brief to House of Commons Standing Committee on Health: Barriers to Access Treatment and Drugs for Canadians Affected by Rare Diseases and Disorders," written submission to HESA, 7 December 2018.

their reimbursement with conditions, which usually incude a price reduction and specific clinical criteria for use of the drug.[98]

To address challenges associated with scientific evidence regarding the clinical efficacy and cost-effectiveness of drugs for rare diseases, Ms. Logan (CADTH) recommended investing in infrastructure and support for the collection of real world evidence.[99] This support would enable public drug plans to provide conditional coverage of a drug when there is limited evidence; and then reassess or renegotiate with drug manufacturers when additional evidence is available, a managed access approach to rare disease drugs that is used in other jurisdictions.[100] Dr. Campbell, Children's Hospital, London Health Sciences Centre echoed this view, recommending investment in rare disease registries in which expert clinicians collect long-term, high-quality patient data on health outcomes and biomarkers to monitor the impact of novel therapies.[101]

The Committee heard that there is also a need to improve the timeliness of drug reimbursement processes through CADTH and the pCPA through better coordination among these bodies and Health Canada's market approval process to improve access to drugs for rare diseases. Mr. Andrew McFadyen (Executive Director, the Isaac Foundation) explained that despite Health Canada's priority review process, patients are still often left waiting for access to a drug because they must also wait for both CADTH's review, which could take an additional 6 to 12 months and pCPA negotiations, which can take 12 months or longer.[102] Ms. Tammy Moore (Chief Executive Officer, Amyotrophic Lateral Sclerosis Society of Canada) explained that this lengthy timeline for regulatory approval and drug cost reimbursement processes through CADTH and the pCPA in Canada is particularly detrimental to patients with rare diseases because their conditions can decline rapidly without access to treatment:

> In the 180 days during Health Canada's priority review period, 500 Canadians have died of ALS. How many will die awaiting the CADTH decision? After that, how many will have to die while they're awaiting the availability through a publicly funded drug program?

98 Ibid.

99 HESA, *Evidence*, 6 November 2018, 0950 (Logan) and pCPA, "Brief to House of Commons Standing Committee on Health: Barriers to Access Treatment and Drugs for Canadians Affected by Rare Diseases and Disorders," written submission to HESA, 7 December 2018.

100 Ibid.

101 HESA, *Evidence*, 4 October 2018, 0920 (Campbell).

102 Ibid., 0910 (McFadyen).

> We are dealing with a community that measures time by loss of their own function and the number of members who will die during this process.[103]

To reduce the timeliness associated with drug approval and reimbursement processes, Mr. McFadyen recommended a more coordinated drug approval and reimbursement process in which Health Canada and CADTH reviews would take place simultaneously, and pCPA negotiations would also begin at the same time.[104] The Committee heard from Ms. Parker that Health Canada is starting to move in this direction, working with CADTH to have their respective review processes occur in tandem.[105] In its brief, pCPA recommended that Health Canada, in collaboration with CADTH and the pCPA, provide advice and support to drug manufacturers regarding the design of clinical trials to ensure that they are able to meet the scientific evidence requirements for both drug approval by Health Canada and the price negotiation and cost reimbursement processes of provincial and territorial drug plans.[106]

103 HESA, *Evidence*, 27 September 2018, 1005 (Moore).

104 HESA, *Evidence*, 4 October 2018, 0910 (McFadyen).

105 HESA, *Evidence*, 27 September 2018, 0905 (Parker).

106 pCPA, "Brief to House of Commons Standing Committee on Health: Barriers to Access Treatment and Drugs for Canadians Affected by Rare Diseases and Disorders," written submission to HESA, 7 December 2018.

The Committee also heard from witnesses that it is necessary to provide time-limited coverage for the costs of drugs for rare diseases for patients during the approval and reimbursement processes to ensure that they have uninterrupted access to these drugs.[107] The Committee heard that some drug manufacturers cover the costs of medications for patients while the drugs are in the regulatory approval processes through compassionate care programs. However, these programs also pose challenges for patients and public drug coverage plans. Ms. Little, President, Liv-A-Little Foundation explained that once patients are part of these programs, they may not be able to obtain coverage for the drug from their private insurance companies or are unable to switch drugs, if a new one comes on the market.[108] A representative from the pCPA indicated that it had experienced numerous situations where manufacturers threatened to stop their compassionate supply as part of their negotiating position with public drug plans.[109] Mr. McFadyen therefore recommended that the federal government set aside a very small percentage of health care transfers to the provinces and territories to provide immediate access to lifesaving drugs that have been approved

> **"In the 180 days during Health Canada's priority review period, 500 Canadians have died of ALS. How many will die awaiting the CADTH decision? After that, how many will have to die while they're awaiting the availability through a publicly funded drug program? We are dealing with a community that measures time by loss of their own function and the number of members who will die during this process."**
>
> *Ms. Tammy Moore,*
> *Chief Executive Officer,*
> *Amyotrophic Lateral Sclerosis*
> *Society of Canada*

107 HESA, *Evidence*, 6 November 2018, 0855 (Logan).

108 HESA, *Evidence*, 30 October 2018, 0940 (Little).

109 pCPA, "Brief to House of Commons Standing Committee on Health: Barriers to Access Treatment and Drugs for Canadians Affected by Rare Diseases and Disorders," written submission to HESA, 7 December 2018.

by Health Canada, but are still undergoing the pricing negotiation and cost-reimbursement process through CADTH and the pCPA.[110]

More broadly, some witnesses told the Committee that patients should be provided with equitable access to drugs for rare diseases through either a national drug coverage program for drugs for rare diseases, or a national pharmacare program for all drugs that would include drugs for rare diseases. In the words of Ms. Maureen Smith (Board Secretary, CORD):

> I have a lot of ideas about recommendations, but I think the thing that strikes me the most is that there is no equity across the country. It's very difficult for a patient to know that someone in B.C. or someone in another province has exactly the same condition as you and receives treatment, when maybe in your province, you don't. People who don't have rare diseases or who don't deal with drugs are flabbergasted by that. We're all Canadians, and they seem to think that universal coverage in hospitals extends to drugs. There's very little understanding of that until you are in that situation yourself.[111]

Finally, the Committee heard that some progress is currently underway to address these issues. Ms. Logan explained that the Expensive Drugs for Rare Disease (EDRD) working group was established by provincial and territorial deputy ministers of health in 2014 to explore ways of managing access to these drugs.[112] The working group has developed a proposal that would involve creating a supplemental process for drugs for rare diseases that would involve:

- a co-ordinated identification and prioritization mechanism for the regulatory review of complex drugs;

> **"It's very difficult for a patient to know that someone in B.C. or someone in another province has the exactly the same condition as you and receives treatment, when maybe in your province, you don't. People who don't have rare diseases or who don't deal with drugs are flabbergasted by that. We're all Canadians…."**
>
> *Ms. Maureen Smith,*
> *Board Secretary, CORD*

110 HESA, *Evidence*, 4 October 2018, 0910 (McFadyen).

111 HESA, *Evidence*, 27 September 2018, 1030 (Ms. Maureen Smith, Board Secretary, CORD).

112 HESA, *Evidence*, 6 November 2018, 0855 (Logan).

- improved use of real-world evidence to inform regulatory and reimbursement decisions;
- centralized panels of experts to evaluate evidence and ensure consistency in decision-making; and
- time-limited access as additional clinical evidence is being gathered.[113]

The Committee heard that consultations regarding this proposal were underway in November 2018. In their written submissions to the Committee, the pCPA and drug manufacturers recommended that the federal government support the supplementary process proposed by the EDRD working group.[114]

Access to Early Diagnosis of Rare Diseases

Dr. Michael Brudno, (professor and Scientific Director, Centre for Computational Medicine, Hospital for Sick Children) told the Committee that obtaining early diagnosis of a rare diseases is critical for patients to access treatment.[115] He explained that genetic testing is available to identify disease-causing mutations and differentiate among 7,000 diseases at a cost of $1,000 per test.[116] He explained that rapid access to genetic testing means that patients gain access to treatment sooner, avoiding unnecessary visits to doctors, investigations and interventions that can cost the health care system upwards of US$8,000 per patient based upon studies conducted in the United States. Dr. Brudno recommended that any approach to address barriers to access to treatment for rare diseases in Canada should include access to rapid diagnostic genetic testing as a critical component. Dr. Alex MacKenzie (Clinician Scientist, Children's Hospital of Eastern Ontario) also recommended that the federal government continue to invest in research initiatives such as Genome Canada's 30,000 genome identification project and the pan-Canadian research consortium Care4Rare that is supporting the identification of rare disease genes.[117]

113 pCPA, "Brief to House of Commons Standing Committee on Health: Barriers to Access Treatment and Drugs for Canadians Affected by Rare Diseases and Disorders," written submission to HESA, 7 December 2018.

114 Ibid.

115 HESA, *Evidence*, 25 October 2018, 0830 (Brudno).

116 Ibid.

117 Ibid., 0835 (MacKenzie).

THE WAY FORWARD: COMMITTEE OBSERVATIONS AND RECOMMENDATIONS

The Committee's study highlighted the numerous challenges that Canadians with rare diseases face in accessing treatments. The Committee heard that current approval, pricing and reimbursement processes for drugs for rare diseases are not meeting the needs of patients, drug manufacturers and provincial and territorial public drug coverage plans. The result is significant tension among different parties within the health care system:

> As it stands, many families have to parade their children through the media. Many drug companies are manipulating physicians and the public. Clinicians and patient groups are reacting in shock to decisions. Regulatory bodies appear to be stifled in real engagement by their internal bylaws and processes.[118]

It is clear to the Committee that something needs to change. With more and more drugs for rare diseases coming to the Canadian market, we need to address their high prices and limitations in the scientific evidence supporting their use, while ensuring that patients have continued access to treatment. In addition, manufacturers must be able to obtain a fair return on their investments and continue to have incentives to seek market authorization in Canada. Witnesses appearing before the Committee highlighted ways in which the federal government, in collaboration with provinces and territories, could help balance these competing priorities and improve access to treatments for Canadians with rare diseases. The witnesses identified the need for a distinct and coordinated process for both the market authorization and reimbursement of these drugs across all levels of government. Such a process would ensure timely access to drugs for rare diseases, which would include a broad and more flexible consideration of scientific evidence in relation to these drugs. Witnesses also indicated that Health Canada needs to do a better job of communicating with physicians and patients regarding their regulatory criteria and decisions, particularly as they relate to the Special Access Programme. Health Canada also needs to provide guidance to drug manufacturers to ensure that they can provide the scientific evidence required for both market approval and reimbursement of drugs for rare diseases.

Finally, witnesses articulated that the single most important factor for ensuring access to drugs for rare diseases is affordability. Consequently, the Committee heard that it is necessary to implement the proposed amendments to the *Patented Medicines Regulations* to reduce drugs prices in Canada and ensure the financial sustainability of public health care systems. Witnesses also recommended federal funding for short and

118 HESA, *Evidence*, 4 October 2018, 0915 (Campbell).

long-term public drug coverage programs for drugs for rare diseases to ensure access for patients. Meanwhile public investments in research on rare diseases will help in the development of new treatments and help monitor the effectiveness of existing ones.

The Committee agrees with the proposals put forward by witnesses during its study and therefore recommends:

Health Canada's Market Authorization of Drugs for Rare Diseases

Recommendation 1

That the Government of Canada, in collaboration with the provinces and territories, develop a coordinated process for the market authorization and reimbursement of drugs for rare diseases.

Recommendation 2

That the Government of Canada work to ensure greater transparency and information sharing throughout the life cycle of drugs for rare diseases to ensure timely access for key decision-makers, including health care providers, health technology assessors and patients.

Recommendation 3

That the Government of Canada in collaboration with the provinces and territories develop a national, independent, expert review panel to provide recommendations and guidance on the regulatory review, pricing and reimbursement of drugs for rare diseases in Canada, including instructions on how to streamline these processes; and report publicly on its findings.

Recommendation 4

That Health Canada and the Canadian Agency for Drugs and Technologies in Health undertake their respective scientific evidence review processes of drugs for rare diseases in tandem as a standard practice.

Recommendation 5

That Health Canada, in collaboration with the Canadian Agency for Drugs and Technologies in Health, provide guidance and advice to drug manufacturers in the design of clinical trials to ensure that they meet the requirements of both market authorization and reimbursement processes in Canada.

Recommendation 6

That Health Canada consider removing regulatory requirements for drug manufacturers to seek additional approval for an open-label extension for drugs at the completion of a clinical trial to ensure that patients have uninterrupted access to these drugs if no safety concerns are present, in line with regulatory practices in the United States.

Recommendation 7

That Health Canada consider reducing regulatory submission fees for manufacturers of drugs for rare diseases seeking to obtain market authorization for the drugs in Canada.

Recommendation 8

That Health Canada be more proactive in its communications with physicians and patients regarding the specific medical need criteria required for obtaining access to drugs through the Special Access Programme.

Recommendation 9

That the Government of Canada remove the requirement to reapply to the Special Access Programme every three to six months when accessing a drug for a permanent, stable condition. Once initially approved, Canadians' approvals should remain in place until a doctor rescinds the approval or the patient's condition changes significantly.

Recommendation 10

That Health Canada ensure that drug manufacturers meet their regulatory obligations when Notice of Compliance with conditions are granted for drugs where limited evidence is available regarding their quality, safety and efficacy.

Drug Prices

Recommendation 11

That the Government of Canada move forward with implementing proposed changes to the *Patented Medicines Regulations* to address high drug prices in Canada.

Recommendation 12

That the Government of Canada consider establishing separate requirements for determining price ceilings for drugs for rare diseases under the *Patented Medicines Regulations* to reflect the small market for these drugs in Canada.

Recommendation 13

That the Patented Medicine Prices Review Board be required to consider the advice and recommendations of the proposed independent advisory committee on drugs for rare diseases in setting the price ceilings for drugs for rare diseases.

Recommendation 14

That the Government of Canada introduce additional regulatory requirements under section 88(1) (c) of the *Patent Act* that require manufacturers of patented pharmaceuticals to provide information to the Patented Medicine Prices Review Board regarding their research and development costs for a drug once they have obtained market authorization from Health Canada.

Recommendation 15

That the Government of Canada undertake a review of the entire pharmaceutical research and manufacturing process to better understand where government regulations and laws are having the unintended consequences of raising final drug costs for patients. This review should include an examination of whether drug costs could be reduced through open science.

Reimbursement of Drugs for Rare Diseases

Recommendation 16

That the Government of Canada, in collaboration with the provinces, territories and drug manufacturers, establish a jointly funded compassionate care program that covers the costs of drugs for rare diseases while they are under review for market authorization and cost reimbursement.

Recommendation 17

That the reimbursement of drugs for rare diseases be included as part of a national pharmacare program established by the Government of Canada, in collaboration with the provinces and territories, through amendments to the *Canada Health Act*, as

recommended by the House of Commons Standing Committee on Health in its report entitled *Pharmacare Now: Prescription Medicine Coverage For All Canadians*.

Recommendation 18

That the Office of the Auditor General conduct an audit of Health Canada to determine whether it has been effective in managing its funding agreement with the Canadian Agency for Drugs and Technologies in Health, including determining whether Health Canada is effectively ensuring that the Agency is fulfilling its mandate in accordance with agreed terms and conditions of the agreement with Health Canada.

Research

Recommendation 19

That the Government of Canada provide funding through the Canadian Institutes of Health Research for research into the diagnosis of patients with rare diseases and the collection of real-world evidence regarding the effectiveness of treatments for these conditions.

APPENDIX A
LIST OF WITNESSES

The following table lists the witnesses who appeared before the Committee at its meetings related to this report. Transcripts of all public meetings related to this report are available on the Committee's webpage for this study.

Organizations and Individuals	Date	Meeting
Amyotrophic Lateral Sclerosis Society of Canada	2018/09/27	112
Tammy Moore, Chief Executive Officer		
Canadian Organization for Rare Disorders	2018/09/27	112
Maureen Smith, Board Secretary		
Durhane Wong-Rieger, President and Chief Executive Officer		
Department of Health	2018/09/27	112
Catherine Parker, Director General Biologics and Genetic Therapies Directorate, Health Products and Food Branch		
Karen Reynolds, Executive Director Office of Pharmaceuticals Management Strategies		
John Patrick Stewart, Director General Therapeutic Products Directorate		
As individuals	2018/10/04	114
Craig Campbell, MD Department Pediatrics and Neurology, Children's Hospital London Health Sciences Centre		
Doug Coyle, Professor School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa		
Julian Midgley, Paediatric Nephrologist		
The Isaac Foundation	2018/10/04	114
Andrew McFadyen, Executive Director		

Organizations and Individuals	Date	Meeting
As individuals	2018/10/25	118
Michael Brudno, Professor and Scientific Director Centre for Computational Medicine, Hospital for Sick Children		
Joel Lexchin, Professor Emeritus School of Health Policy and Management, York University		
Ian Stedman, Osgoode Hall Law School, York University		
Children's Hospital of Eastern Ontario (CHEO)	2018/10/25	118
Alex MacKenzie, Clinician Scientist		
Janssen Inc. Pharmaceutical Companies of Johnson & Johnson	2018/10/25	118
Jacqueline Dobson, Government Affairs and Policy Manager Government Affairs and Market Access		
Stacey Silverberg, Stakeholder Engagement Manager Government Affairs and Market Access		
Atypical Hemolytic Uremic Syndrome Canada	2018/10/30	119
Mary Jane Vowles, Board Member Caryn Vowles, Board Member		
Department of Health	2018/10/30	119
Catherine Parker, Director General Biologics and Genetic Therapies Directorate, Health Products and Food Branch		
Karen Reynolds, Executive Director Office of Pharmaceuticals Management Strategies		
John Patrick Stewart, Director General Therapeutic Products Directorate		
Liv-A-Little Foundation	2018/10/30	119
Erin Little, President		
Canadian Agency for Drugs and Technologies in Health	2018/11/06	121
Heather Logan, Acting Vice-President Pharmaceutical Reviews		
Patented Medicine Prices Review Board	2018/11/06	121
Douglas Clark, Executive Director		

APPENDIX B
LIST OF BRIEFS

The following is an alphabetical list of organizations and individuals who submitted briefs to the Committee related to this report. For more information, please consult the Committee's webpage for this study.

AdamEzra Corporation

Canadian Forum for Rare Disease Innovators

Canadian ME Patients

Canadian Organization for Rare Disorders

Crohn's and Colitis Canada

Horizon Therapeutics Canada

Janssen Inc. Pharmaceutical Companies of Johnson & Johnson

Lexchin, Joel

pan-Canadian Pharmaceutical Alliance

Rawson, Nigel S.

REQUEST FOR GOVERNMENT RESPONSE

Pursuant to Standing Order 109, the Committee requests that the government table a comprehensive response to this Report.

A copy of the relevant *Minutes of Proceedings* (Meetings Nos. 112, 114, 118, 119, 120, 121, 128 and 133) is tabled.

Respectfully submitted,

Bill Casey
Chair

Summary

Having heard the testimony of 24 witnesses over seven meetings, the *DRAFT REPORT ON BARRIERS TO ACCESS TO TREATMENT AND DRUGS FOR CANADIANS AFFECTED BY RARE DISEASES AND DISORDERS* represents both the findings and the recommendations of the majority of committee members. Conservative members believe that Canadians need better access to their rare disease treatments and medications.

While the summary of evidence heard is a good representation of the testimony heard from witnesses, the Conservative members of the committee disagree with several of the proposed recommendations, specifically, the proposed changes to the Patented Medicine Prices Review Board (PMPRB) and making rare disease funding part of a national pharmacare program. As such, there is not unanimous agreement with recommendations 8 and 13.

Recommendation 8: That the Government of Canada move forward with implementing proposed changes to the Patented Medicines Regulations to address high drug prices in Canada.

Evidence gathered outside of the committee testimony from stakeholders engaged in clinical trials, from academia, and from pharmaceutical companies suggests that the proposed changes to the PMPRB process will have unintended negative effects. The changes are predicted to lengthening the time of approvals, increase costs, and eliminate profit opportunities for producers. In turn, this will discourage pharma companies from doing clinical trials in Canada and will restrict the access of Canadians to new medicines.

Testimonies before the House of Commons Standing Committee on Health regarding the *Pharmacare Now* study revealed the adverse results of government-run pharmacare programs when New Zealand implemented similar changes. The program resulted in reduced access to new drugs for patients and drug shortages. Canada is already experiencing drug shortages related to pricing. On four occasions in the last year, for example, epi-pen injectors were unavailable. The price paid in Canada is $100 versus the price in the US (where there was no shortage) was $300. In order to obtain some epi-pen injectors, Canada paid $175 from another vendor. There are so many drug shortages in Canada that the government publishes a webpage listing them https://www.drugshortagescanada.ca/

While we agree that changes to the PMPRB need to be made in order to make approvals faster, less costly, and to strike a balance between low prices for Canadians and high

enough profit margins to encourage pharmaceutical companies to offer the drug. However the changes currently proposed will not accomplish these goals.

Removal of recommendation 13: that the reimbursement of drugs for rare diseases be included as part of a national pharmacare program established by the government of Canada, in collaboration with the provinces and territories, through amendments to the Canada Health Act, as recommended by the House of Commons Standing Committee on Health in its report entitled Pharmacare Now: Prescription Medicine Coverage for All Canadians

As laid out in the dissenting report to the Pharmacare Now report, the Conservatives do not believe that a national pharmacare program is the fastest or most efficient way to address coverage of prescription medications for the small percentage of Canadians who do not currently have access. The Conference Board of Canada recently published the latest information, indicating that 660,000 Canadians, mainly in Ontario and Newfoundland and Labrador, are without coverage. While we do support increased federal government support for rare disease medicines, we do not believe the model outlined in the HESA report is the best approach.

As rare disease conditions are chronic in nature, treating one patient for 10 years can cost from $1 million to $49 million. In its submission to the Committee, the Canadian Forum for Rare Disease Innovators (RAREi) further explained that though these drugs have a high cost per patient, their overall budgetary impact is comparatively low, representing 3.3% to 5.6% of total pharmaceutical expenditures between 2007 and 2013. However, as more medicines are discovered, the costs will escalate.

Mr. Douglas Clark, Executive Director, Patented Medicine Prices Review Board, explained to the committee that these drugs pose a significant risk to the financial sustainability of the health care system. For this reason, a sustainable solution to fund rare disease medicines is needed.

OECD Transfer Pricing Guidelines for Multinational Enterprises and Tax Administrations

JULY 2017

OECD Transfer Pricing Guidelines for Multinational Enterprises and Tax Administrations

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www.oecd.org/about/publishing/corrigenda.htm.

Preface

1. The role of multinational enterprises (MNEs) in world trade has continued to increase dramatically since the adoption of these Guidelines in 1995. This in part reflects the increased pace of integration of national economies and technological progress, particularly in the area of communications. The growth of MNEs presents increasingly complex taxation issues for both tax administrations and the MNEs themselves since separate country rules for the taxation of MNEs cannot be viewed in isolation but must be addressed in a broad international context.

2. These issues arise primarily from the practical difficulty, for both MNEs and tax administrations, of determining the income and expenses of a company or a permanent establishment that is part of an MNE group that should be taken into account within a jurisdiction, particularly where the MNE group's operations are highly integrated.

3. In the case of MNEs, the need to comply with laws and administrative requirements that may differ from country to country creates additional problems. The differing requirements may lead to a greater burden on an MNE, and result in higher costs of compliance, than for a similar enterprise operating solely within a single tax jurisdiction.

4. In the case of tax administrations, specific problems arise at both policy and practical levels. At the policy level, countries need to reconcile their legitimate right to tax the profits of a taxpayer based upon income and expenses that can reasonably be considered to arise within their territory with the need to avoid the taxation of the same item of income by more than one tax jurisdiction. Such double or multiple taxation can create an impediment to cross-border transactions in goods and services and the movement of capital. At a practical level, a country's determination of such income and expense allocation may be impeded by difficulties in obtaining pertinent data located outside its own jurisdiction.

5. At a primary level, the taxing rights that each country asserts depend on whether the country uses a system of taxation that is residence-based, source-based, or both. In a residence-based tax system, a country will include in its tax base all or part of the income, including income from

sources outside that country, of any person (including juridical persons such as corporations) who is considered resident in that jurisdiction. In a source-based tax system, a country will include in its tax base income arising within its tax jurisdiction, irrespective of the residence of the taxpayer. As applied to MNEs, these two bases, often used in conjunction, generally treat each enterprise within the MNE group as a separate entity. OECD member countries have chosen this separate entity approach as the most reasonable means for achieving equitable results and minimising the risk of unrelieved double taxation. Thus, each individual group member is subject to tax on the income arising to it (on a residence or source basis).

6. In order to apply the separate entity approach to intra-group transactions, individual group members must be taxed on the basis that they act at arm's length in their transactions with each other. However, the relationship among members of an MNE group may permit the group members to establish special conditions in their intra-group relations that differ from those that would have been established had the group members been acting as independent enterprises operating in open markets. To ensure the correct application of the separate entity approach, OECD member countries have adopted the arm's length principle, under which the effect of special conditions on the levels of profits should be eliminated.

7. These international taxation principles have been chosen by OECD member countries as serving the dual objectives of securing the appropriate tax base in each jurisdiction and avoiding double taxation, thereby minimising conflict between tax administrations and promoting international trade and investment. In a global economy, coordination among countries is better placed to achieve these goals than tax competition. The OECD, with its mission to contribute to the expansion of world trade on a multilateral, non-discriminatory basis and to achieve the highest sustainable economic growth in member countries, has continuously worked to build a consensus on international taxation principles, thereby avoiding unilateral responses to multilateral problems.

8. The foregoing principles concerning the taxation of MNEs are incorporated in the *OECD Model Tax Convention on Income and on Capital* (OECD Model Tax Convention), which forms the basis of the extensive network of bilateral income tax treaties between OECD member countries and between OECD member and non-member countries. These principles also are incorporated in the Model United Nations Double Taxation Convention between Developed and Developing Nations.

9. The main mechanisms for resolving issues that arise in the application of international tax principles to MNEs are contained in these bilateral treaties. The Articles that chiefly affect the taxation of MNEs are:

Article 4, which defines residence; Articles 5 and 7, which determine the taxation of permanent establishments; Article 9, which relates to the taxation of the profits of associated enterprises and applies the arm's length principle; Articles 10, 11, and 12, which determine the taxation of dividends, interest, and royalties, respectively; and Articles 24, 25, and 26, which contain special provisions relating to non-discrimination, the resolution of disputes, and exchange of information.

10. The Committee on Fiscal Affairs, which is the main tax policy body of the OECD, has issued a number of reports relating to the application of these Articles to MNEs and to others. The Committee has encouraged the acceptance of common interpretations of these Articles, thereby reducing the risk of inappropriate taxation and providing satisfactory means of resolving problems arising from the interaction of the laws and practices of different countries.

11. In applying the foregoing principles to the taxation of MNEs, one of the most difficult issues that has arisen is the establishment for tax purposes of appropriate transfer prices. Transfer prices are the prices at which an enterprise transfers physical goods and intangible property or provides services to associated enterprises. For purposes of these Guidelines, an "associated enterprise" is an enterprise that satisfies the conditions set forth in Article 9, sub-paragraphs 1a) and 1b) of the OECD Model Tax Convention. Under these conditions, two enterprises are associated if one of the enterprises participates directly or indirectly in the management, control, or capital of the other or if "the same persons participate directly or indirectly in the management, control, or capital" of both enterprises (i.e. if both enterprises are under common control). The issues discussed in these Guidelines also arise in the treatment of permanent establishments as discussed in the *Report on the Attribution of Profits to Permanent Establishments* that was adopted by the OECD Council in July 2010, which supersedes the OECD Report *Model Tax Convention: Attribution of Income to Permanent Establishments* (1994). Some relevant discussion may also be found in the OECD Report *International Tax Avoidance and Evasion* (1987).

12. Transfer prices are significant for both taxpayers and tax administrations because they determine in large part the income and expenses, and therefore taxable profits, of associated enterprises in different tax jurisdictions. Transfer pricing issues originally arose in transactions between associated enterprises operating within the same tax jurisdiction. The domestic issues are not considered in these Guidelines, which focus on the international aspects of transfer pricing. These international aspects are more difficult to deal with because they involve more than one tax jurisdiction and therefore any adjustment to the transfer price in one

jurisdiction implies that a corresponding change in another jurisdiction is appropriate. However, if the other jurisdiction does not agree to make a corresponding adjustment the MNE group will be taxed twice on this part of its profits. In order to minimise the risk of such double taxation, an international consensus is required on how to establish for tax purposes transfer prices on cross-border transactions.

13. These Guidelines are intended to be a revision and compilation of previous reports by the OECD Committee on Fiscal Affairs addressing transfer pricing and other related tax issues with respect to multinational enterprises. The principal report is *Transfer Pricing and Multinational Enterprises* (1979) (the "1979 Report") which was repealed by the OECD Council in 1995. Other reports address transfer pricing issues in the context of specific topics. These reports are *Transfer Pricing and Multinational Enterprises -- Three Taxation Issues* (1984) (the "1984 Report"), and *Thin Capitalisation* (the "1987 Report"). A list of amendments made to these Guidelines is included in the Foreword.

14. These Guidelines also draw upon the discussion undertaken by the OECD on the proposed transfer pricing regulations in the United States [see the OECD Report *Tax Aspects of Transfer Pricing within Multinational Enterprises: The United States Proposed Regulations* (1993)]. However, the context in which that Report was written was very different from that in which these Guidelines have been undertaken, its scope was far more limited, and it specifically addressed the United States proposed regulations.

15. OECD member countries continue to endorse the arm's length principle as embodied in the OECD Model Tax Convention (and in the bilateral conventions that legally bind treaty partners in this respect) and in the 1979 Report. These Guidelines focus on the application of the arm's length principle to evaluate the transfer pricing of associated enterprises. The Guidelines are intended to help tax administrations (of both OECD member countries and non-member countries) and MNEs by indicating ways to find mutually satisfactory solutions to transfer pricing cases, thereby minimising conflict among tax administrations and between tax administrations and MNEs and avoiding costly litigation. The Guidelines analyse the methods for evaluating whether the conditions of commercial and financial relations within an MNE satisfy the arm's length principle and discuss the practical application of those methods. They also include a discussion of global formulary apportionment.

16. OECD member countries are encouraged to follow these Guidelines in their domestic transfer pricing practices, and taxpayers are encouraged to follow these Guidelines in evaluating for tax purposes whether their transfer pricing complies with the arm's length principle. Tax

Chapter I

The Arm's Length Principle

A. Introduction

1.1 This Chapter provides a background discussion of the arm's length principle, which is the international transfer pricing standard that OECD member countries have agreed should be used for tax purposes by MNE groups and tax administrations. The Chapter discusses the arm's length principle, reaffirms its status as the international standard, and sets forth guidelines for its application.

1.2 When independent enterprises transact with each other, the conditions of their commercial and financial relations (e.g. the price of goods transferred or services provided and the conditions of the transfer or provision) ordinarily are determined by market forces. When associated enterprises transact with each other, their commercial and financial relations may not be directly affected by external market forces in the same way, although associated enterprises often seek to replicate the dynamics of market forces in their transactions with each other, as discussed in paragraph 1.5 below. Tax administrations should not automatically assume that associated enterprises have sought to manipulate their profits. There may be a genuine difficulty in accurately determining a market price in the absence of market forces or when adopting a particular commercial strategy. It is important to bear in mind that the need to make adjustments to approximate arm's length conditions arises irrespective of any contractual obligation undertaken by the parties to pay a particular price or of any intention of the parties to minimize tax. Thus, a tax adjustment under the arm's length principle would not affect the underlying contractual obligations for non-tax purposes between the associated enterprises, and may be appropriate even where there is no intent to minimize or avoid tax. The consideration of transfer pricing should not be confused with the consideration of problems of tax fraud or tax avoidance, even though transfer pricing policies may be used for such purposes.

1.3 When transfer pricing does not reflect market forces and the arm's length principle, the tax liabilities of the associated enterprises and the tax revenues of the host countries could be distorted. Therefore, OECD member countries have agreed that for tax purposes the profits of associated enterprises may be adjusted as necessary to correct any such distortions and thereby ensure that the arm's length principle is satisfied. OECD member countries consider that an appropriate adjustment is achieved by establishing the conditions of the commercial and financial relations that they would expect to find between independent enterprises in comparable transactions under comparable circumstances.

1.4 Factors other than tax considerations may distort the conditions of commercial and financial relations established between associated enterprises. For example, such enterprises may be subject to conflicting governmental pressures (in the domestic as well as foreign country) relating to customs valuations, anti-dumping duties, and exchange or price controls. In addition, transfer price distortions may be caused by the cash flow requirements of enterprises within an MNE group. An MNE group that is publicly held may feel pressure from shareholders to show high profitability at the parent company level, particularly if shareholder reporting is not undertaken on a consolidated basis. All of these factors may affect transfer prices and the amount of profits accruing to associated enterprises within an MNE group.

1.5 It should not be assumed that the conditions established in the commercial and financial relations between associated enterprises will invariably deviate from what the open market would demand. Associated enterprises in MNEs sometimes have a considerable amount of autonomy and can often bargain with each other as though they were independent enterprises. Enterprises respond to economic situations arising from market conditions, in their relations with both third parties and associated enterprises. For example, local managers may be interested in establishing good profit records and therefore would not want to establish prices that would reduce the profits of their own companies. Tax administrations should keep these considerations in mind to facilitate efficient allocation of their resources in selecting and conducting transfer pricing examinations. Sometimes, it may occur that the relationship between the associated enterprises may influence the outcome of the bargaining. Therefore, evidence of hard bargaining alone is not sufficient to establish that the transactions are at arm’s length.

B. Statement of the arm's length principle

B.1 Article 9 of the OECD Model Tax Convention

1.6 The authoritative statement of the arm's length principle is found in paragraph 1 of Article 9 of the OECD Model Tax Convention, which forms the basis of bilateral tax treaties involving OECD member countries and an increasing number of non-member countries. Article 9 provides:

> [Where] conditions are made or imposed between the two [associated] enterprises in their commercial or financial relations which differ from those which would be made between independent enterprises, then any profits which would, but for those conditions, have accrued to one of the enterprises, but, by reason of those conditions, have not so accrued, may be included in the profits of that enterprise and taxed accordingly.

By seeking to adjust profits by reference to the conditions which would have obtained between independent enterprises in comparable transactions and comparable circumstances (i.e. in "comparable uncontrolled transactions"), the arm's length principle follows the approach of treating the members of an MNE group as operating as separate entities rather than as inseparable parts of a single unified business. Because the separate entity approach treats the members of an MNE group as if they were independent entities, attention is focused on the nature of the transactions between those members and on whether the conditions thereof differ from the conditions that would be obtained in comparable uncontrolled transactions. Such an analysis of the controlled and uncontrolled transactions, which is referred to as a "comparability analysis", is at the heart of the application of the arm's length principle. Guidance on the comparability analysis is found in Section D below and in Chapter III.

1.7 It is important to put the issue of comparability into perspective in order to emphasise the need for an approach that is balanced in terms of, on the one hand, its reliability and, on the other, the burden it creates for taxpayers and tax administrations. Paragraph 1 of Article 9 of the OECD Model Tax Convention is the foundation for comparability analyses because it introduces the need for:

- A comparison between conditions (including prices, but not only prices) made or imposed between associated enterprises and those which would be made between independent enterprises, in order to determine whether a re-writing of the accounts for the purposes of

calculating tax liabilities of associated enterprises is authorised under Article 9 of the OECD Model Tax Convention (see paragraph 2 of the Commentary on Article 9); and

- A determination of the profits which would have accrued at arm's length, in order to determine the quantum of any re-writing of accounts.

1.8 There are several reasons why OECD member countries and other countries have adopted the arm's length principle. A major reason is that the arm's length principle provides broad parity of tax treatment for members of MNE groups and independent enterprises. Because the arm's length principle puts associated and independent enterprises on a more equal footing for tax purposes, it avoids the creation of tax advantages or disadvantages that would otherwise distort the relative competitive positions of either type of entity. In so removing these tax considerations from economic decisions, the arm's length principle promotes the growth of international trade and investment.

1.9 The arm's length principle has also been found to work effectively in the vast majority of cases. For example, there are many cases involving the purchase and sale of commodities and the lending of money where an arm's length price may readily be found in a comparable transaction undertaken by comparable independent enterprises under comparable circumstances. There are also many cases where a relevant comparison of transactions can be made at the level of financial indicators such as mark-up on costs, gross margin, or net profit indicators. Nevertheless, there are some significant cases in which the arm's length principle is difficult and complicated to apply, for example, in MNE groups dealing in the integrated production of highly specialised goods, in unique intangibles, and/or in the provision of specialised services. Solutions exist to deal with such difficult cases, including the use of the transactional profit split method described in Chapter II, Part III of these Guidelines in those situations where it is the most appropriate method in the circumstances of the case.

1.10 The arm's length principle is viewed by some as inherently flawed because the separate entity approach may not always account for the economies of scale and interrelation of diverse activities created by integrated businesses. There are, however, no widely accepted objective criteria for allocating between associated enterprises the economies of scale or benefits of integration resulting from group membership. The issue of possible alternatives to the arm's length principle is discussed in Section C below.

OECD Transfer Pricing Guidelines for Multinational Enterprises and Tax Administrations

The *OECD Transfer Pricing Guidelines for Multinational Enterprise and Tax Administrations* provide guidance on the application of the "arm's length principle", which is the international consensus on transfer pricing, i.e. on the valuation for tax purposes of cross-border transactions between associated enterprises. In a global economy where multinational enterprises (MNEs) play a prominent role, transfer pricing continues to be high on the agenda of tax administrations and taxpayers alike. Governments need to ensure that the taxable profits of MNEs are not artificially shifted out of their jurisdiction and that the tax base reported by MNEs in their country reflects the economic activity undertaken therein. For taxpayers, it is essential to limit the risks of economic double taxation that may result from a dispute between two countries on the determination of the arm's length remuneration for their cross-border transactions with associated enterprises.

This 2017 edition of the *OECD Transfer Pricing Guidelines* incorporates the substantial revisions made in 2016 to reflect the clarifications and revisions agreed in the 2015 BEPS Reports on Actions 8-10 *Aligning Transfer pricing Outcomes with Value Creation* and on Action 13 *Transfer Pricing Documentation and Country-by-Country Reporting*. It also includes the revised guidance on safe harbours approved in 2013 which recognises that properly designed safe harbours can help to relieve some compliance burdens and provide taxpayers with greater certainty. Finally, this edition also contains consistency changes that were made to the rest of the *OECD Transfer Pricing Guidelines*. The *OECD Transfer Pricing Guidelines* were approved by the OECD Council in their original version in 1995.

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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

[X] ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended August 31, 2010

[ ] TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from _____ to _____

Commission file number 000-50720

Raptor Pharmaceutical Corp.

(Exact name of registrant as specified in its charter)

Delaware	**86-0883978**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)

9 Commercial Blvd., Suite 200, Novato, CA 94949
(Address of principal executive offices)

(415) 382-8111
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	**Name of Each Exchange on Which Registered**
Common Stock, $.001 par value	**The NASDAQ Capital Market**
Preferred Share Purchase Rights	

Securities registered under Section 12(g) of the Act:

None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☐ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act:

Large accelerated filer ☐ Accelerated filer ☐ Non-accelerated filer ☐ (Do not check if a smaller reporting company) Smaller reporting company ☒

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act.) Yes ☐ No ☒

Indicate the number of shares outstanding of each of the registrant's classes of common stock, as of the latest practicable date: 30,213,378 shares common stock, par value $0.001, outstanding as of November 5, 2010. The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant as of February 26, 2010 (the last business day of the registrant's most recently completed second quarter) was $44.2 million.

The documents incorporated by reference are as follows:

None.

RAPTOR PHARMACEUTICAL CORP.

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PART I
FORWARD-LOOKING STATEMENTS

In this Annual Report on Form 10-K, in other filings with the Securities and Exchange Commission, or the SEC, and in press releases and other public statements by our officers throughout the year, we make or will make statements that plan for or anticipate the future. These "forward-looking statements," within the meaning of the Private Securities Litigation Reform Act of 1995, include statements about our future business plans and strategies, as well as other statements that are not historical in nature. These forward-looking statements are based on our current expectations.

In some cases, these statements can be identified by the use of terminology such as "believes," "expects," "anticipates," "plans," "may," "might," "will," "could," "should," "would," "projects," "anticipates," "predicts," "intends," "continues," "estimates," "potential," "opportunity" or the negative of these terms or other comparable terminology. All such statements, other than statements of historical facts, including our financial condition, future results of operations, projected revenues and expenses, business strategies, operating efficiencies or synergies, competitive positions, growth opportunities for existing intellectual properties, technologies, products, plans, and objectives of management, markets for our securities, and other matters, are about us and our industry that involve substantial risks and uncertainties and constitute forward-looking statements for the purpose of the safe harbor provided by Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. Such forward-looking statements, wherever they occur, are necessarily estimates reflecting the best judgment of our senior management on the date on which they were made, or if no date is stated, as of the date of the filing made with the SEC in which such statements were made. You should not place undue reliance on these statements, which only reflect information available as of the date that they were made. Our business' actual operations, performance, development and results might differ materially from any forward-looking statement due to various known and unknown risks, uncertainties, assumptions and contingencies, including those described in the section titled "Risk Factors," and including, but not limited to, the following:

- our need for, and our ability to obtain, additional funds;
- uncertainties relating to clinical trials and regulatory reviews;
- our dependence on a limited number of therapeutic compounds;
- the early stage of the products we are developing;
- the acceptance of any of our future products by physicians and patients;
- competition and dependence on collaborative partners;
- loss of key management or scientific personnel;
- our ability to obtain adequate intellectual property protection and to enforce these rights;
- our ability to avoid infringement of the intellectual property rights of others; and
- the other factors and risks described under the section captioned "Risk Factors," as well as other factors not identified therein.

Although we believe that the expectations reflected in the forward-looking statements are reasonable, the factors discussed in this Annual Report on Form 10-K, in other filings with the SEC and in press releases and other public statements by our officers throughout the year, could cause actual results or outcomes to differ materially and/or adversely from those expressed in any forward-looking statements made by us or on our behalf, and therefore we cannot guarantee future results, levels of activity, performance or achievements and you should not place undue reliance on any such forward-looking statements. We cannot give you any assurance that such forward-looking statements will prove to be accurate and such forward-looking events may not occur. In light of the significant uncertainties inherent in such forward-looking statements, you should not regard the inclusion of this information as a representation by us or any other person that the results or conditions described in those statements or our objectives and plans will be achieved.

All subsequent forward-looking statements attributable to us or any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to herein. Unless required by U.S. federal securities laws and the rules and regulations of the SEC, we do not undertake any obligation and disclaim any intention to update or release publicly any revisions to these forward-looking statements after the date of this Annual Report on Form 10-K to reflect later events or circumstances or to reflect the occurrence of unanticipated events or any other reason.

ITEM 1: BUSINESS

All discussions in this Annual Report on Form 10-K regarding our common stock, our stock price, our stock options and warrants to purchase our common stock have been converted to their equivalent post-merger number shares and equivalent post-merger stock prices and exercises prices. See page 3 for further discussion about our Reverse Merger with Raptor Pharmaceuticals Corp.

Overview

We believe that we are building a balanced pipeline of drug candidates that may expand the reach and benefit of existing therapeutics. Our product portfolio includes both candidates from our proprietary drug targeting platforms and in-licensed and acquired product candidates.

Our current pipeline includes three clinical development programs which we are actively developing. We also have three other clinical-stage product candidates, for which we are seeking business development partners but are not actively developing, and we have four preclinical product candidates we are developing, three of which are based upon our proprietary drug-targeting platforms.

Clinical Development Programs

Our three active clinical development programs are based on an existing therapeutic that we are reformulating for potential improvement in safety and/or efficacy and for application in new disease indications. These clinical development programs include the following:

- DR Cysteamine for the potential treatment of nephropathic cystinosis, or cystinosis, a rare genetic disorder;
- DR Cysteamine for the potential treatment of non-alcoholic steatohepatitis, or NASH, a metabolic disorder of the liver; and
- DR Cysteamine for the potential treatment of Huntington's Disease, or HD.

Other Clinical-Stage Product Candidates

We have three clinical-stage product candidates for which we are seeking partners:

- Convivia™ for the potential management of acetaldehyde toxicity due to alcohol consumption by individuals with aldehyde dehydrogenase, or ALDH2 deficiency, an inherited metabolic disorder; and
- Tezampanel and NGX426, non-opioids for the potential treatment of migraine, acute pain, and chronic pain.

Preclinical Product Candidates

Our preclinical platforms consist of targeted therapeutics, which we are developing for the potential treatment of multiple indications, including liver diseases, neurodegenerative diseases and breast cancer. These preclinical platforms include the following:

- Our receptor-associated protein, or RAP, platform consists of: HepTide™ for the potential treatment of primary liver cancer and other liver diseases; and NeuroTrans™ to potentially deliver therapeutics across the blood-brain barrier for treatment of a variety of neurological diseases.

- Our mesoderm development protein, or Mesd, platform consists of WntTide™ for the potential treatment of breast cancer.

We are also examining our glutamate receptor antagonists, tezampanel and NGX426, for the potential treatment of thrombosis disorder.

Future Activities

Over the next 12 months, we plan to conduct research and development activities based upon our DR Cysteamine clinical programs and continued development of our preclinical product candidates. We also plan to seek business development partners for our Convivia™ product candidate and Tezampanel and NGX426. We may also develop future in-licensed technologies and acquired technologies. A brief summary of our primary objectives in the next 12 months for our research and development activities is provided in the section titled "Management's Discussion and Analysis of Financial Condition and Results of Operations." There can be no assurances

that our research and development activities will be successful. In addition, if we do not raise additional funds, we may not be able to continue as a going concern.

Strategic Acquisitions

Reverse Merger with Raptor Pharmaceuticals Corp., or RPC

In July 2009, we, and our then wholly-owned subsidiary ECP Acquisition, Inc., a Delaware corporation, or merger sub, entered into an Agreement and Plan of Merger and Reorganization, or the 2009 Merger Agreement, with Raptor Pharmaceuticals Corp., a Delaware corporation, or RPC. On September 29, 2009, on the terms and subject to the conditions set forth in the 2009 Merger Agreement, merger sub was merged with and into RPC and RPC survived such merger as our wholly-owned subsidiary. This merger is referred to herein as the 2009 Merger. Immediately prior to the 2009 Merger and in connection therewith, we effected a 1-for-17 reverse stock split of our common stock and changed our corporate name to "Raptor Pharmaceutical Corp."

As of immediately following the effective time of the 2009 Merger, RPC's stockholders (as of immediately prior to such 2009 Merger) owned approximately 95% of our outstanding common stock and our stockholders (as of immediately prior to such 2009 Merger) owned approximately 5% of our outstanding common stock, in each case without taking into account any of our or RPC's shares of common stock, respectively, that were issuable pursuant to outstanding options or warrants of ours or RPC, respectively, outstanding as of the effective time of the 2009 Merger. Although RPC became our wholly-owned subsidiary, RPC was the "accounting acquirer" in the 2009 Merger and its board of directors and officers manage and operate the combined company. Our common stock currently trades on the NASDAQ Capital Market under the ticker symbol, "RPTP."

Purchase of Convivia™

In October 2007, prior to the 2009 Merger, RPC purchased certain assets of Convivia, Inc., or Convivia, including intellectual property, know-how and research reports related to a product candidate targeting liver ALDH2 deficiency, a genetic metabolic disorder. RPC hired Convivia's chief executive officer and founder, Thomas E. (Ted) Daley, as the President of its clinical development division. In exchange for the assets related to the ALDH2 deficiency program, what we now call Convivia™, RPC issued to Convivia 46,625 shares of our common stock, an additional 46,625 shares of our common stock to a third party in settlement of a convertible loan between the third party and Convivia, and another 8,742 shares of our common stock in settlement of other obligations of Convivia. Mr. Daley, as the former sole stockholder of Convivia, may earn additional shares of our common stock based on certain triggering events or milestones related to the development of the Convivia assets. In addition, Mr. Daley may earn cash bonuses based on the same triggering events pursuant to his employment agreement. In January 2008, Mr. Daley earned a $30,000 cash bonus pursuant to his employment agreement as a result of the milestone of our execution of a formulation agreement for manufacturing Convivia™ with Patheon. In March 2008, RPC issued to Mr. Daley 23,312 shares of our common stock pursuant to the Convivia purchase agreement as a result of the milestone of our execution of an agreement to supply us with the active pharmaceutical ingredient for Convivia™ and two $10,000 cash bonuses pursuant to his employment agreement for reaching his six-month and one-year employment anniversaries. In October 2008, RPC issued to Mr. Daley 23,312 shares of our common stock valued at $27,000 and a $30,000 cash bonus as a result of fulfilling a clinical milestone. In July 2010, we issued 11,656 shares of our restricted common stock valued at $35,551and paid a $10,000 cash bonus to Mr. Daley as a result of the execution of the license agreement with Uni Pharma for the development of Convivia™ in Taiwan.

Purchase of DR Cysteamine

In December 2007, prior to the 2009 Merger, through a merger between Encode Pharmaceuticals, Inc., or Encode, and Raptor Therapeutics, RPC purchased certain assets, including the clinical development and commercial rights to DR Cysteamine. Under the terms of and subject to the conditions set forth in the merger agreement, RPC issued 802,946 shares of our common stock to the stockholders of Encode, or Encode Stockholders, options, or Encode Options, to purchase up to, in the aggregate, 83,325 shares of our common stock to the optionholders of Encode, or Encode Optionholders, and warrants, or Encode Warrants, to purchase up to, in the aggregate, 256,034 shares of our common stock to the warrantholders of Encode, or Encode Warrantholders, and together with the Encode Stockholders and Encode Optionholders, referred to herein collectively as the Encode Securityholders, as of the date of such agreement. The Encode Securityholders are eligible to receive up to an additional 559,496 shares of our common stock, Encode Options and Encode Warrants to purchase our common stock in the aggregate based on certain triggering events related to regulatory approval of DR Cysteamine, an Encode product program, if completed within the five year anniversary date of the merger agreement.

As a result of the Encode merger, we received the exclusive worldwide license to DR Cysteamine, referred to herein as the License Agreement, developed by clinical scientists at the University of California at San Diego, or UCSD, School of Medicine. In consideration of the grant of the license, we are obligated to pay an annual maintenance fee of $15,000 until we begin commercial sales of any products developed pursuant to the License Agreement. In addition to the maintenance fee, we are obligated to pay during the life of the License Agreement: milestone payments ranging from $20,000 to $750,000 for orphan indications and from $80,000 to $1,500,000 for non-orphan indications upon the occurrence of certain events, if ever; royalties on commercial net sales from products developed pursuant to the

License Agreement ranging from 1.75% to 5.5%; a percentage of sublicense fees ranging from 25% to 50%; a percentage of sublicense royalties; and a minimum annual royalty commencing the

year we begin commercially selling any products pursuant to the License Agreement, if ever. Under the License Agreement, we are obligated to fulfill predetermined milestones within a specified number of years ranging from 0.75 to 6 years from the effective date of the License Agreement, depending on the indication. In addition, we are obligated, among other things, to spend annually at least $200,000 for the development of products (which we satisfied, as of August 31, 2010 and 2009 by spending approximately $6.2 million and $4.1 million, respectively, on such programs) pursuant to the License Agreement. To-date, we have accrued $470,000 in milestone payments to UCSD based upon the initiation of clinical trials in cystinosis and in NASH. To the extent that we fail to perform any of our obligations under the License Agreement, UCSD may terminate the license or otherwise cause the license to become non-exclusive.

Company History

Corporate Structure

We were initially incorporated in Nevada on July 29, 1997 as Axonyx Inc. In October 2006, Axonyx Inc. and its then-wholly-owned subsidiary completed a reverse merger, business combination with TorreyPines Therapeutics, Inc., reincorporated in Delaware and changed our corporate name to "TorreyPines Therapeutics, Inc."

On September 29, 2009, we and a wholly-owned subsidiary completed a reverse merger, business combination with RPC pursuant to which RPC became our wholly-owned subsidiary. Immediately prior to such time, we changed our corporate name to "Raptor Pharmaceutical Corp." After such merger, our common stock began trading on the NASDAQ Capital Market and currently trades under the ticker symbol "RPTP." This merger is referred to herein as the 2009 Merger. Immediately prior to the 2009 Merger and in connection therewith, we effected a 1-for-17 reverse stock split of our common stock.

RPC was incorporated in the State of Nevada on April 1, 2002 under the name of Highland Clan Creations Corp., or HCCC. On June 9, 2006, HCCC merged with RPC which was incorporated on May 5, 2006 in Delaware. As a result, HCCC was reincorporated from the State of Nevada to the State of Delaware and changed its corporate name to "RPC". HCCC was a publicly traded company quoted on the OTC Bulletin Board and upon such merger, its common stock traded on the OTC Bulletin Board under the ticker "RPTP." Our principal executive office is located at 9 Commercial Blvd., Suite 200, Novato, CA 94949. Our phone number is (415) 382-8111.

On May 25, 2006, RPC acquired 100% of the outstanding capital stock of Raptor Discoveries (f/k/a Raptor Pharmaceutical Inc.) (incorporated in Delaware on September 8, 2005), a development-stage research and development company and on June 9, 2006, RPC disposed of its former wholly-owned subsidiary, Bodysentials Health & Beauty Inc., which sold nutritional milkshakes and drinks on the Internet. On August 1, 2007, RPC formed Raptor Therapeutics Inc. (f/k/a Bennu Pharmaceuticals Inc.) as its wholly-owned subsidiary for the purpose of developing clinical-stage drug product candidates through to commercialization.

Financing History of RPC

Initial Investors

On May 25, 2006, in exchange for all of the outstanding common stock of Raptor Pharmaceutical Inc. (now known as Raptor Discoveries Inc.), RPC issued 1,864,987 shares of our common stock to the-then Raptor Pharmaceutical Inc. stockholders including 699,370 shares of our common stock to each of Christopher M. Starr, Ph.D., and Todd C. Zankel, Ph.D., our Chief Executive Officer and Chief Scientific Officer, respectively, 233,123 shares of our common stock to Erich Sager, a member of our board of directors and 233,123 shares of our common stock to an unrelated third party. These initial stockholders of Raptor Pharmaceutical Inc. purchased common stock of Raptor Pharmaceutical Inc. when it was a privately held company for the following amounts of proceeds: Dr. Starr $5,000; Dr. Zankel $5,000; Mr. Sager $100,000 and the unrelated third party $200,000

$5 Million Financing and the 2006 Reverse Merger

Pursuant to an agreement dated March 8, 2006, with HCCC, on May 25, 2006, RPC closed a $5 million financing concurrent with a reverse merger. As part of that agreement, HCCC loaned RPC $0.2 million to be repaid with accrued interest upon the earlier of six months or the closing of the financing. Also, the agreement stated that pending the closing of at least a $3.5 million financing, HCCC would be obligated to issue 186,499 units as fees to a placement agent and $30,000 in commissions to an investment broker. In the financing HCCC sold 1,942,695 units of RPC at $2.57 per unit. Each such unit consisted of one share of our common stock and one common stock purchase warrant exercisable for one share of our common stock at $2.57 per share. The warrants were exercisable for 18 months and expired on November 25, 2007. Gross proceeds from the financing were $5 million and net proceeds after the repayment of

the $0.2 million loan plus interest and the deduction of commissions and legal fees totaled approximately $4.6 million. Prior to the warrants expiring, RPC received $3,895,000 in gross proceeds from the

exercise of warrants in exchange for 1,513,359 shares of our common stock.

Issuance of Common Stock Pursuant to Stock Option Exercises

Since inception, we and RPC have received $72,722 from the exercise of stock options resulting in the issuance of 41,262 shares of common stock. Our common stock outstanding as of November 5, 2010 was 30,213,378 shares.

RPC's 2008 and 2009 Private Placements and Warrant Exchange

During May and June 2008, prior to the 2009 Merger, RPC, issued an aggregate of 4,662,468 units of its securities, each unit comprised of one share of our common stock and one warrant to purchase one half of one share of our common stock, at a unit purchase price of $2.15 per unit, in a private placement with various accredited investors. The warrants, exercisable for two years from closing of such private placement, as initially issued, entitled such investors to purchase up to an aggregate of 2,331,234 shares of RPC's common stock at an exercise price of $3.22 per share during the first year and $3.86 per share during the second year. In connection with this private placement, RPC issued placement agents warrants to purchase in the aggregate 489,559 shares of our common stock at an exercise price of $2.36 per share for a five year term and it paid to such placement agents cash fees totaling $700,000. Such placement agent warrants contained a cashless (net exercise) feature that allows its holders, under certain circumstances, to exercise such warrants without making any cash payment. Of the placement agents compensated, Limetree Capital was issued warrants to purchase 438,890 shares of our common stock and was paid cash commissions of $627,550. Erich Sager, one of our board members, serves on the board of directors of Limetree Capital and is a founding partner thereof.

In July 2009, prior to the 2009 Merger, RPC closed a warrant exchange offer with those investor-warrant holders who were holders of the warrants to purchase its common stock issued in connection with its May and June 2008 private placement, as described above, of the right to exchange such warrants and subscribe for new warrants to purchase shares of RPC's common stock at an exercise price of $1.29 per share (to the extent such new warrants were exercised (in whole or in part) on or before July 17, 2009). Pursuant to such warrant exchange, new warrants were exercised for an aggregate amount of 2,031,670 shares of our common stock which resulted in aggregate proceeds to RPC of $2,614,500.

In August 2009, prior to the 2009 Merger, RPC issued an aggregate of 1,738,226 units of our securities, each unit comprised of one share of our common stock and one warrant to purchase one half of one share of our common stock, at a unit purchase price of $1.37 per unit, in a private placement with various accredited investors. The warrants, exercisable for two years from closing of such private placement, as initially issued, entitled such investors to purchase up to an aggregate of 869,113 shares of our common stock at an exercise price of $2.57 per share during the first year and $3.22 per share during the second year. In connection with this private placement, RPC issued Limetree Capital, the placement agent in such private placement, warrants to purchase in the aggregate 129,733 shares of our common stock at an exercise price of $1.50 per share for a five year term and it paid to such placement agent cash fees totaling $59,360. Such placement agent warrants contained a cashless (net exercise) feature that allows its holders, under certain circumstances, to exercise such warrants without making any cash payment.

We filed a registration statement with the SEC, covering the resale of 5,557,865 shares of our common stock, including common stock issuable upon the exercise of the warrants, on October 13, 2009. Such registration statement covers certain of our common stock as described above.

Post-Merger Financings

Registered Direct Offering

On December 17, 2009, we entered into a Placement Agent Agreement with Ladenburg Thalmann & Co. Inc., or Ladenburg, as placement agent relating to the issuance and sale to the Direct Offering Investors (as defined below) pursuant to a registered direct offering, or the Direct Offering, of up to 3,747,558 units, or the Units, consisting of (i) 3,747,558 shares of our common stock, (ii) warrants to purchase an aggregate of up to 1,873,779 shares of our common stock (and the shares of common stock issuable from time to time upon exercise of such warrants), or the Series A Warrants, and (iii) warrants to purchase an aggregate of up to 1,873,779 shares of our common stock (and the shares of common stock issuable from time to time upon exercise of such warrants), or the Series B Warrants, and collectively with the Series A Warrants we refer to as Investor Warrants.

Ladenburg received a placement fee equal to 6.5% of the gross cash proceeds to us from the Direct Offering of the Units or $487,183 (excluding any consideration that may be paid in the future upon exercise of the Warrants), a warrant to purchase up to an aggregate of 74,951 shares of our common stock at $2.50 per share (valued at approximately $52,000 using the following Black-Scholes pricing model assumptions: risk-free interest rate 2.23%; expected term 5 years and annual volatility 49.28%) and

$25,000 in out-of-pocket accountable expenses. The warrant issued to Ladenburg has the same terms and conditions as the Investor Warrants except that the exercise price is 125% of the public offering price per share or $2.50 per share, and the expiration date is five years from the effective date of that certain shelf registration statement on Form S-3 (Registration No. 333-162374) which was declared effective by the SEC on November 5, 2009.

In connection with the Direct Offering, following execution of the Placement Agent Agreement, we also entered into a definitive securities purchase agreement, or the Direct Offering Purchase Agreement, dated as of December 17, 2009, with 33 investors set forth on the signature pages thereto, collectively referred to as Direct Offering Investors, with respect to the Direct Offering of the Units, whereby, on an aggregate basis, the Direct Offering Investors agreed to purchase 3,747,558 Units for a negotiated purchase price of $2.00 per Unit, amounting to gross proceeds of approximately $7.5 million and estimated net proceeds after commissions and expenses of approximately $6.2 million. Each Unit consists of one share of our common stock, one Series A Warrant exercisable for 0.5 of a share of our common stock and one Series B Warrant exercisable for 0.5 of a share of our common stock. The shares of our common stock and the Warrants were issued separately. The Series A Warrants are exercisable during the period beginning one hundred eighty (180) days after the date of issue and ending on the fifth (5th) anniversary of the date of issue. The Series B Warrants are exercisable during the period beginning one hundred eighty (180) days after the date of issue and ending on the eighteen (18) month anniversary of the date of issue. The Investor Warrants have a per share exercise price of $2.45. The Series A Warrants were valued at $1.3 million (using the following Black-Scholes pricing model assumptions: risk-free interest rate 2.23%; expected term 5 years and annual volatility 49.28%) and the Series B Warrants were valued at $0.5 million (using the following Black-Scholes pricing model assumptions: risk-free interest rate 0.56%; expected term 18 months and annual volatility 49.28%). Based on the underlying terms of the Investor Warrants and Placement Agent Warrants, the Investor Warrants are classified as liability on our consolidated financial statements.

Equity Line Facility with Lincoln Park Capital Fund, LLC, or LPC

On April 16, 2010, we executed a purchase agreement, or the LPC Purchase Agreement, and a registration rights agreement, or the LPC Registration Rights Agreement, with LPC. Under the LPC Purchase Agreement, LPC is obligated to purchase from us up to $15 million of our common stock, from time to time over a twenty-five (25) month period. The issuance of our common stock to LPC under the LPC Purchase Agreement is exempt from registration under the Securities Act in reliance on Section 4(2) of the Securities Act, as the transaction did not involve a public offering.

Pursuant to the LPC Registration Rights Agreement, we filed a registration statement on April 23, 2010 with the SEC, for 4.5 million shares of our common stock covering the shares that have been issued or may be issued to LPC under the LPC Purchase Agreement. The registration statement was declared effective on May 7, 2010. Thereafter, over approximately 25 months, generally we have the right to direct LPC to purchase up to $15,000,000 of our common stock in amounts up to $100,000 as often as every two business days under certain conditions. We can also accelerate the amount of our common stock to be purchased under certain circumstances. No sales of shares may occur at a purchase price below $1.50 per share. The purchase price of the shares will be based on the market prices of our shares at the time of sale as computed under the LPC Purchase Agreement without any fixed discount. We may at any time in our sole discretion terminate the LPC Purchase Agreement without fee, penalty or cost upon one business days notice. We issued 145,033 shares of our common stock to LPC as a commitment fee for entering into the agreement, and we are obligated to issue up to 217,549 shares pro rata as LPC purchases up to $15,000,000 of our common stock as directed by us.

The 4.5 million shares that we registered consist of 4,137,418 shares that we have or may sell to LPC, 145,033 shares we issued as a commitment fee, and 217,549 shares that we have or are obligated to issue to LPC as a commitment fee pro rata as up to $15 million of our common stock is purchased by LPC.

Cumulatively, as of November 5, 2010, we have sold approximately 2.2 million shares under the equity line, raising approximately $4.9 million in gross proceeds to us. See the section titled “Purchase of Equity Securities and Affiliated Purchasers” in the Annual Report on Form 10-K for additional details. We may direct LPC to purchase up to an additional $10.1 million of shares of our common stock under the LPC Purchase Agreement over the next 21 months, generally in amounts of up to $100,000 every 2 business days. The selling price of our common stock to LPC will have to average at least $5.14 per share for us to receive the maximum proceeds of $15 million under the LPC Purchase Agreement. Assuming a purchase price of $1.50 per share (the minimum price of the common stock) and the purchase by LPC of the 1,966,620 shares left under the LPC Purchase Agreement plus the proceeds from the 2,170,798 shares purchased by LPC to-date, proceeds to us would only be approximately $7.8 million unless we choose to register more than 4,137,418 shares for sale to LPC under the LPC Purchase Agreement, which, subject to the approval of our board of directors, we have the right, but not the obligation, to do. In the event we elect to issue more than the 4.5 million shares of our common stock registered under a certain registration statement with the SEC, we must first register under the Securities Act, any additional shares we may elect to sell to LPC before we can sell such additional shares, which could cause substantial dilution to our stockholders. In addition, in the event that we decide to issue more than 4.5 million

shares, i.e., greater than 19.99% of our outstanding shares of common stock as of the date of the LPC Purchase Agreement, we would first be required to seek stockholder approval in order to be in compliance with the NASDAQ Capital Market rules.

2010 Private Placement

On August 9, 2010, we entered into a securities purchase agreement with 23 investors set forth on the signature pages thereto (or, the U.S. Investors) and a separate securities purchase agreement with a certain Canadian investor (or, the Canadian Investor and together with the U.S. Investors, the 2010 Private Placement Investors) set forth on the signature pages thereto (or collectively, the 2010 Private Placement Purchase Agreements), for the private placement, or the 2010 Private Placement, of our common stock and warrants to purchase our common stock, at a purchase price of $3.075 per unit, with each unit comprised of one share of common stock and a warrant to purchase one share of common stock. JMP Securities LLC, or the Placement Agent, served as our placement agent in the 2010 Private Placement.

The closing of this private placement occurred on August 12, 2010. We issued and sold an aggregate of 4,897,614 units, comprised of 4,897,614 shares of common stock and warrants to purchase up to 4,897,614 shares of our common stock for gross proceeds of approximately $15.1 million. Each warrant, exercisable for 5 years from August 12, 2010, has an exercise price of $3.075 per share. As the placement agent for the 2010 Private Placement, the Placement Agent was issued one warrant to purchase 97,952 shares of our common stock, paid a cash commission of $978,911 and reimbursed for certain of its expenses incurred in connection with the 2010 Private Placement.

In connection with the 2010 Private Placement, on August 12, 2010, we entered into a registration rights agreement, or the 2010 Private Placement Registration Rights Agreement, with the 2010 Private Placement Investors, pursuant to which we filed with the SEC a registration statement covering the resale of the common stock issued to the 2010 Private Placement Investors under the 2010 Private Placement Purchase Agreements and the shares of common stock that will be issued to the 2010 Private Placement Investors upon exercise of the warrants, including the warrant issued to the Placement Agent. Such registration statement was declared effective on August 31, 2010.

Our securities offered and sold under the 2010 Private Placement Purchase Agreements to the 2010 Private Placement Investors were offered and sold in reliance upon exemptions from registration under the Securities Act in reliance on Section 4(2) of the Securities Act and Rule 506 of Regulation D promulgated thereunder, as transactions by an issuer not involving a public offering.

Proprietary Rights

We purchased from BioMarin Pharmaceutical Inc., or BioMarin, the intellectual property owned by BioMarin for the research and development of the RAP technologies, including two patents, two pending patent applications and two provisional patent applications in review in the U.S., and countries in Europe and Asia and two trademarks for NeuroTrans™. Subsequent to the purchase from BioMarin, we have filed four additional patent applications for our RAP technologies. As of November 10, 2010, we have 16 patent applications under prosecution in the U.S. and internationally. Two of these applications relate to cysteamine, seven relate to our Convivia™ program and the remaining seven cover our RAP platform. Four patents have been allowed in the U.S. relating to our RAP platform: US 7,700,554 expires in 2022; US 7,560,431 expires in 2023; US 7,569,544 expires in 2023 and US 7,829,537 expires in 2023, and another was allowed in Japan, Australia and Europe which expires in 2022. All other applications are awaiting examination in a variety of countries. We also entered into an exclusive worldwide license agreement with Washington University for our Mesd program for the treatment of cancer and bone diseases. We fund the prosecution of a patent application covering this technology, which entered national phase in the U.S. and internationally in November 2009. In December 2007, we acquired an exclusive worldwide license agreement to pending patent applications from UCSD relating to our DR Cysteamine program. In March 2008, we amended our license with UCSD to add exclusive worldwide rights to develop DR Cysteamine for the potential treatment of NASH. Through the 2009 Merger, we have a license from Eli Lilly & Co. for the intellectual property related to tezampanel and NGX426 for pain indications and a license of tezampanel and NGX426 for the treatment of thrombotic disorder from JHU. We fund the prosecution of a patent covering this technology, which entered national phase in the U.S. in August 2009. In June 2010, we acquired an exclusive worldwide license to two issued patents related to the treatment of Huntington's Disease and other neurological disorders, from the Weizmann Institute of Science in Israel and Niigata University in Japan. These two patents, which expire in 2019, cover the use of transglutaminase inhibitors, a class of molecules chemically similar to cysteamine.

Regulatory Exclusivities

Orphan Drug Designation

We have been granted access to an Orphan Drug Designation from the U.S. Food and Drug Administration, or FDA, for use of DR Cysteamine to potentially treat cystinosis and the use of Cysteamine to potentially treat HD and Batten Disease. The Orphan Drug Act of 1983 generally provides incentives, including marketing exclusivity and tax benefits, to companies that undertake development and marketing of products to treat relatively rare diseases, which are defined as diseases for which fewer than 200,000 persons in the U.S. would be likely to receive the treatment. A drug that receives orphan drug status may receive up to seven years of exclusive marketing in the U.S. for that indication. Equivalent European regulations may give us ten years of marketing exclusivity for that indication in Europe. DR Cysteamine has been granted Orphan Drug Designation by the FDA and the European Medicines Agency, or EMA. If we fail to maintain orphan drug exclusivity for some of our drug product candidates, our competitors may sell products to treat the same conditions and our results of operations and revenues will be affected.

Competition

Cystinosis

The only pharmaceutical product currently approved by the FDA and the EMA, to treat cystinosis that we are aware of is Cystagon® (rapid release cysteamine bitartrate capsules), marketed in the U.S. by Mylan Pharmaceuticals, and by Recordati and Swedish Orphan International in markets outside of the U.S. Cystagon® was approved by FDA in 1994 and is the standard of care for cystinosis treatment.

While we believe that our DR Cysteamine formulation will be well received in the market due to what we believe will be reduced dose frequency and improved tolerability, if we receive marketing approval, we anticipate that Cystagon® will remain a well-established competitive product which may retain many patients, especially those for whom the dose schedule and tolerability do not pose significant problems.

We are not aware of any pharmaceutical company with an active program to develop an alternative therapy for cystinosis. There are companies developing and/or marketing products to treat symptoms and conditions related to, or resulting from cystinosis, but none developing products to treat the underlying metabolic disorder. Academic researchers in the U.S. and Europe are pursuing potential cures for cystinosis through gene therapy and stem cell therapy, as well as pro-drug approaches as alternatives to cysteamine bitartrate for cystinosis treatment. The development timeline for these approaches is many years.

Huntington's Disease

We are not aware of any currently available treatment alternatives for HD, although there are products available such as Haldol, Klonopin and Xenazine to treat uncontrollable movements and mood swings that result from the disease. There are several pharmaceutical companies pursuing potential cures and treatments for HD, as well as numerous academic- and foundation-sponsored research efforts.

Companies with HD product candidates in development include Medivation, Inc., Amarin, Eli Lilly & Co. and Pfizer. Several other companies have drug candidates in preclinical development. Additionally, nutritional supplements including creatinine and coenzyme Q10 have been investigated as potential treatments for HD. The Huntington Study Group sponsors numerous studies of potential therapies for HD, including coenzyme Q10 and the antibiotic minocycline.

NASH

We are not aware of any currently available treatment options for NASH. Weight loss, healthy diet, abstinence from alcohol and increased physical activity are typically suggested to slow the onset of NASH. There are numerous therapies being studied for NASH, including anti-oxidants (Vitamin E, betaine, Moexipril from Univasc), insulin sensitizing agents (Actos® from Takeda Pharmaceuticals for type 2 diabetes, in an ongoing Phase 3 study for NASH sponsored by University of Texas) and drugs to improve blood flow (Trental® from Aventis for treatment of intermittent claudication, which is reported to have failed to meet endpoints in a Phase 2 study for NASH). Gilead Sciences is developing a pan-caspase inhibitor for NASH. Other products being

studied for NASH include Byetta from Amylin, in an ongoing Phase 2/3 study for NASH; and siliphos, or milk thistle, in a UCSD Phase 2 study for NASH.

ALDH2 Deficiency

ALDH2 deficiency affects hundreds of millions of people worldwide and is especially prevalent in East Asian populations. The association of this metabolic disorder with serious health risks, including liver diseases and digestive tract cancers, has been documented in numerous peer-reviewed studies over the last 10 years. We are not aware of any pharmaceutical products currently approved for this indication, either in the U.S. or internationally. However, given the size of the potential patient population and the emerging awareness of this disorder as a serious health risk, we expect there are or will be other pharmaceutical companies, especially those with commercial operations in Asian countries, developing products to treat the symptoms of this condition. Many of these competitors may have greater resources, and existing commercial operations in the Asian countries which we expect will be the primary markets for this product.

Additionally, there are non-pharmaceutical products available such as supplements and traditional remedies, especially in some Asian countries, which are claimed to be effective in reducing the symptoms associated with ALDH2 deficiency and other physical reactions to ethanol consumption. Although we are not aware of any study which has demonstrated the efficacy of such non-pharmaceutical alternatives, these products may compete with our ALDH2 deficiency product candidate if it is approved for marketing.

Migraine

Triptans are the most commonly prescribed drugs for the treatment of moderate to severe migraine. There are currently seven triptans approved for use and Imitrex®, marketed by GlaxoSmithKline, dominates the market. Other triptans are: Zomig®, Maxalt®, Amerge®, Frova™, Axert®, and Relpax®. According to PhRMA's 2008 report, Medicines in Development for Neurologic Disorders, there are more than 30 companies seeking to develop compounds to treat migraine and pain disorders or to obtain additional indications to broaden the use of currently approved pain relieving prescription medications. This list includes most of the large pharmaceutical companies such as Abbott Laboratories, AstraZeneca, Eisai, Elan, Eli Lilly, GlaxoSmithKline, Merck, Pfizer, and Wyeth Pharmaceuticals as well as small and mid-sized biotechnology companies.

Pain

In the neuropathic pain market, we would compete with companies such as Pfizer, marketing Neurontin and Lyrica®, and Eli Lilly, marketing Cymbalta® in addition to opioids approved for treating neuropathic pain, off-label uses of products to treat neuropathic pain and generic products. Given the size of the neuropathic pain market, approximately $3.5 billion in 2006 and expected to double by 2016, it is likely that most of the large pharmaceutical companies as well as many biotechnology companies will look to develop compounds to treat neuropathic pain. Since the licensing of tezampanel, Eli Lilly has continued development of more potent and specific molecules (e.g., iGluR5 antagonists) targeting the same receptors as tezampanel and NGX424 and based on the same chemistry (i.e., tetrahydroisoquinoline moiety) as tezampanel and NGX424. Eli Lilly's third generation candidate is currently in Phase 2 studies for osteoarthritis and peripheral neuropathy.

Primary Liver Cancer

Surgical resection of the primary tumor or liver transplantation remains the only curative options for HCC patients. The acute and tragic nature of this aggressive cancer and the widely preserved unmet medical need continues to attract a significant level of interest in finding ways of treating this disease. For example, there are currently over 140 ongoing clinical trials actively recruiting patients with HCC listed in the ClinicalTrials.gov website. Many of these trials are designed to evaluate ways of locally administering chemotherapeutics or various ways of performing surgical resections of the tumors. One drug that was approved in 2007 for treatment of inoperable HCC is currently the standard-of-care for this disease due to its claims of enhancing overall survival time. This enhancement was determined to be minimal in the study population and to be even smaller within the Asian population of inoperable HCC patients. We believe that a number of biotechnology and pharmaceutical companies may have internal programs targeting the development of new therapeutics that may be useful in treating HCC in the future.

Brain Delivery

We believe we will be competing with other pharmaceutical and biotechnology companies that provide, or are attempting to develop product candidates to provide, remedies and treatments for brain and neurodegenerative diseases.

Three approaches are primarily used to solve the problem of reaching the brain with therapeutic compounds:

- Neurosurgery or invasive techniques.
- Pharmacological techniques, which include less than 2% of currently available drugs.
- Physiologically based techniques, such as transcytosis.

Invasive techniques include bone marrow transplants or implants of polymers with drugs imbedded in the material for slow release. These implants extend from the skull surface to deep into brain tissue sites and use a permeation enhancer. Mannitol induced osmotic shock that creates leaks in the blood-brain barrier allowing intravenous administered chemotherapeutics into the brain is used in the treatment of brain tumors, but is not appropriate for administration of drugs for chronic therapies. Companies active in developing treatments based on these invasive technologies include Alza Corporation, Ethypharm, Guilford Pharmaceuticals, Medtronic Inc., Neurotech, and Sumitomo Pharmaceutical.

Other invasive procedures utilize catheter-based delivery of the drug directly into the brain. This technique has proven useful in the treatment of brain tumors, but has not been successful in distributing drugs throughout the entire brain. Amgen Inc. recently conducted clinical trials for the treatment of Parkinson's disease using intrathecal delivery through the use of various catheter/pump techniques.

The physiological route is a popular approach to cross the blood-brain barrier via lipid mediated free diffusion or by facilitated transport. This is the most common strategy used for the development of new neuropharmaceuticals, but has experienced limited success as it requires that the drug have sufficient lipophilic or fat-soluble properties so that it can pass through lipid membranes. The current method of delivery by this route, however, is nonspecific to the brain and side effects are common since most organs are exposed to the drug. Furthermore, many of the potential lipophilic therapeutic molecules are substrates for the blood-brain barrier's multi-drug resistant proteins, which actively transport the therapeutic agent back into the blood. Consequently, large doses need to be used so that sufficient amounts of the drug reach the brain. These high doses can result in significant side effects as the drug is delivered to essentially all tissues of the body, which is extremely inefficient. Companies and organizations that are developing treatments based on various physiological approaches include Angiochem, AramGen Technology, to-BBB, Xenoport Inc., Bioasis, Oregon Health and Science University Neuro-oncology, Xenova Group Ltd., d-Pharm, Neurochem Inc., and Vasogen Inc.

Thrombotic Disorder

A number of anti-platelet drugs are already available on the market. These include the ADP receptor antagonist Plavix, the cyclooxygenase (and hence thromboxane) inhibitor, aspirin, and injectable integrin (IIb/IIIA) blockers such as Integrelin. Each drug has strengths and weaknesses (which predominantly involve excess bleeding). Since anti-thrombotic drugs are a multi-billion dollar market, it is likely that a large number of companies have additional therapies in development.

Because, many of our competitors have greater capital resources and larger overall research and development staffs and facilities, than us, there can be no assurances that we will be successful in competing in the areas discussed above. See the section under "Risk Factors" titled, "If our competitors succeed in developing products and technologies that are more effective than ours, or if scientific developments change our understanding of the potential scope and utility of our drug product candidates, then our technologies and future drug product candidates may be rendered less competitive."

Government Regulations of the Biotechnology Industry

Regulation by governmental authorities in the U.S. and foreign countries is a significant factor in the development, manufacture, and expected marketing of our drug product candidates and in our ongoing research and development activities. The nature and extent to which such regulation will apply to us will vary depending on the nature of any drug product candidates developed. We anticipate that all of our drug product candidates will require regulatory approval by governmental agencies prior to commercialization.

In particular, human therapeutic products are subject to rigorous preclinical and clinical testing and other approval procedures of the FDA and similar regulatory authorities in other countries. Various federal statutes and regulations also govern or influence testing, manufacturing, safety, labeling, storage, and record-keeping related to such products and their marketing. The process of obtaining these approvals and the subsequent compliance with the appropriate federal statutes and regulations requires substantial time and financial resources. Any failure by us or our collaborators to obtain, or any delay in obtaining, regulatory approval could adversely affect the marketing of any of our drug product candidates, our ability to receive product revenues, and our liquidity and capital resources.

The FDA's Modernization Act codified the FDA's policy of granting "fast track" review of certain therapies targeting "orphan" indications and other therapies intended to treat severe or life threatening diseases and having potential to address unmet medical needs. Orphan indications are defined by the FDA as having a prevalence of less than 200,000 patients in the U.S. We anticipate that certain genetic diseases and primary liver cancer which could potentially be treated using our technology could qualify for fast track review under these revised guidelines. There can be no assurances, however, that we will be able to obtain fast track designation and, even with fast track designation, it is not guaranteed that the total review process will be faster or that approval will be obtained, if at all, earlier than would be the case if the drug product candidate had not received fast-track designation.

Before obtaining regulatory approvals for the commercial sale of any of our products under development, we must demonstrate through preclinical studies and clinical trials that the product is safe and efficacious for use in each target indication. The results from preclinical studies and early clinical trials might not be predictive of results that will be obtained in large-scale testing. Our clinical trials might not successfully demonstrate the safety and efficacy of any product candidates or result in marketable products.

In order to clinically test, manufacture, and market products for therapeutic use, we will have to satisfy mandatory procedures and safety and effectiveness standards established by various regulatory bodies. In the U.S., the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act, as amended, and the regulations promulgated thereunder, and other federal and state statutes and regulations govern, among other things, the testing, manufacture, labeling, storage, record keeping, approval, advertising, and promotion of our current and proposed product candidates. Product development and approval within this regulatory framework takes a number of years and involves the expenditure of substantial resources.

The steps required by the FDA before new drug products may be marketed in the U.S. include:

- completion of preclinical studies;
- the submission to the FDA of a request for authorization to conduct clinical trials on an investigational new drug application, or IND, which must become effective before clinical trials may commence;
- adequate and well-controlled Phase 1, Phase 2 and Phase 3 clinical trials to establish and confirm the safety and efficacy of a drug candidate;
- submission to the FDA of a new drug application, or NDA, for the drug candidate for marketing approval; and
- review and approval of the NDA by the FDA before the product may be shipped or sold commercially.

In addition to obtaining FDA approval for each product, each product manufacturing establishment must be registered with the FDA and undergo an inspection prior to the approval of an NDA. Each manufacturing facility and its quality control and manufacturing procedures must also conform and adhere at all times to the FDA's cGMP regulations. In addition to preapproval inspections, the FDA and other government agencies regularly inspect manufacturing facilities for compliance with these requirements. If, as a result of these inspections, the FDA determines that any equipment, facilities, laboratories or processes do not comply with applicable FDA regulations and conditions of product approval, the FDA may seek civil, criminal, or administrative sanctions and/or remedies against us, including the suspension of the manufacturing operations. Manufacturers must expend substantial time, money and effort in the area of production and quality control to ensure full technical compliance with these standards.

Preclinical testing includes laboratory evaluation and characterization of the safety and efficacy of a drug and its formulation. Preclinical testing results are submitted to the FDA as a part of an IND which must become effective prior to commencement of clinical trials. Clinical trials are typically conducted in three sequential phases following submission of an IND. Phase 1 represents the initial administration of the drug to a small group of humans, either patients or healthy volunteers, typically to test for safety (adverse effects), dosage tolerance, absorption, distribution, metabolism, excretion and clinical pharmacology, and, if possible, to gain early evidence of effectiveness. Phase 2 involves studies in a small sample of the actual intended patient population to assess the efficacy of the drug for a specific indication, to determine dose tolerance and the optimal dose range and to gather additional information relating to safety and potential adverse effects. Once an investigational drug is found to have some efficacy and an acceptable safety profile in the targeted patient population, Phase 3 studies are initiated to further establish clinical safety and efficacy of the therapy in a broader sample of the general patient population, in order to determine the overall risk-benefit ratio of the drug and to provide an adequate basis for any physician labeling. During all clinical studies, we must adhere to Good Clinical Practice, or GCP, standards. The results of the research and product development, manufacturing, preclinical studies, clinical studies and related information are submitted in an NDA to the FDA.

The process of completing clinical testing and obtaining FDA approval for a new drug is likely to take a number of years and require the expenditure of substantial resources. If an application is submitted, there can be no assurance that the FDA will review and approve the NDA. Even after initial FDA approval has been obtained, further studies, including post-market studies, might be required to provide additional data on safety and will be required to gain approval for the use of a product as a treatment for clinical indications other than those for which the product was initially tested and approved. Also, the FDA will require post-market reporting and might require surveillance programs to monitor the side effects of the drug. Results of post-marketing programs might limit or expand the further marketing of the products. Further, if there are any modifications to the drug, including changes in indication, manufacturing process, labeling or a change in manufacturing facility, an NDA supplement might be required to be submitted to the FDA.

The rate of completion of any clinical trials will be dependent upon, among other factors, the rate of patient enrollment. Patient enrollment is a function of many factors, including the size of the patient population, the nature of the trial, the availability of alternative therapies and drugs, the proximity of patients to clinical sites and the eligibility criteria for the study. Delays in planned patient enrollment might result in increased costs and delays, which could have a material adverse effect on us.

We do not know whether our IND for future products or the protocols for any future clinical trials will be accepted by the FDA. We do not know if our clinical trials will begin or be completed on schedule or at all. Even if completed, we do not know if these trials will produce clinically meaningful results sufficient to support an application for marketing approval. The commencement of our planned clinical trials could be substantially delayed or prevented by several factors, including:

- a limited number of, and competition for, suitable patients with particular types of disease for enrollment in clinical trials;
- delays or failures in obtaining regulatory clearance to commence a clinical trial;
- delays or failures in obtaining sufficient clinical materials;
- delays or failures in reaching agreement on acceptable clinical trial agreement terms or clinical trial protocols with prospective sites; and
- delays or failures in obtaining Institutional Review Board, or IRB, approval to conduct a clinical trial at a prospective site.

The completion of our clinical trials could also be substantially delayed or prevented by several factors, including:

- slower than expected rates of patient recruitment and enrollment;
- failure of patients to complete the clinical trial;
- unforeseen safety issues;
- lack of efficacy during clinical trials;
- inability or unwillingness of patients or medical investigators to follow our clinical trial protocols;

- inability to monitor patients adequately during or after treatment; and
- regulatory action by the FDA for failure to comply with regulatory requirements.

Failure to comply with applicable FDA requirements may result in a number of consequences that could materially and adversely affect us. Failure to adhere to approved trial standards and GCPs in conducting clinical trials could cause the FDA to place a clinical hold on one or more studies which would delay research and data collection necessary for product approval. Noncompliance with GCPs could also have a negative impact on the FDA's evaluation of an NDA. Failure to adhere to GMPs and other applicable requirements could result in FDA enforcement action and in civil and criminal sanctions, including but not limited to fines, seizure of product, refusal of the FDA to approve product approval applications, withdrawal of approved applications, and prosecution.

Whether or not FDA approval has been obtained, approval of a product by regulatory authorities in foreign countries must be obtained prior to the commencement of marketing of the product in those countries. The requirements governing the conduct of clinical trials and product approvals vary widely from country to country, and the time required for approval might be longer or shorter than that required for FDA approval. Although there are some procedures for unified filings for some European countries, in general, each country at this time has its own procedures and requirements. There can be no assurance that any foreign approvals would be obtained.

In most cases, if the FDA has not approved a drug product candidate for sale in the U.S., the drug product candidate may be exported for sale outside of the U.S. only if it has been approved in any one of the following: the European Union, Canada, Australia, New Zealand, Japan, Israel, Switzerland and South Africa. Specific FDA regulations govern this process.

In addition to the regulatory framework for product approvals, we and our collaborative partners must comply with federal, state, and local laws and regulations regarding occupational safety, laboratory practices, the use, handling and disposition of radioactive materials, environmental protection and hazardous substance control, and other local, state, federal and foreign regulation. All facilities and manufacturing processes used by third parties to produce our drug candidates for clinical use in the United States must conform with cGMPs. These facilities and practices are subject to periodic regulatory inspections to ensure compliance with cGMP requirements. Their failure to comply with applicable regulations could extend, delay, or cause the termination of clinical trials conducted for our drug candidates. The impact of government regulation upon us cannot be predicted and could be material and adverse. We cannot accurately predict the extent of government regulation that might result from future legislation or administrative action.

Medical and Scientific Advisory Board

Our Medical and Scientific Advisory Board members work with our management team in the planning, development and execution of scientific and business strategies. The advisory board is composed of experienced academic and industry leaders with diverse expertise and knowledge in a variety of areas, including drug discovery, translational research, drug development, and business development. The following describes the background of our Medical and Scientific Advisory Board.

Stephen C. Blacklow, M.D., Ph.D. Over the last ten years, Dr. Blacklow's research team has achieved international recognition both for their mechanistic and structural studies of proteins of the LDL receptor family, and for their work on the structure and function of human Notch proteins. Recently, Dr. Blacklow's team determined the structure of a RAP d3- receptor complex by X-ray crystallography. Dr. Blacklow graduated from Harvard College summa cum laude in 1983, and received his M.D. and Ph.D. in bioorganic chemistry from Harvard University in 1991. Dr. Blacklow is a board-certified pathologist and an Associate Professor of Pathology at Harvard Medical School where he is the Director of the Harvard M.D.-Ph.D. program, basic sciences track. He has directed a research laboratory at the Brigham and Women's Hospital, a teaching affiliate of the Harvard Medical School, since 1998, and he will be joining the Department of Cancer Biology at the Dana Farber Cancer Institute in 2010.

Guojun Bu, Ph.D., is a molecular and cell biologist and a leader in the field of the LDL receptor family. Dr. Bu obtained his undergraduate degree from the Beijing Normal University in China. He then studied biochemistry and molecular biology in the Department of Biochemistry at Virginia Tech where he received his Ph.D. Dr. Bu moved to the Washington University School of Medicine for a postdoctoral training in cell biology where he later became a member of the faculty. He is currently Professor of Pediatrics, and of Cell Biology and Physiology in the Department of Neuroscience at the Mayo Clinic in Jacksonville, Florida. Among the numerous awards that he has received, Dr. Bu has been an Established Investigator of the American Heart Association and a recipient of a Zenith Fellows Award from the Alzheimer's Association. He currently serves as an Editorial Board member for the Journal of Biological Chemistry and Journal of Lipid Research, and is the Editor-in-Chief of Molecular Neurodegeneration.

Ranjan Dohil, M.D., is Professor of Pediatrics at the University of California, San Diego, within the Division of Gastroenterology, Hepatology and Nutrition. An interest in childhood acid-peptic disorders led Dr. Dohil to study patients with cystinosis taking cysteamine. He has published the results of a number of studies trying to better understand the pharmacokinetics of cysteamine with the intent of developing a new formulation of cysteamine that would result in an improved quality of life for patients with cystinosis. Dr. Dohil also has a research interest in eosinophilic esophagitis, a condition that over the past few years has increased in incidence. Within this field, his work has led to the development of a treatment that is becoming more widely used. Dr. Dohil undertook his medical training at the University of Wales College of Medicine in Cardiff, U.K. He has served as a physician in many hospitals over his career including the University Hospital of Wales in Cardiff, U.K., the British Columbia's Children's Hospital in Vancouver, Canada and at St. Bartholemew and The London Medical School.

Jerry Schneider, M.D. is Research Professor of Pediatrics and Dean for Academic Affairs Emeritus at the University of California, San Diego (UCSD) School of Medicine. He also serves as a member of the Board of Directors and Chair of the Scientific Review Board for the Cystinosis Research Foundation. Over the course of his distinguished career, Dr. Schneider has been actively involved in the study of metabolic diseases. An expert on the diagnosis and treatment of cystinosis, Dr. Schneider has published over 150 papers on cystinosis and related subjects over the past 40 years. Since 1969 he has been associated with the UCSD School of Medicine in both academic and research capacities. Dr. Schneider earned his M.D. from Northwestern University. He received postgraduate training at Johns Hopkins University, the National Institutes of Health (NIH), and the Centre de Genetique Moleculaire, Gif-sur-Yvette, France. He was also a Guggenheim Fellow and a Fogarty Senior Fellow at the Imperial Cancer Research Fund Laboratories in London, England.

Legal Proceedings

We know of no material, active or pending legal proceedings against us, nor are we involved as a plaintiff in any material proceedings or pending litigation. There are no proceedings in which any of our directors, officers or affiliates, or any registered or beneficial stockholders are an adverse party or have a material interest adverse to us.

Research and Development

We are a research and development company and our plan is to focus our efforts in the discovery, research, preclinical and clinical development of our RAP based platforms, complementary technologies and clinical drug candidates to provide therapies that we believe will be safer, less intrusive, and more effective than current approaches in treating a wide variety of brain disorders and neurodegenerative diseases, genetic disorders and cancer. During the period from September 8, 2005 (inception of Raptor Pharmaceuticals Corp.) to August 31, 2010, we incurred approximately $24.2 million ($9.3 million and $6.6 million for the years ended August 31, 2010 and 2009, respectively) in research and development costs. Please see the section titled, "Management's Discussion and Analysis of Financial Condition and Results of Operations" in this Annual Report on Form 10-K for our planned research and development activities for the twelve months subsequent to August 31, 2010.

Compliance with Environmental Laws

We estimate the annual cost of compliance with environmental laws, comprised primarily of hazardous waste removal, will be approximately $5,000.

Employees

We presently have ten full time employees, including five executives, one scientist, one program director, one clinical operations director, one senior manager in our regulatory department and one senior manager in our finance department. We also have one part-time scientist. Based on our current plan, over the next 12 month period, we anticipate hiring one or two commercial operations specialists in preparation for the commercial launch of DR Cysteamine for cystinosis. We also plan to supplement our human resources needs through consultants and contractors as needed.

Facilities

Our primary offices are located at 9 Commercial Blvd., Suite 200, Novato, CA 94949. Our phone number is (415) 382-8111 and our facsimile number is (415) 382-1368. Our website is located at www.raptorpharma.com.

ITEM 1A: RISK FACTORS

An investment in our common stock involves a high degree of risk. Before investing in our common stock, you should consider carefully the specific risks detailed in this "Risk Factors" section before making a decision to invest in our common stock, together with all of the other information contained in this Annual Report on Form 10-K. If any of these risks occur, our business, results of operations and financial condition could be harmed, the price of our common stock could decline, and you may lose all or part of your investment.

Risks Related to Our Business

If we fail to obtain the capital necessary to fund our operations, our financial results, financial condition and our ability to continue as a going concern will be adversely affected and we will have to delay or terminate some or all of our product development programs.

Our consolidated financial statements as of August 31, 2010 have been prepared assuming that we will continue as a going concern. As of August 31, 2010, we had an accumulated deficit of approximately $40.8 million. We expect to continue to incur losses for the foreseeable future and will have to raise substantial cash to fund our planned operations. Our recurring losses from operations and our stockholders' deficit raise substantial doubt about our ability to continue as a going concern and, as a result, our independent registered public accounting firm included an explanatory paragraph in its report on our consolidated financial statements for the year ended August 31, 2010, with respect to this uncertainty. We will need to generate significant revenue or raise additional capital to continue to operate as a going concern. In addition, the perception that we may not be able to continue as a going concern may cause others to choose not to deal with us due to concerns about our ability to meet our contractual obligations and may adversely affect our ability to raise additional capital.

We believe our cash and cash equivalents as of August 31, 2010 of $16.9 million will be sufficient to meet our obligations into December 2011. We are currently in the process of negotiating strategic partnerships, collaborations and potential equity sales to supplement the funding of our preclinical and clinical programs beyond December 2011. If we are unable to obtain such additional capital when needed, we may be forced to scale down our expenditures.

On August 9, 2010, we entered into the 2010 Private Placement Purchase Agreements with the 2010 Private Placement Investors for the private placement of units comprised of our common stock, and warrants to purchase our common stock, at a purchase price of $3.075 per unit, with each unit comprised of one share of common stock and a warrant to purchase one share of common stock. We issued and sold an aggregate of 4,897,614 units, comprised of an aggregate of 4,897,614 shares of common stock and warrants to purchase up to 4,897,614 shares of our common stock for gross proceeds of approximately $15.1 million. Each warrant, exercisable for 5 years from August 12, 2010, has an exercise price of $3.075 per share. As the placement agent to this private placement, JMP Securities LLC was issued one warrant to purchase 97,952 shares of our common stock, paid a cash commission of $978,911 and reimbursed for certain of its expenses incurred in connection with the 2010 Private Placement. Even with the 2010 Private Placement, in the future, we may need to sell equity or debt securities to raise additional funds. The sale of additional securities is likely to result in additional dilution to our stockholders. Additional financing may not be available in amounts or on terms satisfactory to us or at all. We may be unable to raise additional financing due to a variety of factors, including our financial condition, the status of our research and development programs, and the general condition of the financial markets. If we fail to raise additional financing when needed, we may have to delay or terminate some or all of our research and development programs, our financial condition and operating results may be adversely affected and we may have to scale back our operations.

While we were restricted from selling additional shares of our common stock under the 2010 Private Placement Purchase Agreements until November 10, 2010, we may issue shares in connection with the exercise of warrants and/or stock options, and after the expiration of such "lock-up" period, we may draw on the equity line with LPC. The extent to which we rely on LPC as a source of funding will depend on a number of factors including, the prevailing market price of our common stock and the extent to which we are able to secure working capital from other sources. Specifically, LPC does not have the right nor the obligation to purchase any shares of our common stock on any business days that the purchase price of our common stock is less than $1.50 per share. If obtaining sufficient funding from LPC were to prove unavailable or prohibitively dilutive, and if other sources of funding are available to us, we may determine not to sell shares to LPC under the LPC Purchase Agreement.

If we obtain additional financing, we expect to continue to spend substantial amounts of capital on our operations for the foreseeable future. The amount of additional capital we will need depends on many factors, including:

- the progress, timing and scope of our preclinical studies and clinical trials;
- the time and cost necessary to obtain regulatory approvals;
- the time and cost necessary to develop commercial manufacturing processes, including quality systems, and to build or acquire manufacturing capabilities;
- the time and cost necessary to launch and successfully commercialize our product candidates, once approved;
- the time and cost necessary to respond to technological and market developments; and
- any changes made or new developments in our existing collaborative, licensing and other corporate relationships or any new collaborative, licensing and other commercial relationships that we may establish.

Moreover, our fixed expenses such as rent, collaboration and license payments and other contractual commitments are substantial and will likely increase in the future. These fixed expenses are likely to increase because we expect to enter into:

- additional licenses and collaborative agreements;
- contracts for manufacturing, clinical and preclinical research, consulting, maintenance and administrative services; and
- financing facilities.

We are an early development stage company and have not generated any revenues to date and have a limited operating history. Many of our drug product candidates are in the concept stage and have not undergone significant testing in preclinical studies or any testing in clinical trials. Moreover, we cannot be certain that our research and development efforts will be successful or, if successful, that our drug product candidates will ever be approved for sale or generate commercial revenues. We have a limited relevant operating history upon which an evaluation of our performance and prospects can be made. We are subject to all of the business risks associated with a new enterprise, including, but not limited to, risks of unforeseen capital requirements, failure of drug product candidates either in preclinical testing or in clinical trials, failure to establish business relationships, and competitive disadvantages against larger and more established companies.

The current disruptions in the financial markets could affect our ability to obtain financing on favorable terms (or at all).

The U.S. credit markets have recently experienced historic dislocations and liquidity disruptions which have caused financing to be unavailable in many cases and, even if available, have caused the cost of prospective financings to increase. These circumstances have materially impacted liquidity in the debt markets, making financing terms for borrowers able to find financing less attractive, and in many cases have resulted in the unavailability of certain types of debt financing. Continued uncertainty in the debt and equity markets may negatively impact our ability to access financing on favorable terms or at all. In addition, Federal legislation to deal with the current disruptions in the financial markets could have an adverse affect on our ability to raise other types of financing.

Even if we are able to develop our drug product candidates, we may not be able to receive regulatory approval, or if approved, we may not be able to generate significant revenues or successfully commercialize our products, which would adversely affect our financial results and financial condition and we would have to delay or terminate some or all of our research product development programs.

All of our drug product candidates are at an early stage of development and will require extensive additional research and development, including preclinical testing and clinical trials, as well as regulatory approvals, before we can market them. Since our inception in 1997, and since Raptor Pharmaceuticals Corp. began operations in 2005, both companies have dedicated substantially all of their resources to the research and development of their technologies and related compounds. All of our compounds currently are in preclinical or clinical development, and none have been submitted for marketing approval. Our preclinical compounds may not enter human clinical trials on a timely basis, if at all, and we may not develop any product candidates suitable for commercialization. We cannot predict if or when any of the drug product candidates we intend to develop will be approved for marketing. There are many reasons that we may fail in our efforts to develop our drug product candidates.

These include:

- the possibility that preclinical testing or clinical trials may show that our drug product candidates are ineffective and/or cause harmful side effects;
- our drug product candidates may prove to be too expensive to manufacture or administer to patients;
- our drug product candidates may fail to receive necessary regulatory approvals from the FDA or foreign regulatory authorities in a timely manner, or at all;
- our drug product candidates, if approved, may not be produced in commercial quantities or at reasonable costs;
- our drug product candidates, if approved, may not achieve commercial acceptance;
- regulatory or governmental authorities may apply restrictions to our drug product candidates, which could adversely affect their commercial success; and
- the proprietary rights of other parties may prevent us or our potential collaborative partners from marketing our drug product candidates.

If we fail to develop our drug product candidates, our financial results and financial condition will be adversely affected, we will have to delay or terminate some or all of our research product development programs and may be forced to cease operations.

If we are limited in our ability to utilize acquired or licensed technologies, we may be unable to develop, out-license, market and sell our product candidates, which could cause delayed new product introductions, and/or adversely affect our reputation, any of which could have a material adverse effect on our business, prospects, financial condition, and operating results.

We have acquired and licensed certain proprietary technologies, discussed in the following risk factors, and plan to further license and acquire various patents and proprietary technologies owned by third parties. These agreements are critical to our product development programs. These agreements may be terminated, and all rights to the technologies and product candidates will be lost, if we fail to perform our obligations under these agreements and licenses in accordance with their terms including, but not limited to, our ability to make all payments due under such agreements. Our inability to continue to maintain these technologies could materially adversely affect our business, prospects, financial condition, and operating results. In addition, our business strategy depends on the successful development of these licensed and acquired technologies into commercial products, and, therefore, any limitations on our ability to utilize these technologies may impair our ability to develop, out-license, market and sell our product candidates, delay new product introductions, and/or adversely affect our reputation, any of which could have a material adverse effect on our business, prospects, financial condition, and operating results.

If the purchase or licensing agreements we entered into are terminated, we will lose the right to use or exploit our owned and licensed technologies, in which case we will have to delay or terminate some or all of our research and development programs, our financial condition and operating results will be adversely affected and we may have to cease our operations.

We entered into an asset purchase agreement with BioMarin, for the purchase of intellectual property related to the RAP, technology, a licensing agreement with Washington University for mesoderm development protein, or Mesd, and a licensing agreement with UCSD for DR Cysteamine. BioMarin, Washington University and UCSD may terminate their respective agreements with us upon the occurrence of certain events, including if we enter into certain bankruptcy proceedings or if we materially breach our payment obligations and fail to remedy the breach within the permitted cure periods. Although we are not currently involved in any bankruptcy proceedings or in breach of these agreements, there is a risk that we may be in the future, giving BioMarin, Washington University and UCSD the right to terminate their respective agreements with us. We have the right to terminate these agreements at any time by giving prior written notice. If the BioMarin, Washington University or UCSD agreements are terminated by either party, we would be forced to assign back to BioMarin, in the case of the BioMarin agreement, all of our rights, title and interest in and to the intellectual property related to the RAP technology, would lose our rights to the Mesd technology, in the case of the Washington University agreement and would lose our rights to DR Cysteamine, in the case of UCSD. Under such circumstances, we would have no further right to use or exploit the patents, copyrights or trademarks in those respective technologies. If this happens, we will have to delay or terminate some or all of our research and development programs, our financial condition and operating results will be adversely affected, and we may have to cease our operations. If we lose our rights to the intellectual property related to the RAP technology purchased by us from BioMarin, our agreement with Roche regarding the evaluation of therapeutic delivery across the blood-brain barrier utilizing NeuroTrans™ would likely be terminated and any milestone or royalty payments from Roche to us would thereafter cease to accrue.

If we fail to compete successfully with respect to acquisitions, joint venture and other collaboration opportunities, we may be limited in our ability to develop our drug product candidates.

Our competitors compete with us to attract established biotechnology and pharmaceutical companies or organizations for acquisitions, joint ventures, licensing arrangements or other collaborations. Collaborations include licensing proprietary technology from, and other relationships with, academic research institutions. If our competitors successfully enter into partnering arrangements or license agreements with academic research institutions, we will then be precluded from pursuing those specific opportunities. Since each of these opportunities is unique, we may not be able to find a substitute. Other companies have already begun many drug development programs, which may target diseases that we are also targeting, and have already entered into partnering and licensing arrangements with academic research institutions, reducing the pool of available opportunities.

Universities and public and private research institutions also compete with us. While these organizations primarily have educational or basic research objectives, they may develop proprietary technology and acquire patents that we may need for the development of our drug product candidates. We will attempt to license this proprietary technology, if available. These licenses may not be available to us on acceptable terms, if at all. If we are unable to compete successfully with respect to acquisitions, joint venture and other collaboration opportunities, we may be limited in our ability to develop new products.

If we do not achieve our projected development goals in the time frames we announce and expect, the credibility of our management and our technology may be adversely affected and, as a result, the price of our common stock may decline.

For planning purposes, we estimate the timing of the accomplishment of various scientific, clinical, regulatory and other product development goals, which we sometimes refer to as milestones. These milestones may include the commencement or completion of scientific studies and clinical trials and the submission of regulatory filings.

From time to time, we may publicly announce the expected timing of some of these milestones. All of these milestones will be based on a variety of assumptions. The actual timing of these milestones can vary dramatically compared to our estimates, in many cases for reasons beyond our control. If we do not meet these milestones as publicly announced, our stockholders may lose confidence in our ability to meet these milestones and, as a result, the price of our common stock may decline.

Our product development programs will require substantial additional future funding which could impact our operational and financial condition.

It will take several years before we are able to develop marketable drug product candidates, if at all. Our product development programs will require substantial additional capital to successfully complete them, arising from costs to:

- conduct research, preclinical testing and human studies;
- establish pilot scale and commercial scale manufacturing processes and facilities; and
- establish and develop quality control, regulatory, marketing, sales, finance and administrative capabilities to support these programs.

Our future operating and capital needs will depend on many factors, including:

- the pace of scientific progress in our research and development programs and the magnitude of these programs;
- the scope and results of preclinical testing and human clinical trials;
- our ability to obtain, and the time and costs involved in obtaining regulatory approvals;
- our ability to prosecute, maintain, and enforce, and the time and costs involved in preparing, filing, prosecuting, maintaining and enforcing patent claims;
- competing technological and market developments;
- our ability to establish additional collaborations;
- changes in our existing collaborations;
- the cost of manufacturing scale-up; and
- the effectiveness of our commercialization activities.

We base our outlook regarding the need for funds on many uncertain variables. Such uncertainties include the success of our research initiatives, regulatory approvals, the timing of events outside our direct control such as negotiations with potential strategic partners and other factors. Any of these uncertain events can significantly change our cash requirements as they determine such one-time events as the receipt or payment of major milestones and other payments.

Significant additional funds will be required to support our operations and if we are unable to obtain them on favorable terms, we may be required to cease or reduce further development or commercialization of our drug product programs, to sell some or all of our technology or assets, to merge with another entity or cease operations.

Uncertainties regarding healthcare reform and third-party reimbursement may impair our ability to raise capital, form collaborations and if any of our product candidates become marketable, sell such products.

The continuing efforts of governmental and third-party payers to contain or reduce the costs of healthcare through various means may harm our business. For example, in some foreign markets, the pricing or profitability of healthcare products is subject to government control. In the United States, there have been, and we expect there will continue to be, a number of federal and state proposals to implement similar government control. The implementation or even the announcement of any of these legislative or regulatory proposals or reforms could harm our business if any of our product candidates become marketable by reducing the prices we or our partners are able to charge for our products (if marketable), impeding our ability to achieve profitability, raise capital or form collaborations. In addition, the availability of reimbursement from third-party payers determines, in large part, the demand for healthcare products in the United States and elsewhere. Examples of such third-party payers are government and private insurance plans. Significant uncertainty exists as to the reimbursement status of newly approved healthcare products and third-party payers are increasingly challenging the prices charged for medical products and services. If we succeed in bringing one or more products to the market, reimbursement from third-party payers may not be available or may not be sufficient to allow us to sell such products on a competitive or profitable basis.

If we fail to demonstrate efficacy in our preclinical studies and clinical trials our future business prospects, financial condition and operating results will be materially adversely affected.

The success of our development and commercialization efforts will be greatly dependent upon our ability to demonstrate drug product candidate efficacy in preclinical studies, as well as in clinical trials. Preclinical studies involve testing drug product candidates in appropriate non-human disease models to demonstrate efficacy and safety. Regulatory agencies evaluate these data carefully before they will approve clinical testing in humans. If certain preclinical data reveals potential safety issues or the results are inconsistent with an expectation of the drug product candidate's efficacy in humans, the regulatory agencies may require additional more rigorous testing, before allowing human clinical trials. This additional testing will increase program expenses and extend timelines. We may decide to suspend further testing on our drug product candidates or technologies if, in the judgment of our management and advisors, the preclinical test results do not support further development.

Moreover, success in preclinical testing and early clinical trials does not ensure that later clinical trials will be successful, and we cannot be sure that the results of later clinical trials will replicate the results of prior clinical trials and preclinical testing. The clinical trial process may fail to demonstrate that our drug product candidates are safe for humans and effective for indicated uses. This failure would cause us to abandon a drug product candidate and may delay development of other drug product candidates. Any delay in, or termination of, our preclinical testing or clinical trials will delay the filing of our investigational new drug application, or IND, and new drug application, or NDA, as applicable, with the FDA and, ultimately, our ability to commercialize our drug product candidates and generate product revenues. In addition, some of our clinical trials will involve small patient populations. Because of the small sample size, the results of these early clinical trials may not be indicative of future results. Following successful preclinical testing, drug product candidates will need to be tested in a clinical development program to provide data on safety and efficacy prior to becoming eligible for product approval and licensure by regulatory agencies. From first clinical trial through product approval can take at least eight years, on average in the U.S.

If any of our future clinical development drug product candidates become the subject of problems, including those related to, among others:

- efficacy or safety concerns with the drug product candidates, even if not justified;
- unexpected side-effects;
- regulatory proceedings subjecting the drug product candidates to potential recall;
- publicity affecting doctor prescription or patient use of the drug product candidates;
- pressure from competitive products; or
- introduction of more effective treatments,

our ability to sustain our development programs will become critically compromised. For example, efficacy or safety concerns may arise, whether or not justified, that could lead to the suspension or termination of our clinical programs.

Each clinical phase is designed to test attributes of drug product candidates and problems that might result in the termination of the entire clinical plan can be revealed at any time throughout the overall clinical program. The failure to demonstrate efficacy in our

clinical trials would have a material adverse effect on our future business prospects, financial condition and operating results.

If we do not obtain the support of new, and maintain the support of existing, key scientific collaborators, it may be difficult to establish products using our technologies as a standard of care for various indications, which may limit our revenue growth and profitability and could have a material adverse effect on our business, prospects, financial condition and operating results.

We will need to establish relationships with additional leading scientists and research institutions. We believe that such relationships are pivotal to establishing products using our technologies as a standard of care for various indications. Although we have established a Medical and Scientific Advisory Board and research collaborations, there is no assurance that our Advisory Board members and our research collaborators will continue to work with us or that we will be able to attract additional research partners. If we are not able to maintain existing or establish new scientific relationships to assist in our research and development, we may not be able to successfully develop our drug product candidates.

If the manufacturers upon whom we rely fail to produce in the volumes and quality that we require on a timely basis, or to comply with stringent regulations applicable to pharmaceutical manufacturers, we may face delays in the development and commercialization of, or be unable to meet demand for, our products, if any, and may lose potential revenues.

We do not currently manufacture our drug product candidates and do not currently plan to develop the capacity to do so. The manufacture of pharmaceutical products requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of pharmaceutical products often encounter difficulties in production, particularly in scaling up initial production. These problems include difficulties with production costs and yields, quality control, including stability of the product candidate and quality assurance testing, shortages of qualified personnel, as well as compliance with strictly enforced federal, state and foreign regulations. Our third-party manufacturers and key suppliers may experience manufacturing difficulties due to resource constraints or as a result of labor disputes, unstable political environments at foreign facilities or financial difficulties. If these manufacturers or key suppliers were to encounter any of these difficulties, or otherwise fail to comply with their contractual obligations, our ability to timely launch any potential product candidate, if approved, would be jeopardized.

In addition, all manufacturers and suppliers of pharmaceutical products must comply with current good manufacturing practices, or cGMP, requirements enforced by the FDA, through its facilities inspection program. The FDA is likely to conduct inspections of our third party manufacturer and key supplier facilities as part of their review of any of our NDAs. If our third party manufacturers and key suppliers are not in compliance with cGMP requirements, it may result in a delay of approval, particularly if these sites are supplying single source ingredients required for the manufacture of any potential product. These cGMP requirements include quality control, quality assurance and the maintenance of records and documentation. Furthermore, regulatory qualifications of manufacturing facilities are applied on the basis of the specific facility being used to produce supplies. As a result, if one of the manufacturers that we rely on shifts production from one facility to another, the new facility must go through a complete regulatory qualification and be approved by regulatory authorities prior to being used for commercial supply. Our manufacturers may be unable to comply with these cGMP requirements and with other FDA, state and foreign regulatory requirements. A failure to comply with these requirements may result in fines and civil penalties, suspension of production, suspension or delay in product approval, product seizure or recall, or withdrawal of product approval. If the safety of any quantities supplied is compromised due to a our third party manufacturer’s or key supplier’s failure to adhere to applicable laws or for other reasons, we may not be able to obtain regulatory approval for or successfully commercialize our products.

If we fail to obtain or maintain orphan drug exclusivity for some of our drug product candidates, our competitors may sell products to treat the same conditions and our revenues will be reduced.

As part of our business strategy, we intend to develop some drugs that may be eligible for FDA and European Union, or EU, orphan drug designation. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug intended to treat a rare disease or condition, defined as a patient population of less than 200,000 in the U.S. The company that first obtains FDA approval for a designated orphan drug for a given rare disease receives marketing exclusivity for use of that drug for the stated condition for a period of seven years. Orphan drug exclusive marketing rights may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug. Similar regulations are available in the EU with a 10-year period of market exclusivity.

Because the extent and scope of patent protection for some of our drug products is particularly limited, orphan drug designation is especially important for our products that are eligible for orphan drug designation. For eligible drugs, we plan to rely on the exclusivity period under Orphan Drug Act designation to maintain a competitive position. If we do not obtain orphan drug exclusivity for our drug products that do not have patent protection, our competitors may then sell the same drug to treat the same condition and our revenues will be reduced.

Even though we have obtained orphan drug designation for DR Cysteamine for the potential treatment of nephropathic cystinosis, the potential treatment of HD and the potential treatment of Batten Disease and even if we obtain orphan drug designation for our future drug product candidates, due to the uncertainties associated with developing pharmaceutical products, we may not be the first to obtain marketing approval for any orphan indication. Further, even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs can be approved for the same condition. Even after an orphan drug is approved, the FDA can subsequently approve the same drug for the same condition if the FDA concludes that the later drug is safer, more effective or makes a major contribution to patient care. Orphan drug designation neither shortens the development time or regulatory review time of a drug, nor gives the drug any advantage in the regulatory review or approval process.

The fast-track designation for our drug product candidates, if obtained, may not actually lead to a faster review process and a delay in the review process or in the approval of our products will delay revenue from the sale of the products and will increase the capital necessary to fund these product development programs.

Although we have received Orphan Drug Designations from the FDA as described above, our drug product candidates may not receive an FDA fast-track designation or priority review. Without fast-track designation, submitting an NDA and getting through the regulatory process to gain marketing approval is a lengthy process. Under fast-track designation, the FDA may initiate review of sections of a fast-track drug's NDA before the application is complete. However, the FDA's time period goal for reviewing an application does not begin until the last section of the NDA is submitted. Additionally, the fast-track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process. Under the FDA policies, a drug candidate is eligible for priority review, or review within a six-month time frame from the time a complete NDA is accepted for filing, if the drug candidate provides a significant improvement compared to marketed drugs in the treatment, diagnosis or prevention of a disease. A fast-track designated drug candidate would ordinarily meet the FDA's criteria for priority review. The fast-track designation for our drug product candidates, if obtained, may not actually lead to a faster review process and a delay in the review process or in the approval of our products will delay revenue from the sale of the products and will increase the capital necessary to fund these product development programs.

Because the target patient populations for some of our products are small, we must achieve significant market share and obtain high per-patient prices for our products to achieve profitability.

Our clinical development of DR Cysteamine targets diseases with small patient populations, including nephropathic cystinosis and HD. If we are successful in developing DR Cysteamine and receive regulatory approval to market DR Cysteamine for a disease with a small patient population, the per-patient prices at which we could sell DR Cysteamine for these indications are likely to be relatively high in order for us to recover our development costs and achieve profitability. We believe that we will need to market DR Cysteamine for these indications worldwide to achieve significant market penetration of this product.

We may not be able to market or generate sales of our products to the extent anticipated.

Assuming that we are successful in developing our drug product candidates and receive regulatory clearances to market our products, our ability to successfully penetrate the market and generate sales of those products may be limited by a number of factors, including the following:

- Certain of our competitors in the field have already received regulatory approvals for and have begun marketing similar products in the U.S., the EU, Japan and other territories, which may result in greater physician awareness of their products as compared to ours.
- Information from our competitors or the academic community indicating that current products or new products are more effective than our future products could, if and when it is generated, impede our market penetration or decrease our future market share.
- Physicians may be reluctant to switch from existing treatment methods, including traditional therapy agents, to our future products.
- The price for our future products, as well as pricing decisions by our competitors, may have an effect on our revenues.
- Our future revenues may diminish if third-party payers, including private healthcare coverage insurers and healthcare maintenance organizations, do not provide adequate coverage or reimbursement for our future products.

There are many difficult challenges associated with developing proteins that can be used to transport therapeutics across the blood-brain barrier.

Our RAP technology has a potential clinical use as a drug transporter through the blood-brain barrier. However, we do not know that our technology will work or work safely. Many groups and companies have attempted to solve the critical medical challenge of developing an efficient method of transporting therapeutic proteins from the blood stream into the brain. Unfortunately, these efforts to date have met with little success due in part to a lack of adequate understanding of the biology of the blood-brain barrier and to the enormous scientific complexity of the transport process itself. In the research and development of our RAP technology, we will certainly face many of the same issues that have caused these earlier attempts to fail. It is possible that:

- We or our collaborator/licensee will not be able to produce enough RAP drug product candidates for testing;
- the pharmacokinetics, or where the drug distributes in the body, of our RAP drug product candidates will preclude sufficient binding to the targeted receptors on the blood-brain barrier;
- the targeted receptors are not transported across the blood-brain barrier;
- other features of the blood-brain barrier, apart from the cells, block access molecules to brain tissue after transport across the cells;
- the targeted receptors are expressed on the blood-brain barrier at densities insufficient to allow adequate transport of our RAP drug product candidates into the brain;
- targeting of the selected receptors induces harmful side-effects which prevent their use as drugs; or
- that we or our collaborator/licensee's RAP drug product candidates cause unacceptable side-effects.

Any of these conditions may preclude the use of RAP or RAP fusion compounds from potentially treating diseases affecting the brain.

If our competitors succeed in developing products and technologies that are more effective than our own, or if scientific developments change our understanding of the potential scope and utility of our drug product candidates, then our technologies and future drug product candidates may be rendered less competitive.

We face significant competition from industry participants that are pursuing similar technologies that we are pursuing and are developing pharmaceutical products that are competitive with our drug product candidates. Nearly all of our industry competitors have greater capital resources, larger overall research and development staffs and facilities, and a longer history in drug discovery and development, obtaining regulatory approval and pharmaceutical product manufacturing and marketing than we do. With these additional resources, our competitors may be able to respond to the rapid and significant technological changes in the biotechnology and pharmaceutical industries faster than we can. Our future success will depend in large part on our ability to maintain a competitive position with respect to these technologies. Rapid technological development, as well as new scientific developments, may result in our compounds, drug product candidates or processes becoming obsolete before we can recover any of the expenses incurred to develop them. For example, changes in our understanding of the appropriate population of patients who should be treated with a targeted therapy like we are developing may limit the drug's market potential if it is subsequently demonstrated that only certain subsets of patients should be treated with the targeted therapy.

Our reliance on third parties, such as collaborators, university laboratories, contract manufacturing organizations and contract or clinical research organizations, may result in delays in completing, or a failure to complete, preclinical testing or clinical trials if they fail to perform under our agreements with them.

In the course of product development, we may engage university laboratories, other biotechnology or companies or contract or clinical manufacturing organizations to manufacture drug material for us to be used in preclinical and clinical testing and collaborators and contract or clinical research organizations to conduct and manage preclinical studies and clinical trials. If we engage these organizations to help us with our preclinical and clinical programs, many important aspects of this process have been and will be out of our direct control. If any of these organizations we may engage in the future fail to perform their obligations under our agreements with them or fail to perform preclinical testing and/or clinical trials in a satisfactory manner, we may face delays in completing our clinical trials, as well as commercialization of any of our drug product candidates. Furthermore, any loss or delay in obtaining contracts with such entities may also delay the completion of our clinical trials, regulatory filings and the potential market approval of our drug product candidates.

Companies and universities that have licensed product candidates to us for research, clinical development and marketing are sophisticated competitors that could develop similar products to compete with our products which could reduce our future revenues.

Licensing our product candidates from other companies, universities or individuals does not always prevent them from developing non-identical but competitive products for their own commercial purposes, nor from pursuing patent protection in areas that are competitive

with us. While we seek patent protection for all of our owned and licensed product candidates, our

licensors or assignors who created these product candidates are experienced scientists and business people who may continue to do research and development and seek patent protection in the same areas that led to the discovery of the product candidates that they licensed or assigned to us. By virtue of the previous research that led to the discovery of the drugs or product candidates that they licensed or assigned to us, these companies, universities, or individuals may be able to develop and market competitive products in less time than might be required to develop a product with which they have no prior experience and may reduce our future revenues from such product candidates.

Any product revenues could be reduced by imports from countries where our product candidates are available at lower prices.

Even if we obtain FDA approval to market our potential products in the United States, our sales in the United States may be reduced if our products are imported into the United States from lower priced markets, whether legally or illegally. In the United States, prices for pharmaceuticals are generally higher than in the bordering nations of Canada and Mexico. There have been proposals to legalize the import of pharmaceuticals from outside the United States. If such legislation were enacted, our potential future revenues could be reduced.

The use of any of our drug product candidates in clinical trials may expose us to liability claims.

The nature of our business exposes us to potential liability risks inherent in the testing, manufacturing and marketing of our drug product candidates. While we are in clinical stage testing, our drug product candidates could potentially harm people or allegedly harm people and we may be subject to costly and damaging product liability claims. Some of the patients who participate in clinical trials are already critically ill when they enter a trial. The waivers we obtain may not be enforceable and may not protect us from liability or the costs of product liability litigation. Although we currently carry a $3 million clinical product liability insurance policy, it may not be sufficient to cover future claims. We currently do not have any clinical or product liability claims or threats of claims filed against us.

Our future success depends, in part, on the continued service of our management team.

Our success is dependent in part upon the availability of our senior executive officers, including our Chief Executive Officer, Dr. Christopher M. Starr, our Chief Scientific Officer, Dr. Todd C. Zankel, our Chief Financial Officer, Kim R. Tsuchimoto, Ted Daley, the President of our clinical development subsidiary and Dr. Patrice P. Rioux, Chief Medical Officer of our clinical development subsidiary. The loss or unavailability to us of any of these individuals or key research and development personnel, and particularly if lost to competitors, could have a material adverse effect on our business, prospects, financial condition, and operating results. We have no key-man insurance on any of our employees. There is intense competition for qualified scientists and managerial personnel from numerous pharmaceutical and biotechnology companies, as well as from academic and government organizations, research institutions and other entities. In addition, we will rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development strategy. All of our consultants and advisors will be employed by other employers or be self-employed, and will have commitments to or consulting or advisory contracts with other entities that may limit their availability to us. There is no assurance that we will be able to retain key employees and/or consultants. If key employees terminate their employment, or if insufficient numbers of employees are retained to maintain effective operations, our development activities might be adversely affected, management's attention might be diverted from managing our operations to hiring suitable replacements, and our business might suffer. In addition, we might not be able to locate suitable replacements for any key employees that terminate, or that are terminated from, their employment with us and we may not be able to offer employment to potential replacements on reasonable terms, which could negatively impact our product candidate development timelines and may adversely affect our future revenues and financial condition.

Our success depends on our ability to manage our growth.

If we are able to raise significant additional financing, we expect to continue to grow, which could strain our managerial, operational, financial and other resources. With the addition of our clinical-stage programs and with our plan to in-license and acquire additional clinical-stage product candidates, we will be required to retain experienced personnel in the regulatory, clinical and medical areas over the next several years. Also, as our preclinical pipeline diversifies through the acquisition or in-licensing of new molecules, we will need to hire additional scientists to supplement our existing scientific expertise over the next several years.

Our staff, financial resources, systems, procedures or controls may be inadequate to support our operations and our management may be unable to take advantage of future market opportunities or manage successfully our relationships with third parties if we are unable to adequately manage our anticipated growth and the integration of new personnel.

Our executive offices and laboratory facility are located near known earthquake fault zones, and the occurrence of an earthquake or other catastrophic disaster could cause damage to our facility and equipment, or that of our third-party manufacturers or single-source suppliers, which could materially impair our ability to continue our product development programs.

Our executive offices and laboratory facility are located in the San Francisco Bay Area near known earthquake fault zones and are vulnerable to significant damage from earthquakes. We and the third-party manufacturers with whom we contract and our single-source suppliers of raw materials are also vulnerable to damage from other types of disasters, including fires, floods, power loss and similar events. If any disaster were to occur, our ability to continue our product development programs, could be seriously, or potentially completely impaired. The insurance we maintain may not be adequate to cover our losses resulting from disasters or other business interruptions.

We will incur increased costs as a result of recently enacted and proposed changes in laws and regulations and our management will be required to devote substantial time to comply with such laws and regulations.

We face burdens relating to the recent trend toward stricter corporate governance and financial reporting standards. Legislation or regulations such as Section 404 of the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, as well as other rules implemented by the SEC and NASDAQ, follow the trend of imposing stricter corporate governance and financial reporting standards have led to an increase in the costs of compliance for companies similar to us, including increases in consulting, auditing and legal fees. New rules could make it more difficult or more costly for us to obtain certain types of insurance, including directors' and officers' liability insurance, and we may be forced to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. The impact of these events could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers. Failure to comply with these new laws and regulations may impact market perception of our financial condition and could materially harm our business. Additionally, it is unclear what additional laws or regulations may develop, and we cannot predict the ultimate impact of any future changes in law. Our management and other personnel will need to devote a substantial amount of time to these requirements.

In addition, the Sarbanes-Oxley Act requires, among other things, that we maintain effective internal control over financial reporting and disclosure controls and procedures. In particular, we must perform system and process evaluation and testing of our internal controls over financial reporting to allow management to report on the effectiveness of our internal controls over financial reporting, as required by Section 404 of the Sarbanes-Oxley Act. Our compliance with Section 404 will require that we incur substantial accounting and related expense and expend significant management efforts. In the future, we may need to hire additional accounting and financial staff to satisfy the ongoing requirements of Section 404. Moreover, if we are not able to comply with the requirements of Section 404, or we or our independent registered public accounting firm identifies deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses, the market price of our stock could decline and we could be subject to sanctions or investigations by NASDAQ, the SEC or other regulatory authorities.

We may be required to suspend, repeat or terminate our clinical trials if they do not meet regulatory requirements, the results are negative or inconclusive, or if the trials are not well designed, which may result in significant negative repercussions on our business and financial condition.

Before regulatory approval for any potential product can be obtained, we must undertake extensive clinical testing on humans to demonstrate the tolerability and efficacy of the product, both on our own terms, and as compared to the other principal drugs on the market that have the same therapeutic indication. We cannot provide assurance that we will obtain authorization to permit product candidates that are already in the preclinical development phase to enter the human clinical testing phase. In addition, we cannot provide assurance that any authorized preclinical or clinical testing will be completed successfully within any specified time period by us, or without significant additional resources or expertise to those originally expected to be necessary. We cannot provide assurance that such testing will show potential products to be safe and efficacious or that any such product will be approved for a specific indication. Further, the results from preclinical studies and early clinical trials may not be indicative of the results that will be obtained in later-stage clinical trials. In addition, we or regulatory authorities may suspend clinical trials at any time on the basis that the participants are being exposed to unacceptable health risks.

Completion of clinical tests depends on, among other things, the number of patients available for testing, which is a function of many factors, including the number of patients with the relevant conditions, the nature of the clinical testing, the proximity of patients to clinical testing centers, the eligibility criteria for tests as well as competition with other clinical testing programs involving the same patient profile but different treatments. We will rely on third parties, such as contract research organizations and/or co-operative groups, to assist us in overseeing and monitoring clinical trials as well as to process the clinical results and manage test requests, which may result in delays or failure to complete trials, if the third parties fail to perform or to meet the applicable standards. A failure by us or such third parties to keep to the terms of a product program development for any particular product candidate or to complete the clinical trials for a product candidate in the envisaged time frame could have significant negative repercussions on our business and financial condition.

If we fail to establish and maintain collaborations or if our partners do not perform, we may be unable to develop and commercialize our product candidates, which may adversely affect our future revenues and financial condition.

We have entered into collaborative arrangements with third parties to develop and/or commercialize product candidates. Additional collaborations might be necessary in order for us to fund our research and development activities and third-party manufacturing arrangements, seek and obtain regulatory approvals and successfully commercialize existing and future product candidates. If we fail to maintain the existing collaborative arrangements held by us or fail to enter into additional collaborative arrangements, the number of product candidates from which we could receive future revenues would decline.

Our dependence on collaborative arrangements with third parties will subject us to a number of risks that could harm our ability to develop and commercialize products:

- collaborative arrangements might not be on terms favorable to us;
- disagreements with partners may result in delays in the development and marketing of products, termination of collaboration agreements or time consuming and expensive legal action;
- we cannot control the amount and timing of resources partners devote to product candidates or their prioritization of product candidates, and partners may not allocate sufficient funds or resources to the development, promotion or marketing of our product candidates, or may not perform their obligations as expected;
- partners may choose to develop, independently or with other companies, alternative products or treatments, including products or treatments which compete with ours;
- agreements with partners may expire or be terminated without renewal, or partners may breach collaboration agreements with us;
- business combinations or significant changes in a partner's business strategy might adversely affect that partner's willingness or ability to complete their obligations to us; and
- the terms and conditions of the relevant agreements may no longer be suitable.

We cannot assure you that we will be able to negotiate future collaboration agreements or that those currently in existence will make it possible for us to fulfill our objectives.

We may not complete our clinical trials in the time expected, which could delay or prevent the commercialization of our products, which may adversely affect our future revenues and financial condition.

Although for planning purposes we forecast the commencement and completion of clinical trials, the actual timing of these events can vary dramatically due to factors such as delays, scheduling conflicts with participating clinicians and clinical institutions and the rate of patient enrollment. Clinical trials involving our product candidates may not commence nor be completed as forecasted. In certain circumstances we will rely on academic institutions or clinical research organizations to conduct, supervise or monitor some or all aspects of clinical trials involving our product candidates. We will have less control over the timing and other aspects of these clinical trials than if we conducted them entirely on our own. These trials may not commence or be completed as we expect. They may not be conducted successfully. Failure to commence or complete, or delays in, any of our planned clinical trials could delay or prevent the commercialization of our product candidates and harm our business and may adversely affect our future revenues and financial condition.

If we fail to keep pace with rapid technological change in the biotechnology and pharmaceutical industries, our product candidates could become obsolete, which may adversely affect our future revenues and financial condition.

Biotechnology and related pharmaceutical technology have undergone and are subject to rapid and significant change. We expect that the technologies associated with biotechnology research and development will continue to develop rapidly. Our future will depend in large part on our ability to maintain a competitive position with respect to these technologies. Any compounds, products or processes that we develop may become obsolete before we recover any expenses incurred in connection with developing such products, which may adversely affect our future revenues and financial condition.

If we are unable to protect our proprietary technology, we may not be able to compete as effectively and our business and financial prospects may be harmed.

Where appropriate, we seek patent protection for certain aspects of our technology. Patent protection may not be available for some of the drug product candidates we are developing. If we must spend significant time and money protecting our patents, designing around patents held by others or licensing, potentially for large fees, patents or other proprietary rights held by others, our business and financial prospects may be harmed.

The patent positions of biopharmaceutical products are complex and uncertain.

We own or license patent applications related to certain of our drug product candidates. However, these patent applications do not ensure the protection of our intellectual property for a number of reasons, including the following:

- We do not know whether our patent applications will result in issued patents. For example, we may not have developed a method for treating a disease before others developed similar methods.

- Competitors may interfere with our patent process in a variety of ways. Competitors may claim that they invented the claimed invention prior to us. Competitors may also claim that we are infringing on their patents and therefore cannot practice our technology as claimed under our patents, if issued. Competitors may also contest our patents, if issued, by showing the patent examiner that the invention was not original, was not novel or was obvious. In litigation, a competitor could claim that our patents, if issued, are not valid for a number of reasons. If a court agrees, we would lose that patent. As a company, we have no meaningful experience with competitors interfering with our patents or patent applications.

- Enforcing patents is expensive and may absorb significant time of our management. Management would spend less time and resources on developing drug product candidates, which could increase our operating expenses and delay product programs.

- Receipt of a patent may not provide much practical protection. If we receive a patent with a narrow scope, then it will be easier for competitors to design products that do not infringe on our patent.

- In addition, competitors also seek patent protection for their technology. Due to the number of patents in our field of technology, we cannot be certain that we do not infringe on those patents or that we will not infringe on patents granted in the future. If a patent holder believes our drug product candidate infringes on its patent, the patent holder may sue us even if we have received patent protection for our technology. If someone else claims we infringe on their technology, we would face a number of issues, including the following:

    - Defending a lawsuit takes significant time and can be very expensive.

    - If a court decides that our drug product candidate infringes on the competitor's patent, we may have to pay substantial damages for past infringement.

- A court may prohibit us from selling or licensing the drug product candidate unless the patent holder licenses the patent to us. The patent holder is not required to grant us a license. If a license is available, we may have to pay substantial royalties or grant cross licenses to our patents.

- Redesigning our drug product candidates so we do not infringe may not be possible or could require substantial funds and time.

It is also unclear whether our trade secrets are adequately protected. While we use reasonable efforts to protect our trade secrets, our employees or consultants may unintentionally or willfully disclose our information to competitors. Enforcing a claim that someone else illegally obtained and is using our trade secrets, like patent litigation, is expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the U.S. are sometimes less willing to protect trade secrets. Our competitors may independently develop equivalent knowledge, methods and know-how. We may also support and collaborate in research conducted by government organizations, hospitals, universities or other educational institutions. These research partners may be unwilling to grant us any exclusive

rights to technology or products derived from these collaborations prior to entering into the relationship. If we do not obtain required licenses or rights, we could encounter delays in our product development efforts while

we attempt to design around other patents or even be prohibited from developing, manufacturing or selling drug product candidates requiring these licenses. There is also a risk that disputes may arise as to the rights to technology or drug product candidates developed in collaboration with other parties.

If our agreements with employees, consultants, advisors and corporate partners fail to protect our intellectual property, proprietary information or trade secrets, it could have a significant adverse effect on us.

We have taken steps to protect our intellectual property and proprietary technology, by entering into confidentiality agreements and intellectual property assignment agreements with our employees, consultants, advisors and corporate partners. Such agreements may not be enforceable or may not provide meaningful protection for our trade secrets or other proprietary information in the event of unauthorized use or disclosure or other breaches of the agreements, and we may not be able to prevent such unauthorized disclosure. Monitoring unauthorized disclosure is difficult, and we do not know whether the steps we have taken to prevent such disclosure are, or will be, adequate. Furthermore, the laws of some foreign countries may not protect our intellectual property rights to the same extent as do the laws of the United States.

Risks Related to Our Common Stock

There are a substantial number of shares of our common stock eligible for future sale in the public market, and the issuance or sale of equity, convertible or exchangeable securities in the market, or the perception of such future sales or issuances, could lead to a decline in the trading price of our common stock.

Any issuance of equity, convertible or exchangeable securities, including for the purposes of financing acquisitions and the expansion of our business, may have a dilutive effect on our existing stockholders. In addition, the perceived risk associated with the possible issuance of a large number of shares of our common stock or securities convertible or exchangeable into a large number of shares of our common stock could cause some of our stockholders to sell their common stock, thus causing the trading price of our common stock to decline. Subsequent sales of our common stock in the open market or the private placement of our common stock or securities convertible or exchangeable into our common stock could also have an adverse effect on the trading price of our common stock. If our common stock price declines, it may be more difficult for us to or we may be unable to raise additional capital.

In addition, future sales of substantial amounts of our currently outstanding common stock in the public market, or the perception that such sales could occur, could adversely affect prevailing trading prices of our common stock, and could impair our ability to raise capital through future offerings of equity or equity-related securities. We cannot predict what effect, if any, future sales of our common stock, or the availability of shares for future sales, will have on the trading price of our common stock.

In December 2009, we entered into a definitive securities purchase agreement or the Direct Offering Purchase Agreement, dated as of December 17, 2009, with 33 investors, collectively, the Direct Offering Investors, with respect to the offering of Units, whereby, on an aggregate basis, the Direct Offering Investors agreed to purchase 3,747,558 Units for a negotiated purchase price of $2.00 per Unit for aggregate gross proceeds of approximately $7.5 million. Each Unit consists of one share of our common stock, one Series A Warrant exercisable for 0.5 of a share of our common stock and one Series B Warrant exercisable for 0.5 of a share of our common stock. The Series A Warrants are exercisable during the period beginning on June 20, 2010 and ending on December 22, 2014. The Series B Warrants are exercisable during the period beginning on June 20, 2010 and ending on June 22, 2011. The Investor Warrants have a per share exercise price of $2.45. In connection with this offering we paid a placement agent cash compensation equaled to 6.5% of the gross proceeds or $487,183 plus a five-year warrant at an exercise price of $2.50 per share for the purchase of up to 74,951 shares of our common stock, on the same terms as the investor warrants described above.

In April 2010, we entered into a $15 million equity line facility with LPC, which allows us to sell shares of our common stock every two days if our selling price to LPC is over $1.50 per share. Cumulatively, as of November 5, 2010, we have sold approximately 2.2 million shares under the equity line raising approximately $4.9 million in gross proceeds to us. We plan to continue to utilize, when available and if needed, the equity line to fund our future cash needs which could create additional pressure on our common stock price as LPC resells its shares of our common stock into the market. On April 23, 2010, we filed a registration statement on Form S-1 registering the resale by LPC of up to 4.5 million shares of our common stock that have been issued or may be issued to LPC under the equity line. Such registration statement was declared effective by the SEC on May 7, 2010.

In August 2010, we entered into the 2010 Private Placement Purchase Agreements with the 2010 Private Placement Investors for the private placement of our common stock and warrants to purchase our common stock, at a purchase price of $3.075 per unit, with each unit comprised of one share of common stock and a warrant to purchase one share of common stock. We issued and sold an aggregate of 4,897,614 units, comprised of an aggregate of 4,897,614 shares of common stock and warrants to purchase up to 4,897,614 shares of our

common stock for gross proceeds of approximately $15.1 million. Each warrant, exercisable for 5 years from August 12, 2010, has an exercise price of $3.075 per share.

Our Chief Executive Officer, our Chief Financial Officer and each of the members of our Board of Directors own, in the aggregate, 935,405 shares, or approximately 3% of our outstanding common stock as of November 5, 2010. Sales of a substantial number of shares of our common stock by such officers and directors in the public trading market, whether in a single transaction or a series of transactions, or the perception that these sales may occur, could also have a significant effect on volatility and the trading price of our common stock.

As of November 5, 2010, there were (i) outstanding warrants to purchase 10,236,609 shares of our common stock at a weighted average exercise price of $2.86 per share issued in connection with the transactions described above and other equity issuances, (ii) outstanding options to purchase 1,777,179 shares of our common stock outstanding under our 2010 and 2006 Raptor stock option plans at a weighted-average exercise price of $2.58, (iii) options to purchase 157,667 shares of our common stock outstanding under our TorreyPines Therapeutics stock option plans at a weighted-average exercise price of $106.89 and (iv) 2,153,670 shares of our common stock available for issuance under our 2010 Raptor Pharmaceutical stock option plan. The shares issuable under our stock option plans will be available for immediate resale in the public market. The shares issuable under the warrants are available for immediate resale in the public market. The market price of our common stock could decline as a result of such resales due to the increased number of shares available for sale in the market.

Future milestone payments, as more fully set forth under “Contractual Obligations with Thomas E. Daley (as assignee of the dissolved Convivia, Inc.)” and “Contractual Obligations with Former Encode Securityholders” discussed in certain of our periodic filings with the SEC relating to our acquisition of the Convivia assets and merger with Encode will result in dilution. We may be required to make additional contingent payments of up to 699,369 shares of our common stock, in the aggregate, under the terms of our acquisition of Convivia assets and merger with Encode, based on milestones related to certain future marketing and development approvals obtained with respect to Convivia and Encode product candidates. The issuance of any of these shares will result in further dilution to our existing stockholders.

These stock issuances and other future issuances of common stock underlying unexpired and unexercised warrants have and will result in, significant dilution to our stockholders. In connection with other collaborations, joint ventures, license agreements or future financings that we may enter into in the future, we may issue additional shares of common stock or other equity securities, and the value of the securities issued may be substantial and create additional dilution to our existing and future common stockholders.

Because we do not intend to pay any cash dividends on our common stock, investors will benefit from an investment in our common stock only if it appreciates in value. Investors seeking dividend income or liquidity should not purchase shares of our common stock.

We have not declared or paid any cash dividends on our common stock since our inception. We anticipate that we will retain our future earnings, if any, to support our operations and to finance the growth and development of our business and do not expect to pay cash dividends in the foreseeable future. As a result, the success of an investment in our common stock will depend upon any future appreciation in the value of our common stock. There is no guarantee that our common stock will appreciate in value or even maintain its current price. Investors seeking dividend income or liquidity should not invest in our common stock.

Our stock price is volatile, which could result in substantial losses for our stockholders, and the trading in our common stock may be limited.

Our common stock is quoted on the NASDAQ Capital Market. The trading price of our common stock has been and may continue to be volatile. Our operating performance does and will continue to significantly affect the market price of our common stock. We face a number of risks including those described herein, which may negatively impact the price of our common stock.

The market price of our common stock also may be adversely impacted by broad market and industry fluctuations regardless of our operating performance, including general economic and technology trends. The NASDAQ Capital Market has, from time to time, experienced extreme price and trading volume fluctuations, and the market prices of biopharmaceutical development companies such as ours have been extremely volatile. Market prices for securities of early-stage pharmaceutical, biotechnology and other life sciences companies have historically been particularly volatile and trading in such securities has often been limited. Some of the factors that may cause the market price of our common stock to fluctuate include:

- the results of our current and any future clinical trials of our drug candidates;
- the results of ongoing preclinical studies and planned clinical trials of our preclinical drug candidates;
- the entry into, or termination of, key agreements, including key strategic alliance agreements;
- the results and timing of regulatory reviews relating to the approval of our drug candidates;
- the initiation of, material developments in, or conclusion of litigation to enforce or defend any of our intellectual property rights;
- failure of any of our drug candidates, if approved, to achieve commercial success;
- general and industry-specific economic conditions that may affect our research and development expenditures;
- the results of clinical trials conducted by others on drugs that would compete with our drug candidates;
- issues in manufacturing our drug candidates or any approved products;
- the loss of key employees;
- the introduction of technological innovations or new commercial products by our competitors;
- changes in estimates or recommendations by securities analysts, if any, who cover our common stock;
- future sales of our common stock;
- changes in the structure of health care payment systems; and
- period-to-period fluctuations in our financial results.

Moreover, the stock markets in general have experienced substantial volatility that has often been unrelated to the operating performance of individual companies. These broad market fluctuations may also adversely affect the trading price of our common stock. In the past, following periods of volatility in the market price of a company's securities, stockholders have often instituted class action securities litigation against those companies. Such litigation can result in substantial costs and diversion of management attention and resources, which could significantly harm our profitability and reputation.

The sale of our common stock to LPC may cause dilution and the sale of the shares of common stock acquired by LPC could cause the price of our common stock to decline.

In connection with entering into the LPC Purchase Agreement, we authorized the sale to LPC of up to 4,137,418 shares of our common stock and the issuance of an additional 362,582 shares of our common stock as a commitment fee. The number of shares ultimately offered for sale by LPC is dependent upon the number of shares purchased by LPC under the LPC Purchase Agreement. The purchase price for the common stock to be sold to LPC pursuant to the LPC Purchase Agreement will fluctuate based on the price of our common stock. All 4.5 million shares of our common stock which may be sold by us to LPC under the LPC Purchase Agreement are expected to be freely tradable. Depending upon market liquidity at the time, a sale of shares by LPC at any given time could cause the trading price of our common stock to decline. We can elect to direct purchases by LPC in our sole discretion but no sales to LPC may occur if the purchase price for our common stock under the Purchase Agreement is below $1.50 per share and therefore, LPC may ultimately purchase all or some of the 4,137,418 shares of common stock. As of November 5, 2010, we have sold approximately 2.2 million shares to LPC under the LPC Purchase Agreement. After LPC has acquired such shares, it may sell all, some or none of such shares. Therefore, sales to LPC by us under the LPC Purchase Agreement may result in substantial dilution to the interests of other holders of our common stock. The sale of a substantial number of shares of our common stock, or anticipation of such sales, by LPC could make it more difficult for us to sell equity or equity-related securities in the future at a time and at a price that we might otherwise wish to effect sales.

The sale of our common stock and common stock underlying warrants to the 2010 Private Placement Investors could cause the price of our common stock to decline.

In connection with the 2010 Private Placement, we issued and sold an aggregate of 4,897,614 units, comprised of an aggregate of 4,897,614 shares of common stock and warrants to purchase up to 4,897,614 shares of our common stock. Each warrant, exercisable for 5 years from August 12, 2010, has an exercise price of $3.075 per share. In connection with the 2010 Private Placement, the Placement Agent was issued one warrant, with an exercise price of $3.075 per share, to purchase 97,952 shares of our common stock. The warrant issued to the Placement Agent may not be exercised until the sixth month anniversary of the issuance date of August 12, 2010. The resale of all 9,893,180 shares which have been sold or upon exercise of the warrants may be sold by us to the 2010 Private Placement Investors and the Placement Agent has been registered on a Form S-1, which was declared effective by the SEC on August 31, 2010. Depending upon market liquidity at the time, a sale of shares under this offering at any given time could cause the trading price of our common stock to decline. Sales of our common stock to the 2010 Private Placement Investors and the Placement Agent upon exercise of the warrants they received in connection with 2010 Private Placement by us may result in substantial dilution to the interests of other holders of our common stock. The sale of a substantial number of shares of our common stock or anticipation of sales, by the 2010 Private Placement Investors and the Placement Agent could make it more difficult for us to sell equity or equity-related securities in the future at a time and at a price that we might otherwise wish to effect sales.

Our stock is a penny stock. Trading of our stock may be restricted by the SEC's penny stock regulations and the FINRA's sales practice requirements, which may limit a stockholder's ability to buy and sell our stock.

Our common stock is a penny stock. The SEC has adopted Rule 15g-9 under the Exchange Act which generally defines "penny stock" to be any equity security that has a market price less than $5.00 per share or an exercise price of less than $5.00 per share, subject to certain exceptions. Our securities are covered by the penny stock rules, which impose additional sales practice requirements on broker-dealers who sell to persons other than established customers and institutional accredited investors. The penny stock rules require a broker-dealer, prior to a transaction in a penny stock not otherwise exempt from the rules, to deliver a standardized risk disclosure document in a form prepared by the SEC which provides information about penny stocks and the nature and level of risks in the penny stock market. The broker-dealer also must provide the customer with current bid and offer quotations for the penny stock, the compensation of the broker-dealer and its salesperson in the transaction and monthly account statements showing the market value of each penny stock held in the customer's account. The bid and offer quotations, and the broker- dealer and salesperson compensation information, must be given to the customer orally or in writing prior to effecting the transaction and must be given to the customer in writing before or with the customer's confirmation. In addition, the penny stock rules require that prior to a transaction in a penny stock not otherwise exempt from these rules, the broker-dealer must make a special written determination that the penny stock is a suitable investment for the purchaser and receive the purchaser's written agreement to the transaction. These disclosure requirements may have the effect of reducing the level of trading activity in the secondary market for the stock that is subject to these penny stock rules. Consequently, these penny stock rules may affect the ability of broker-dealers to trade our securities. We believe that the penny stock rules discourage investor interest in and limit the marketability of our common stock.

In addition to the "penny stock" rules promulgated by the SEC, the Financial Industry Regulatory Authority, or FINRA, has adopted rules that require that in recommending an investment to a customer, a broker-dealer must have reasonable grounds for believing that the investment is suitable for that customer. Prior to recommending speculative low priced securities to their non-institutional customers, broker-dealers must make reasonable efforts to obtain information about the customer's financial status, tax status, investment objectives and other information. Under interpretations of these rules, the FINRA believes that there is a high probability that speculative low priced securities will not be suitable for at least some customers. The FINRA requirements make it more difficult for broker-dealers to recommend that their customers buy our common stock, which may limit your ability to buy and sell our stock.

We can issue shares of preferred stock that may adversely affect the rights of a stockholder of our common stock.

Our certificate of incorporation authorizes us to issue up to 15,000,000 shares of preferred stock with designations, rights and preferences determined from time-to-time by our board of directors. Accordingly, our board of directors is empowered, without stockholder approval, to issue preferred stock with dividend, liquidation, conversion, voting or other rights superior to those of stockholders of our common stock.

Anti-takeover provisions under Delaware law, in our stockholder rights plan and in our certificate of incorporation and bylaws may prevent or complicate attempts by stockholders to change the board of directors or current management and could make a third-party acquisition of us difficult.

We are incorporated in Delaware. Certain anti-takeover provisions of Delaware law as currently in effect may make a change in control of our Company more difficult, even if a change in control would be beneficial to the stockholders. Our board of directors has the authority to issue up to 15,000,000 shares of preferred stock, none of which are issued or outstanding. The rights of holders of our

common stock are subject to the rights of the holders of any preferred stock that may be issued. The issuance of preferred stock could make it more difficult for a third-party to acquire a majority of our outstanding voting stock. Our

charter contains provisions that may enable our management to resist an unwelcome takeover attempt by a third party, including: a prohibition on actions by written consent of our stockholders; the fact that stockholder meetings must be called by our board of directors; and provisions requiring stockholders to provide advance notice of proposals. Delaware law also prohibits corporations from engaging in a business combination with any holders of 15% or more of their capital stock until the holder has held the stock for three years unless, among other possibilities, the board of directors approves the transaction. Our board of directors may use these provisions to prevent changes in the management and control of our Company. Also, under applicable Delaware law, our board of directors may adopt additional anti-takeover measures in the future.

We are a party to a stockholder rights plan, also referred to as a poison pill, which is intended to deter a hostile takeover of us by making such proposed acquisition more expensive and less desirable to the potential acquirer. The stockholder rights plan and our certificate of incorporation and bylaws, as amended, contain provisions that may discourage, delay or prevent a merger, acquisition or other change in control that stockholders may consider favorable, including transactions in which stockholders might otherwise receive a premium for their shares. These provisions could limit the price that investors might be willing to pay in the future for shares of our common stock.

ITEM 1B: UNRESOLVED STAFF COMMENTS

None.

ITEM 2: PROPERTIES

In March 2006, we entered into a lease for our executive offices and research laboratory in Novato, California. Base monthly payments were $5,206 per month subject to annual rent increase of between 3% to 5%, based on the Consumer Price Index (“CPI”). In March 2006, we paid $20,207 as a security deposit on this lease. Effective April 1, 2007, we leased additional office space adjoining the existing leased space, increasing our base rent to $9,764 per month without extending the term of the original lease. The original lease allows for one three-year extension at the market rate and up to $18,643 in reimbursement for tenant improvements. In June 2008, our rent increased to $10,215, reflecting a CPI increase of 3% plus an increase in operating costs for the period from April 1, 2008 to March 31, 2009. In September 2008, we executed a lease addendum replacing the one three-year extension with two two-year extensions commencing on April 1, 2009 and renegotiated the first two-year extension base rent to $10,068 with an adjustment after the first year for CPI between 3% (minimum) and 5% (maximum). In January 2010, we entered into a one year lease for administrative offices in San Mateo, California for $2,655 per month. During the years ended August 31, 2010 and 2009 and the cumulative period from September 8, 2005 (inception) to August 31, 2010, we paid $150,536, $128,830, and $518,947, respectively, in rent. We plan to continue to lease administrative offices in San Mateo, California and we plan to expand our Novato office space by approximately 3,100 square feet ($5,309 per month) in January 2011. We anticipate that the expanded space in Novato will be sufficient for the near future.

ITEM 3: LEGAL PROCEEDINGS

We know of no material, active or pending legal proceedings against us, or any of our property, and we are not involved as a plaintiff in any material proceedings or pending litigation. There are no proceedings in which any of our directors, officers or affiliates, or any registered or beneficial stockholders are an adverse party or have a material interest adverse to us.

ITEM 4: (REMOVED AND RESERVED)

PART II

ITEM 5: MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

Market Information

In connection with the closing of the 2009 Merger, our common stock commenced trading on the NASDAQ Capital Market on September 30, 2009, under the ticker symbol "RPTPD" with 18,822,162 shares outstanding. Effective October 27, 2009, our ticker symbol changed to "RPTP." There is no public trading market for our warrants. The closing price for our common stock on November 17, 2010 was $3.52.

The following table sets forth the range of high and low sales prices of our common stock for the quarterly periods indicated, as reported by NASDAQ. Such quotations represent inter-dealer prices without retail mark up, mark down or commission and may not necessarily represent actual transactions.

	High	Low
Year Ended August 31, 2010:		
First Quarter (through September 29)*	$ 7.14	$ 3.23
First Quarter (September 30 – November 30, 2009)	4.90	1.16
Second Quarter (December 1, 2009 – February 28, 2010)	3.30	1.75
Third Quarter (March 1 – May 31, 2010)	3.88	1.41
Fourth Quarter (June 1, 2010 – August 31, 2010)	3.57	2.37
Year Ended August 31, 2009:		
First Quarter *	$ 11.73	$ 2.72
Second Quarter *	5.95	2.72
Third Quarter *	7.65	2.55
Fourth Quarter	11.73	1.19

* Market prices reported have been adjusted to give retroactive effect to material changes resulting from the reverse stock split that occurred immediately prior to the consummation of the 2009 Merger on September 29, 2009 by multiplying the reported sales prices for such periods by 17.

Holders of Record

As of November 5, 2010, there were approximately 83 holders of record of our common stock and 30,213,378 shares of our common stock outstanding, excluding shares held in book-entry form through The Depository Trust Company, and we estimate that the number of beneficial owners of shares of our common stock was approximately 5,400 as of such date. Additionally, on such date, options, held by 64 persons to acquire up to, in the aggregate, 1,934,846 shares, and warrants held by 53 persons to acquire up to, in the aggregate, 10,236,609 shares, of our common stock, were outstanding.

Dividends

We have never declared or paid cash dividends on our common stock and do not anticipate paying any cash dividends on our shares of common stock in the foreseeable future. We expect to retain future earnings, if any, for use in our development activities and the operation of our business. The payment of any future cash dividends will be subject to the discretion of our board of directors and will depend, among other things, upon our results of operations, financial condition, cash requirements, prospects and other factors that our board of directors may deem relevant. Additionally, our ability to pay future cash dividends may be restricted by the terms of any future financing.

Purchase of Equity Securities and Affiliated Purchasers

We have not repurchased any shares of our common stock since inception. For a discussion regarding our unregistered equity issuances during our fiscal year ended August 31, 2010, please refer to the shares issued pursuant to the LPC Purchase Agreement and to the 2010 Private Placement described under the heading, "Post-Merger Financings - Equity Line Facility with Lincoln Park Capital Fund, LLC, or LPC," and "2010 Private Placement", respectively, under Part I, Item 1 to this Annual Report on Form 10-K which discussion is

incorporated herein by reference. The table below reflects all of the shares of our common stock issued pursuant to the LPC Purchase Agreement:

Issuance Date	Number of Shares of Common Stock Issued
April 16, 2010	145,033
May 7, 2010	190,576
May 11, 2010	188,169
May 13, 2010	183,844
May 17, 2010	173,923
May 19, 2010	163,702
May 24, 2010	149,002
May 25, 2010	143,363
May 27, 2010	133,614
June 1, 2010	113,466
June 3, 2010	99,326
June 7, 2010	101,614
June 9, 2010	104,129
June 11, 2010	104,239
June 15, 2010	104,129
June 29, 2010	41,449
July 2, 2010	40,975
July 7, 2010	42,266
July 9, 2010	39,960
July 13, 2010	39,960
July 15, 2010	40,512
July 17, 2010	43,644
	2,386,895

ITEM 6: SELECTED FINANCIAL DATA

Per Item 301(c) of Regulation S-K, information is not required.

ITEM 7: MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

PLAN OF OPERATION

Overview

You should read the following discussion in conjunction with our consolidated financial statements as of August 31, 2010, and the notes to such consolidated financial statements included elsewhere in this Annual Report on Form 10-K. This "Management's Discussion and Analysis of Financial Condition and Results of Operations" section contains forward-looking statements. Please see "Forward-Looking Statements" for a discussion of the uncertainties, risks and assumptions associated with these statements. Our actual results and the timing of certain events could differ materially from those anticipated in these forward-looking statements as a result of certain factors, including those discussed below and elsewhere in this Annual Report on Form 10-K, particularly under the heading "Risk Factors."

Unless otherwise mentioned or unless the context requires otherwise (e.g., our consolidated financial statements as of August 31, 2010, and the notes to such consolidated financial statements included elsewhere in this Annual Report on Form 10-K, or a reference to an event or circumstance that occurred prior to the effective time of the 2009 Merger on September 29, 2009), all references in this Annual Report on Form 10-K to "we," "us," "our," the "Company," "Raptor" and similar references refer to the public company formerly known as TorreyPines Therapeutics, Inc. and now known as Raptor Pharmaceutical Corp., including its wholly-owned direct and indirect subsidiaries (which includes Raptor Pharmaceuticals Corp., Raptor Discoveries Inc., Raptor Therapeutics Inc. and Raptor Pharmaceuticals Europe BV), following the name change and completion of the 2009 Merger. On August 30, 2010, our former wholly-owned subsidiary, TPTX, Inc. was merged into Raptor Therapeutics Inc.

Plan of Operation and Overview

We believe that we are building a balanced pipeline of drug candidates that may expand the reach and benefit of existing therapeutics. Our product portfolio includes both candidates from our proprietary drug targeting platforms and in-licensed and acquired product candidates.

Our current pipeline includes three clinical development programs which we are actively developing. We also have three other clinical-stage product candidates, for which we are seeking business development partners but are not actively developing, and we have four preclinical product candidates we are developing, three of which are based upon our proprietary drug-targeting platforms.

Clinical Development Programs

Our three active clinical development programs are based on an existing therapeutic that we are reformulating for potential improvement in safety and/or efficacy and for application in new disease indications. These clinical development programs include the following:

- DR Cysteamine for the potential treatment of nephropathic cystinosis, or cystinosis, a rare genetic disorder;
- DR Cysteamine for the potential treatment of non-alcoholic steatohepatitis, or NASH, a metabolic disorder of the liver; and
- DR Cysteamine for the potential treatment of Huntington's Disease, or HD, an inherited neurodegenerative disorder.

Other Clinical-Stage Product Candidates

We have three clinical-stage product candidates for which we are seeking partners:

- Convivia™ for the potential management of acetaldehyde toxicity due to alcohol consumption by individuals with aldehyde dehydrogenase, or ALDH2 deficiency, an inherited metabolic disorder; and

- Tezampanel and NGX426, non-opioids for the potential treatment of migraine, acute pain, and chronic pain.

Preclinical Product Candidates

Our preclinical platforms consist of targeted therapeutics, which we are developing for the potential treatment of multiple indications, including liver diseases, neurodegenerative diseases and breast cancer. These preclinical platforms include the following:

- Our receptor-associated protein, or RAP, platform consists of: HepTide™ for the potential treatment of primary liver cancer and other liver diseases; and NeuroTrans™ to potentially deliver therapeutics across the blood-brain barrier for treatment of a variety of neurological diseases.

- Our mesoderm development protein, or Mesd, platform consists of WntTide™ for the potential treatment of breast cancer.

We are also examining our glutamate receptor antagonists, tezampanel and NGX426, for the potential treatment of thrombosis disorder.

Future Activities

Over the next 12 months, we plan to conduct research and development activities based upon our DR Cysteamine clinical programs and continued development of our preclinical product candidates. We also plan to seek new business development partners for our Convivia™ product candidate and Tezampanel and NGX426. We may also develop future in-licensed technologies and acquired technologies. A brief summary of our primary objectives in the next 12 months for our research and development activities is provided below. There can be no assurances that our research and development activities will be successful. In addition, if we do not raise additional funds, we may not be able to continue as a going concern.

Clinical Development Programs

We develop clinical-stage drug product candidates which are: internally discovered therapeutic candidates based on our novel drug delivery platforms and in-licensed or purchased clinical-stage products which may be new chemical entities in mid-to-late stage clinical development, currently approved drugs with potential efficacy in additional indications, and treatments that we could repurpose or reformulate as potentially more effective or convenient treatments for a drug's currently approved indications.

Lead Clinical Development Program: Development of DR Cysteamine for the Potential Treatment of Nephropathic Cystinosis or Cystinosis

Our DR Cysteamine product candidate is a proprietary delayed-release, enteric-coated microbead formulation of cysteamine bitartrate contained in a gelatin capsule. We are investigating DR Cysteamine for the potential treatment of cystinosis.

Immediate-release cysteamine bitartrate, a cystine-depleting agent, is currently the only FDA and the EMA, approved drug to treat cystinosis, a rare genetic disease. Immediate-release cysteamine has been reported to be effective at preventing or delaying kidney failure and other serious health problems in cystinosis patients. However, we believe that patient compliance is challenging due to the requirement for every six-hour dosing and gastrointestinal side effects. Our DR Cysteamine for the potential treatment of cystinosis is designed to mitigate some of these difficulties. It is expected to be dosed twice daily, compared to the current every-six-hour dosing schedule. In addition, DR Cysteamine is designed to pass through the stomach and deliver the drug directly to the small intestine, where it is more easily absorbed into the bloodstream and may result in fewer gastrointestinal side effects.

The EMA and FDA granted orphan drug designation for DR Cysteamine for the treatment of cystinosis in 2010 and 2006, respectively.

In June 2009, we commenced our Phase 2b clinical trial of DR Cysteamine in cystinosis, in which we enrolled nine cystinosis patients with histories of compliance using the currently available immediate-release form of cysteamine bitartrate. The clinical trial, which was conducted at the University of California at San Diego, or UCSD, evaluated safety, tolerability, pharmacokinetics and pharmacodynamics of a single dose of DR Cysteamine in patients. In November 2009, we released the data from the study which indicated improved tolerability and the potential to reduce total daily dosage and administration frequency compared to immediate-release cysteamine bitartrate.

On June 28, 2010, we commenced our Phase 3 clinical trial, designed as a multi-center, randomized, crossover, outpatient study of the safety, tolerability, pharmacokinetics, or PK, and pharmacodynamics, or PD, of every 12-hour DR Cysteamine compared to immediate-release cysteamine bitartrate in cystinosis patients. The design of our Phase 3 clinical trial is a result of discussions with the FDA under a Special Protocol Assessment, or SPA, process by which the FDA provided significant guidance on trial protocol design, clinical endpoints, and statistical analyses. The primary endpoint of our study is the steady-state white blood cell, or WBC, cystine levels of patients taking DR Cysteamine compared to immediate-release cysteamine bitartrate. Secondary endpoints are the safety and tolerability of DR Cysteamine and the comparability of steady-state PK of DR Cysteamine and immediate-release cysteamine bitartrate in cystinosis patients. Our Phase 3 clinical trial is being conducted at nine sites in North America and Europe. We expect to enroll at least 30 patients. Patients who complete the nine-week clinical trial will be offered enrollment into our long-term follow-on study. We anticipate that our Phase 3 clinical trial enrollment will be completed in December 2010. If DR Cysteamine is approved by the FDA, we plan to commercialize DR Cysteamine in the U.S. by ourselves. However, we may enter into marketing partnerships for certain markets outside of the U.S.

Development of DR Cysteamine for the Potential Treatment of Non-Alcoholic Steatohepatitis or NASH

In October 2008, we commenced a clinical trial in collaboration with UCSD to investigate a prototype formulation of DR Cysteamine for the treatment of NASH in juvenile patients. In May 2010, we presented positive Phase 2a clinical trial results from our pilot study of delayed-release cysteamine bitartrate in 11 adolescent patients with NASH, a progressive form of liver disease believed to affect 5% to 11% of the U.S. population. The results were presented at the Digestive Disease Week 2010 conference in New Orleans, Louisiana on May 2, 2010. Our open-label Phase 2a clinical trial was conducted under a collaboration agreement with UCSD at UCSD's General Clinical Research Center. Eligible patients with baseline levels of the liver enzymes alanine transaminase, or ALT, and aspartate aminotransferase, or AST, that were at least twice that of normal levels, were enrolled to receive twice-daily, escalating oral doses of up to 1,000 mg of delayed-release cysteamine bitartrate (a prototype of our DR Cysteamine) for six months, followed by a six-month post-treatment monitoring period.

Patients showed a marked decline in ALT levels during the treatment period with 7 of 11 patients achieving a greater than 50% reduction and 6 of 11 reduced to within normal range. AST levels also saw significant improvements with patients averaging 41% reduction by the end of the treatment phase. The reduction in liver enzymes was largely sustained during the 6 month post-treatment monitoring phase. Other important liver function markers showed positive trends. Levels of cytokeratin 18, a potential marker of disease activity in Non-alcoholic Fatty Liver Disease, or NAFLD, decreased by an average of 45%. Adiponectin levels increased by an average of 35% during the treatment period. Reduced adiponectin levels are thought to be a marker of the pathogenesis and progression of NASH. Body Mass Index, or BMI, did not change significantly during both the treatment and post-treatment phases. Delayed-release cysteamine bitartrate demonstrated a strong, favorable safety profile, with mean gastrointestinal symptom scores of 1.1 at baseline and 0.7 after 6 months of treatment using a rating system in which the maximum score of 14 indicates most severe gastrointestinal symptoms.

There are no currently approved drug therapies for NASH, and patients are limited to lifestyle changes such as diet, exercise and weight reduction to manage the disease. DR Cysteamine may provide a potential treatment option for patients with NASH. Although NASH is most common in insulin-resistant obese adults with diabetes and abnormal serum lipid profiles, its prevalence is increasing among juveniles as obesity rates rise within this patient population. Although most patients are asymptomatic and feel healthy, NASH causes decreased liver function and can lead to cirrhosis, liver failure and end-stage liver disease.

We are currently working with our clinical trial material manufacturer to provide an appropriate formulation of DR Cysteamine for our next potential clinical trial in NASH and are preparing an IND submission in 2011 in anticipation of such clinical trial. Although it is our intention to continue the clinical development of DR Cysteamine in NASH, we are currently not funded for, and therefore do not have a timetable for, the initiation of a Phase 2b clinical trial. We are in early stages of discussions to co-develop or partner the clinical development of DR Cysteamine in NASH.

Development of DR Cysteamine for the Potential Treatment of Huntington's Disease or HD

Huntington's Disease, or HD, is a fatal, inherited degenerative neurological disease affecting about 30,000 people in the U.S. and a comparable number of people in Europe. We are not aware of any treatment for HD other than therapeutics that minimize symptoms such as the uncontrollable movements and mood swings resulting from HD. We are collaborating with a French institution, CHU d' Angers, on a Phase 2 clinical trial investigating DR Cysteamine in HD patients, which began in October 2010. We are providing the clinical trial materials for the study, which is sponsored by CHU d' Angers and funded in part by a grant from the French government. Eight clinical sites in France are being set up by CHU d' Angers for a 96 patient, placebo-controlled, 18-month trial, followed by an open-label trial with all placebo patients rolling onto DR Cysteamine and all non-placebo patients continuing on DR Cysteamine for up to another 18 months. The primary end point of the trial will be based upon the Unified Huntington's Disease Rating Scale, or UHDRS. We were granted Orphan Drug Designation in the U.S. by the FDA for cysteamine as a potential treatment for HD in 2008 and are in the process of applying for Orphan Drug Designation in the E.U.

In June 2010, we acquired an exclusive worldwide license to intellectual property related to the potential treatment of Huntington's Disease from the Weizmann Institute of Science in Israel and Niigata University in Japan. The Weizmann and Niigata patents cover the use of transglutaminase inhibitors, a class of molecules chemically similar to cysteamine, in the potential treatment of Huntington's Disease and other neurological disorders. These patents add to our portfolio of intellectual property related to our programs utilizing DR Cysteamine.

Other Clinical-Stage Product Candidates

We have three clinical-stage product candidates for which we are seeking partners.

Convivia™ for Liver Aldehyde Dehydrogenase Deficiency

Convivia™ is our proprietary oral formulation of 4-methylpyrazole, or 4-MP, intended for the potential treatment of acetaldehyde toxicity resulting from alcohol consumption in individuals with ALDH2 deficiency, which is an inherited disorder of the body's ability to breakdown ethanol, commonly referred to as alcohol intolerance. 4-MP is presently marketed in the U.S. and E.U. in an intravenous form as an anti-toxin. Convivia™ is designed to lower systemic levels of acetaldehyde (a carcinogen) and reduce symptoms, such as tachycardia and flushing, associated with alcohol consumption by ALDH2-deficient individuals.

Convivia™ is a capsule designed to be taken approximately 30 minutes prior to consuming an alcoholic beverage.

In 2008, we completed a Phase 2a dose escalation clinical trial of oral 4-MP with ethanol in ALDH2 deficient patients. The study results demonstrated that the active ingredient in Convivia™ significantly reduced heart palpitations (tachycardia), which are commonly experienced by ALDH2 deficient people who drink, at all dose levels tested. The study also found that the 4-MP significantly reduced peak acetaldehyde levels and total acetaldehyde exposure in a subset of the study participants who possess specific genetic variants of the liver ADH and ALDH2 enzymes. We believe that this subset represents approximately one-third of East Asian populations.

In June 2010, we entered into an exclusive agreement with Uni Pharma Co., Ltd., or Uni Pharma to commercialize Convivia™ in Taiwan. Under terms of the agreement, we will grant to Uni Pharma an exclusive license under all relevant patent applications, trademarks and future patents controlled by us to market Convivia™ in Taiwan, with an option to expand the license to South Korea under the same terms. Uni Pharma will register Convivia™ for drug licensure for existing indications and will conduct a clinical trial and register Convivia™ for acetaldehyde toxicity resulting from ALDH2 deficiency. Uni Pharma will be responsible for marketing and sales activities for the commercialization of Convivia™ in the markets covered under the license agreement. We continue to seek potential partners in other Asian countries to continue clinical development of Convivia™ in those countries.

Tezampanel and NGX426 for the Potential Treatment of Migraine and Pain

Tezampanel and NGX426, the oral prodrug of tezampanel, are what we believe to be first-in-class compounds that may represent novel treatments for both pain and non-pain indications. Tezampanel and NGX426 are receptor antagonists that target and inhibit a specific group of receptors—the AMPA and kainate glutamate receptors—found in the brain and other tissues. While normal glutamate production is essential, excess glutamate production, either through injury or disease, has been implicated in a number of diseases and disorders. Published data show that during a migraine, increased levels of glutamate activate AMPA and kainate receptors, result in the transmission of pain and, in many patients, the development of increased pain sensitivity. By acting at both the AMPA and kainate receptor sites to competitively block the binding of glutamate, tezampanel and NGX426 have the potential to treat a number of diseases

and disorders. These include chronic pain, such as migraine and neuropathic pain, muscle spasticity and a condition known as central sensitization, a persistent and acute sensitivity to pain.

Results of a Phase 2b clinical trial of tezampanel were released in October 2007. In the trial, a single dose of tezampanel given by injection was statistically significant compared to placebo in treating acute migraine headache. This was the sixth Phase 2 trial in which tezampanel has been shown to have analgesic activity. Based on a review of the Phase 2 data, the FDA has agreed that tezampanel may move forward into a Phase 3 program for acute migraine.

In December 2008, results of NGX426 in a human experimental model of cutaneous pain, hyperalgesia and allodynia demonstrated a statistically significant reduction in spontaneous pain, hyperalgesia and allodynia compared to placebo following injections of capsaicin (i.e., chili oil) under the skin. In February 2009, results from a Phase 1 multiple dose trial of NGX426 showed that the compound is safe and well-tolerated in healthy male and female subjects when dosed once daily for five consecutive days.

In November 2009, we announced the presentation of clinical trial data on NGX426 at the 12th International Conference on the Mechanisms and Treatment of Neuropathic Pain. The results of the study led by Mark Wallace, M.D., Professor of Clinical Anesthesiology at the Center for Pain Medicine of the University of California at San Diego, suggested that NGX426 has the potential to be effective in a variety of neuropathic pain states, which are caused by damage to or dysfunction of the peripheral or central nervous system rather than stimulation of pain receptors.

We are currently seeking out-licensing partners for the migraine and pain programs and no development costs will be incurred for further development of these indications.

Preclinical Product Candidates

We are also developing a drug-targeting platform based on the proprietary use of RAP and Mesd. We believe that these proteins may have therapeutic applications in cancer, infectious diseases and neurodegenerative diseases, among others.

These applications are based on the assumption that our targeting molecules can be engineered to bind to a selective subset of receptors with restricted tissue distribution under particular conditions of administration. We believe these selective tissue distributions can be used to deliver drugs to the liver or to other tissues, such as the brain.

In addition to selectively transporting drugs to specific tissues, selective receptor binding constitutes a means by which receptor function might be specifically controlled, either through modulating its binding capacity or its prevalence on the cell surface. Mesd is being engineered for this latter application.

HepTide™ for Hepatocellular Carcinoma or HCC and Other Liver Diseases

Drugs currently used to treat primary liver cancer are often toxic to other organs and tissues. We believe that the pharmacokinetic behavior of RAP (i.e., the determination of the fate or disposition of RAP once administered to a living organism) may diminish the non-target toxicity and increase the on-target efficacy of attached therapeutics.

In preclinical studies of our radio-labeled HepTide™ (a variant of RAP), HepTide™, our proprietary drug-targeting peptide was shown to distribute predominately to the liver. Radio-labeled HepTide™, which was tested in a preclinical research model of HCC at the National Research Council in Winnipeg, Manitoba, Canada, showed 4.5 times more delivery to the liver than the radio-labeled control. Another study of radio-labeled HepTide™ in a non-HCC preclinical model, showed 7 times more delivery to the liver than the radio-labeled control, with significantly smaller amounts of radio-labeled HepTide™ delivery to other tissues and organs.

HCC is caused by the malignant transformation of hepatocytes, epithelial cells lining the vascular sinusoids of the liver, or their progenitors. HepTide™ has shown to bind to lipoprotein receptor-related protein, or LRP1, receptors on hepatocytes. We believe that the pharmacokinetics and systemic toxicity of a number of potent anti-tumor agents may be controlled in this way.

There are additional factors that favor the suitability of RAP as an HCC targeting agent:

- RAP is captured by hepatocytes with efficiency, primarily on first-pass.

- Late-stage HCC is perfused exclusively by the hepatic artery, while the majority of the liver is primarily perfused through the portal vein.

Studies have shown that the RAP receptor, LRP1, is well expressed on human HCC and under-expressed on non-cancerous, but otherwise diseased, hepatocytes. Also, LRP1 expression is maintained on metastasized HCC. These factors will favor delivery of RAP peptide-conjugated anti-tumor agents to tumor cells, whether in the liver or at metastasized sites.

We are evaluating conjugates between HepTide™ and other molecules for testing in vitro and in appropriate preclinical models for the potential treatment of HCC and other liver diseases.

NeuroTrans™ for the Potential Treatment of Diseases Affecting the Brain

Hundreds of known genetic and neurodegenerative diseases affect the brain. Drugs often have difficulty reaching these disease-affected areas because the brain has evolved a protective barrier, commonly referred to as the blood-brain barrier.

Part of the solution to the medical problem of neurodegenerative diseases is the creation of effective brain targeting and delivery technologies. One of the most obvious ways of delivering therapeutics to the brain is via the brain's extensive vascular network. Treating these diseases by delivering therapeutics into the brain in a minimally invasive way, including through a natural receptor mediated transport mechanism called transcytosis, is a vision shared by many researchers and clinicians in the neuroscience and neuromedical fields.

NeuroTrans™ is our proprietary RAP-based technology program to research the delivery of therapeutics across the blood-brain barrier. We believe our NeuroTrans™ platform may provide therapies that will be safer, less intrusive and more effective than current approaches in treating a wide variety of brain disorders.

In preclinical studies, NeuroTrans™ has been conjugated to a variety of protein drugs, including enzymes and growth factors, without interfering with the function of either fusion partner. Studies indicate that radio-labeled NeuroTrans™ may be transcytosed across the blood-brain barrier and that fusions between NeuroTrans™ and therapeutic proteins may be manufactured economically. Experiments conducted in collaboration with Stanford University in 2008 support the NeuroTrans™ peptide's ability to enhance the transport of cargo molecules into the cells that line the blood-brain barrier.

In June 2009, we entered into a collaboration and licensing agreement with F. Hoffman — La Roche Ltd. and Hoffman—La Roche Inc., or Roche, to evaluate therapeutic delivery across the blood-brain barrier utilizing NeuroTrans™. Under the terms of the agreement, Roche has funded studies of select molecules attached to NeuroTrans™. The agreement provides Roche with an exclusive worldwide license to NeuroTrans™ for use in the delivery of diagnostic and therapeutic molecules across the blood-brain barrier. Roche's and our scientists are actively collaborating on the project. We have received an initial upfront payment for the collaboration to cover our portion of the initial studies, and may earn development milestone payments and royalties in exchange for the licensing of NeuroTrans™ to Roche.

WntTide™ for the Potential Treatment of Cancer

Human Mesd is a natural inhibitor of the receptor LRP6. LRP6 has recently been shown to play a role in the progression of some breast tumors. Studies in the laboratory of Professor Guojun Bu, one of our scientific advisors, at the Washington University in St. Louis Medical School support the potential of Mesd and related peptides to target these tumors. These molecules and applications are licensed to us from Washington University.

WntTide™ is our proprietary, Mesd-based peptide that we are developing as a potential therapeutic to inhibit the growth and metastasis of tumors over-expressing LRP5 or LRP6. We have licensed the use of Mesd from Washington University for the potential treatment of cancer and bone density disorders.

In April 2009, Washington University conducted a preclinical study of WntTide™ in a breast cancer model which showed tumor inhibition. The results of this study were presented at the 2nd Annual Wnt Conference in Washington, D.C., in June 2009 and have been published in the peer-reviewed publication, the Proceedings of the National Academy of Sciences, on March 1, 2010. The paper, titled, *"LRP6 Overexpression Defines a Class of Breast Cancer Subtype and Is a Target for Therapy,"* presented results that support the potential efficacy of WntTide™ as a targeted treatment for triple-negative breast cancers, a particularly aggressive and difficult-to-treat indication for recurrent and metastatic disease. Abnormal Wnt activation, found in 40% to 60% of breast cancers, is often associated with triple-negative breast cancers. We are currently evaluating WntTide™ in a preclinical breast cancer model to inhibit the Wnt-signaling pathway designed to block cancers dependent upon signaling through LRP6, as well as other IND enabling studies.

Tezampanel and NGX426 for the Potential Treatment of Thrombotic Disorder

Research conducted at Johns Hopkins University, or JHU, by Craig Morrell, D.V.M., Ph.D., and Charles Lowenstein, M.D. demonstrated the importance of glutamate release in promoting platelet activation and thrombosis. Research shows that platelets treated with an AMPA/kainate receptor antagonist such as tezampanel or NGX426 are more resistant to glutamate-induced aggregation than

untreated platelets. This identifies the AMPA/kainate receptors on platelets targeted by tezampanel or NGX426 as a new antithrombotic target with a different mechanism of action than Plavix®, aspirin or tPA. We have licensed the

intellectual property of Tezampanel and NGX 426 for the treatment of thrombotic disorder from JHU and are currently manufacturing drug product for a Phase 1 clinical trial in collaboration with a university hospital anticipated to commence in mid-calendar 2011.

Other Development Areas

Securing Additional and Complementary Technology Licenses from Others

We plan to establish additional research collaborations with prominent universities and research labs currently working on the development of potential targeting molecules, and to secure licenses from these universities and labs for technology resulting from the collaboration. No assurances can be made regarding our ability to establish such collaborations over the next 12 months, or at all. We intend to focus our in-licensing and product candidate acquisition activities on identifying complementary therapeutics, therapeutic platforms that offer a number of therapeutic targets, and clinical-stage therapeutics based on existing approved drugs in order to create proprietary reformulations to improve safety and efficacy or to expand such drugs' clinical indications through additional clinical trials. We may obtain these products through collaborations, joint ventures or through merger and/or acquisitions with other biotechnology companies.

Strategic Acquisitions

Reverse Merger with Raptor Pharmaceuticals Corp.

In July 2009, we, and our then wholly-owned subsidiary ECP Acquisition, Inc., a Delaware corporation, or merger sub, entered into an Agreement and Plan of Merger and Reorganization, or the 2009 Merger Agreement, with Raptor Pharmaceuticals Corp., a Delaware corporation. On September 29, 2009, on the terms and subject to the conditions set forth in the 2009 Merger Agreement, merger sub was merged with and into Raptor Pharmaceuticals Corp. and Raptor Pharmaceuticals Corp. survived such merger as our wholly-owned subsidiary. This merger is referred to herein as the 2009 Merger. Immediately prior to the 2009 Merger and in connection therewith, we effected a 1-for-17 reverse stock split of our common stock and changed our corporate name to "Raptor Pharmaceutical Corp."

As of immediately following the effective time of the 2009 Merger, Raptor Pharmaceuticals Corp.'s stockholders (as of immediately prior to such 2009 Merger) owned approximately 95% of our outstanding common stock and our stockholders owned approximately 5% of our outstanding common stock, in each case without taking into account any of our or Raptor Pharmaceuticals Corp.'s shares of common stock, respectively, that were issuable pursuant to outstanding options or warrants of ours or Raptor Pharmaceuticals Corp., respectively, outstanding as of the effective time of the 2009 Merger. Although Raptor Pharmaceuticals Corp. became our wholly-owned subsidiary, Raptor Pharmaceuticals Corp. was the "accounting acquirer" in the 2009 Merger and its board of directors and officers manage and operate the combined company. Our common stock currently trades on the NASDAQ Capital Market under the ticker symbol, "RPTP."

Purchase of Convivia™

In October 2007, prior to the 2009 Merger, Raptor Pharmaceuticals Corp. purchased certain assets of Convivia, Inc., or Convivia, including intellectual property, know-how and research reports related to a product candidate targeting liver ALDH2 deficiency, a genetic metabolic disorder. Raptor Pharmaceuticals Corp. hired Convivia's chief executive officer and founder, Thomas E. (Ted) Daley, as the President of its clinical development division. In exchange for the assets related to the ALDH2 deficiency program, what we now call Convivia™, Raptor Pharmaceuticals Corp. issued to Convivia 46,625 shares of our common stock, an additional 46,625 shares of our common stock to a third party in settlement of a convertible loan between the third party and Convivia, and another 8,742 shares of our common stock in settlement of other obligations of Convivia. Mr. Daley, as the former sole stockholder of Convivia, may earn additional shares of our common stock based on certain triggering events or milestones related to the development of the Convivia assets. In addition, Mr. Daley may earn cash bonuses based on the same triggering events pursuant to his employment agreement. In January 2008, Mr. Daley earned a $30,000 cash bonus pursuant to his employment agreement as a result of the milestone of our execution of a formulation agreement for manufacturing Convivia™ with Patheon. In March 2008, Raptor Pharmaceuticals Corp. issued to Mr. Daley 23,312 shares of our common stock pursuant to the Convivia purchase agreement as a result of the milestone of our execution of an agreement to supply us with the active pharmaceutical ingredient for Convivia™ and two $10,000 cash bonuses pursuant to his employment agreement for reaching his six-month and one-year employment anniversaries. In October 2008, Raptor Pharmaceuticals Corp. issued to Mr. Daley 23,312 shares of our common stock valued at $27,000 and a $30,000 cash bonus as a result of fulfilling a

clinical milestone. In July 2010, we issued 11,656 shares of our restricted common stock valued at $35,551 and paid a $10,000 cash bonus to Mr. Daley as result of the execution of the license agreement with Uni Pharma for the development of Convivia™ in Taiwan.

Purchase of DR Cysteamine

In December 2007, prior to the 2009 Merger, through a merger between Encode Pharmaceuticals, Inc., or Encode, and Raptor Therapeutics, Raptor Pharmaceuticals Corp. purchased certain assets, including the clinical development and commercial rights to DR Cysteamine. Under the terms of and subject to the conditions set forth in the merger agreement, Raptor Pharmaceuticals Corp. issued 802,946 shares of its common stock to the stockholders of Encode, or Encode Stockholders, options, or Encode Options, to purchase up to, in the aggregate, 83,325 shares of its common stock to the optionholders of Encode, or Encode Optionholders, and warrants, or Encode Warrants, to purchase up to, in the aggregate, 256,034 shares of its common stock to the warrantholders of Encode, or Encode Warrantholders, and together with the Encode Stockholders and Encode Optionholders, referred to herein collectively as the Encode Securityholders, as of the date of such agreement. The Encode Securityholders are eligible to receive up to an additional 559,496 shares of our common stock, Encode Options and Encode Warrants to purchase our common stock in the aggregate based on certain triggering events related to regulatory approval of DR Cysteamine, an Encode product program, if completed within the five year anniversary date of the merger agreement.

As a result of the Encode merger, we received the exclusive worldwide license to DR Cysteamine, referred to herein as the License Agreement, developed by clinical scientists at the UCSD School of Medicine. In consideration of the grant of the license, we are obligated to pay an annual maintenance fee of $15,000 until we begin commercial sales of any products developed pursuant to the License Agreement. In addition to the maintenance fee, we are obligated to pay during the life of the License Agreement: milestone payments ranging from $20,000 to $750,000 for orphan indications and from $80,000 to $1,500,000 for non-orphan indications upon the occurrence of certain events, if ever; royalties on commercial net sales from products developed pursuant to the License Agreement ranging from 1.75% to 5.5%; a percentage of sublicense fees ranging from 25% to 50%; a percentage of sublicense royalties; and a minimum annual royalty commencing the year we begin commercially selling any products pursuant to the License Agreement, if ever. Under the License Agreement, we are obligated to fulfill predetermined milestones within a specified number of years ranging from 0.75 to 6 years from the effective date of the License Agreement, depending on the indication. In addition, we are obligated, among other things, to spend annually at least $200,000 for the development of products (which we satisfied, as of August 31, 2010 and 2009 by spending approximately $6.2 million and $4.1 million, respectively, on such programs) pursuant to the License Agreement. To-date, we have accrued $470,000 in milestone payments to UCSD based upon the initiation of clinical trials in cystinosis and in NASH. To the extent that we fail to perform any of our obligations under the License Agreement, UCSD may terminate the license or otherwise cause the license to become non-exclusive.

Application of Critical Accounting Policies

Our consolidated financial statements and accompanying notes are prepared in accordance with generally accepted accounting principles used in the U.S. Preparing financial statements requires management to make estimates and assumptions that affect the reported amounts of assets, liabilities, revenue and expenses. These estimates and assumptions are affected by management's application of accounting policies. We believe that understanding the basis and nature of the estimates and assumptions involved with the following aspects of our consolidated financial statements is critical to an understanding of our consolidated financial position.

We believe the following critical accounting policies require us to make significant judgments and estimates in the preparation of our consolidated financial statements.

Fair Value of Financial Instruments

The carrying amounts of certain of our financial instruments, including cash and cash equivalents, prepaid expenses, accounts payable, accrued liabilities and capital lease liability, approximate fair value due to their short maturities.

Cash and Cash Equivalents

We consider all highly liquid investments with original maturities of three months or less to be cash equivalents.

Intangible Assets

Intangible assets include the intellectual property and other rights relating to DR Cysteamine, to the RAP technology and to the out-license and the rights to NGX 426 acquired in the 2009 Merger. The intangible assets related to DR Cysteamine and the RAP technology are amortized using the straight-line method over the estimated useful life of 20 years, which is the life of the intellectual

property patents. The 20 year estimated useful life is also based upon the typical development, approval, marketing and life cycle management timelines of pharmaceutical drug products. The intangible assets related to the out-license will be

amortized using the straight-line method over the estimated useful life of 16 years, which is the life of the intellectual property patents. The intangible assets related to NGX 426, which has been classified as in-process research and development, will not be amortized until development is completed.

Goodwill

Goodwill represents the excess of the value of the purchase consideration over the identifiable assets acquired in the 2009 Merger. Goodwill will be reviewed annually, or when an indication of impairment exists, to determine if any impairment analysis and resulting write-down in valuation is necessary.

Fixed Assets

Fixed assets, which mainly consist of leasehold improvements, lab equipment, computer hardware and software and capital lease equipment, are stated at cost. Depreciation is computed using the straight-line method over the related estimated useful lives, except for leasehold improvements and capital lease equipment, which are depreciated over the shorter of the useful life of the asset or the lease term. Significant additions and improvements that have useful lives estimated at greater than one year are capitalized, while repairs and maintenance are charged to expense as incurred.

Impairment of Long-Lived Assets

We evaluate our long-lived assets for indicators of possible impairment by comparison of the carrying amounts to future net undiscounted cash flows expected to be generated by such assets when events or changes in circumstances indicate the carrying amount of an asset may not be recoverable. Should an impairment exist, the impairment loss would be measured based on the excess carrying value of the asset over the asset's fair value or discounted estimates of future cash flows. We have not identified any such impairment losses to date.

Common Stock Warrant Liabilities

The warrants issued in the 2010 Private Placement contain a cash-out provision which may be triggered upon request by the warrant holders if we are acquired or upon the occurrence of certain other fundamental transactions involving our Company. This provision requires these warrants to be classified as liabilities and will be marked to market at each period end commencing on August 31, 2010. The warrants we issued in our December 2009 Direct Offering contain a conditional obligation that may require us to transfer assets to repurchase the warrants upon the occurrence of potential future events. Under the Financial Accounting Standards Board, or FASB, Accounting Standards Codification, or ASC, Topic 480, Distinguishing Liabilities from Equity, or ASC 480, a financial instrument that may require the issuer to settle the obligation by transferring assets is classified as a liability. Therefore, we have classified the warrants issued in the Direct Offering as liabilities and will mark them to fair value at each period end.

Marked-to-Market

The warrants to purchase our common stock issued in our 2010 Private Placement and our Direct Offering are classified as liabilities under ASC 480 and are, therefore, re-measured at the end of every reporting period with the change in value reported in our consolidated statements of operations.

Income Taxes

Income taxes are recorded under the liability method, under which deferred tax assets and liabilities are determined based on the difference between the financial statement and tax bases of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to affect taxable income. Valuation allowances are established when necessary to reduce deferred tax assets to the amount expected to be realized.

Research and Development

We are an early development stage company. Research and development costs are charged to expense as incurred. Research and development expenses include medical, clinical, regulatory and scientists' salaries and benefits, lab collaborations, preclinical studies,

clinical trials, clinical trial materials, regulatory and clinical consultants, lab supplies, lab services, lab equipment maintenance and small equipment purchased to support the research laboratory, amortization of intangible assets and allocated executive, human resources and facilities expenses.

In-Process Research and Development

Prior to September 1, 2009, we recorded in-process research and development expense for a product candidate acquisition where there is not more than one potential product or usage for the assets being acquired. Upon the adoption of the revised guidance on business combinations, effective September 1, 2009, the fair value of acquired in-process research and development is capitalized and tested for impairment at least annually. Upon completion of the research and development activities, the intangible asset is amortized into earnings over the related product's useful life. We review each product candidate acquisition to determine the existence of in-process research and development.

Stock-Based Compensation

In February 2010, our Board of Directors approved, and in March 2010 our stockholders approved, our 2010 Equity Incentive Plan, or the 2010 Plan, to grant up to an aggregate of 3,000,000 stock options or restricted stock or restricted stock units over the ten year life of the 2010 Plan. Our board of directors has determined not to make any new grants under any of our former plans, but rather under the 2010 Plan. The 2010 Plan's term is ten years and allows for the granting of options to employees, directors and consultants.

In May 2006, Raptor Pharmaceuticals Corp.'s stockholders approved the 2006 Equity Compensation Plan, as amended, referred to herein as the 2006 Plan. The 2006 Plan's term is ten years and allows for the granting of options to employees, directors and consultants. Effective as of the effective time of the 2009 Merger, we assumed the outstanding stock options of Raptor Pharmaceuticals Corp. granted under the 2006 Plan. Such assumed options are subject to the terms of the 2006 Plan and, in each case, are also subject to the terms and conditions of an incentive stock option agreement, non-qualified stock option agreement or other option award, as the case may be, issued under such 2006 Plan. Prior to the 2009 Merger, and subject to the 2009 Merger becoming effective, our board of directors adopted the 2006 Plan such that the 2006 Plan became an equity incentive plan of ours after the 2009 Merger. Typical option grants under the 2010 and 2006 Plans are for ten years with exercise prices at or above market price based on the last closing price as of the date prior to the grant date on the relevant stock market or exchange and vest over four years as follows: 6/48ths on the six month anniversary of the date of grant; and 1/48th per month thereafter.

Effective September 1, 2006, our stock-based compensation is accounted for in accordance with ASC Topic 718, Accounting for Compensation Arrangements, or ASC 718 (previously listed as Statement of Financial Accounting Standards, or SFAS, No. 123 (revised 2004), Share-Based Payment), and related interpretations. Under the fair value recognition provisions of this statement, share-based compensation cost is measured at the grant date based on the value of the award and is recognized as expense over the vesting period. Determining the fair value of share-based awards at the grant date requires judgment, including estimating future stock price volatility and employee stock option exercise behavior. If actual results differ significantly from these estimates, stock-based compensation expense and results of operations could be materially impacted.

In March 2005, the FASB issued ASC 718 (previously listed as Staff Accounting Bulletin, or SAB, No. 107, or SAB 107), which offers guidance for what was previously referred to as SFAS 123(R). ASC 718 was issued to assist preparers by simplifying some of the implementation challenges of SFAS 123(R) while enhancing the information that investors receive. ASC 718 creates a framework that is premised on two overarching themes: (a) considerable judgment will be required by preparers to successfully implement SFAS 123(R), specifically when valuing employee stock options; and (b) reasonable individuals, acting in good faith, may conclude differently on the fair value of employee stock options. Key topics covered by ASC 718 include valuation models, expected volatility and expected term.

For the year ended August 31, 2010, stock-based compensation expense was based on the Black-Scholes option-pricing model assuming the following: risk-free interest rate of 2.07% to 3.1%; 6 to 7 year expected life; 55% to 245% volatility; 2.5% to 10% turnover rate; and 0% dividend rate.

We based our Black-Scholes inputs on the following factors: the risk-free interest rate was based upon our review of current constant maturity treasury bill rates for seven and five years (average); the expected life was based upon our assessment of the ten-year term of the stock options issued along with the fact that we are a development-stage company and our anticipation that option holders will exercise stock options when the company is at a more mature stage of development; the volatility was based on the actual volatility of our common stock price as quoted on NASDAQ since the closing of our 2009 Merger on September 30, 2009; the turnover rate was based on our assessment of our historical employee turnover; and the dividend rate was based on our current decision to not pay dividends on our stock at our current development stage. If factors change and different assumptions are employed in the application of ASC 718, the compensation expense recorded in future periods may differ significantly from what was recorded in the current period. See Note 8 of our consolidated financial statements for further discussion of our accounting for stock based compensation.

We recognize as consulting expense the fair value of options granted to persons who are neither employees nor directors. Stock options issued to consultants are accounted for in accordance with the provisions of the FASB ASC Topic 505-50, Equity-Based Payments to Non-Employees, or ASC 505-50 (previously listed as Emerging Issues Task Force, or EITF, Consensus No. 96-18, Accounting for Equity Instruments That Are Issued to Other Than Employees for Acquiring, or in Conjunction with Selling Goods or Services). The fair value of expensed options is based on the Black-Scholes option-pricing model assuming the same factors as stock-based compensation expense discussed above.

Results of Operations

Years ended August 31, 2010 and 2009

General and Administrative Expenses

General and administrative expenses include finance and executive compensation and benefits, corporate costs, such as legal and auditing fees, business development expenses, travel, board of director fees and expenses, investor relations expenses, intellectual property costs associated with filed (but not issued) patents, administrative consulting and allocated human resources and facilities costs. General and administrative expenses for the year ended August 31, 2010 increased by approximately $1,032,000 compared to the prior fiscal year. The increase was primarily due to:

Reason for Variance	Variance in $ Thousands
Legal expenses for clinical trial agreements, licenses and establishment of a European subsidiary	274
Additional investor relations costs relating to press releases and annual meeting costs in fiscal 2010 that did not occur in fiscal 2009	258
Transfer agent and NASDAQ fees related to 2009 Merger and two post-2009 Merger financings in fiscal 2010 that did not occur in fiscal 2009	197
Cash bonuses paid or accrued in fiscal 2010 that did not occur in fiscal 2009	196
Additional accounting and professional fees due to additional complexities related to the 2009 Merger	165
Salary increases in 2010 retroactive to September 1, 2009	137
Increase in clinical patents application costs	122
Increase in administrative consulting related to business development and maintaining the European subsidiary	115
Increase in services to maintain TorreyPines data and inventory	79
Increase in D&O insurance to cover TorreyPines officers and to provide tail coverage less reduction in Raptor coverage	63
Increase in HR costs allocated to G&A based upon salaries	63
Increase in board fees and board expenses due to new board member in Sept. 2009	54
Increase in benefits costs and due to new employees	39
Increase in rent expense due to San Mateo lease and increase in operating expenses for Novato lease	22
Decrease in recruiting fee paid for CMO in 2009 and not in 2010	(41)
Decrease in stock option expense due to options that were fully vested in 2009	(153)
Decrease in legal expenses incurred in fiscal 2009 for the 2009 Merger that did not occur in fiscal 2010	(215)
Increase in G&A costs allocated to R&D due to additional R&D personnel	(348)
Various other	5
General and Administrative variance year ended August 31, 2010 vs. August 31, 2009	1,032

Research and Development

Research and development expenses include medical, clinical, regulatory and scientists' compensation and benefits, lab collaborations, preclinical studies, clinical trials, clinical trial materials, regulatory and clinical consultants, lab supplies, lab services, lab equipment maintenance and small equipment purchased to support the research laboratory, amortization of intangible assets and allocated executive, human resources and facilities expenses Research and development expenses for the year ended August 31, 2010 increased by approximately $2,764,000 over the prior fiscal year primarily due to:

Reason for Variance	Variance in $ Thousands
Clinical costs of preparing for and commencement of Phase 3 cystinosis trial	1,582
Manufacture of DR Cysteamine for cystinosis and Huntington's clinical trials	1,188
Increase in executive costs to R&D	348
Hiring of CMO in April 2009, salary increases retroactive to Sept. 1, 2009, addition of director of clinical operations in March 2010	312
Reduction of collaboration reimbursement received in fiscal 2009 not repeated in fiscal 2010	300
Cash bonuses paid/accrued in fiscal 2010 that did not occur in fiscal 2009	113
Increase in patent fees for preclinical issued patents	84
Increase in clinical liability insurance due to the Phase 3 cystinosis trial	53
Additional travel for clinical trial preparation and commencement	45
Decrease in HR costs allocated to R&D based upon salaries	(63)
Reduction of reagent purchases by preclinical development	(257)
Reduction of HepTide and WntTide preclinical studies	(306)
Reduction of R&D consultants replaced by CMO, Director of Program Mgmt. and Director of Clinical Operations	(602)
Various other	(33)
Research and Development variance year ended August 31, 2010 vs. August 31, 2009	2,764

Research and development expenses include the following: (in $ millions)

Major Program (stage of development)	Estimated next 12 months	Cumulative through August 31, 2010	Year ended August 31, 2010	Year ended August 31, 2009
DR Cysteamine – All Indications (clinical)	8.7	11.2	6.2	4.0
Convivia™ (clinical)		2.2	0.1	0.4
HepTide™ (preclinical)	-	1.6	-	0.4
NeuroTrans™ (preclinical)	-	0.4	0.1	(0.3)
WntTide™ (preclinical)	0.1	0.4	0.1	0.1
Minor or Inactive Programs	-	0.8	0.1	0.1
R & D Personnel and Other Costs Not Allocated to Programs	3.0	7.6	2.7	1.9
Total Research & Development Expenses	11.8	24.2	9.3	6.6

Major Program expenses recorded as general and administrative expenses: (in $ millions)

Major Program (stage of development)	Estimated next 12 months	Cumulative through August 31, 2010	Year ended August 31, 2010	Year ended August 31, 2009
DR Cysteamine – All Indications (clinical)	0.15	0.34	0.14	0.12
Convivia™ (clinical)	0.05	0.17	0.08	0.05
HepTide™ (preclinical)	0.05	0.32	0.15	0.07
NeuroTrans™ (preclinical)	0.05	0.20	0.05	0.05
WntTide™ (preclinical)	0.06	0.13	0.07	0.01

Additional major program expenses include patent fees and patent expenses which were recorded as general and administrative expenses as these fees are to support patent applications (not issued patents).

Any of our major programs could be partnered for further development and/or could be accelerated, slowed or ceased due to scientific results or challenges in obtaining funding. We anticipate that we will need additional funding in order to pursue our plans beyond the next 12 months. In addition, the timing and costs of development of our programs beyond the next 12 months is highly uncertain and difficult to estimate. See Part I Item 1A of this Annual Report on Form 10-K titled “Risk Factors” for further discussion about the risks and uncertainties pertaining to drug development.

Current Status of Major Programs

Please refer to the section titled, “Future Activities” above in Item 1 of this Annual Report on Form 10-K for a detailed discussion of each of our major programs. In summary, DR Cysteamine is being developed in cystinosis, NASH and HD. In November 2009, we released data from our Phase 2b clinical trial and in June 2010, we commenced our Phase 3 clinical trial to study DR Cysteamine in cystinosis patients. We anticipate completion of enrollment by the end of 2010. In May 2010, we presented the data from our NASH Phase 2a clinical trial and are reformulating the drug product candidate for a potential Phase 2 trial in 2011. In October 2010, our collaborator commenced a Phase 2a clinical trial of DR Cysteamine in HD patients.

Our Convivia™ product candidate completed its initial clinical study in 2008 and in June 2010, we licensed Convivia ™ to Uni Pharma for further clinical development in Taiwan, with an option to develop Convivia™ in South Korea. We continue to seek other potential partners for Convivia™ in other Asian countries where its potential market exists. We are seeking to out-license our Tezampanel and NGX426 product candidates and no development costs will be incurred for the pain indication. NeuroTrans™ is currently being studied under a collaboration agreement with Roche. HepTide™ will be undergoing further preclinical proof of concept studies and

WntTide™ is being considered for potential out-licensing for further development. All preclinical product candidates will require further study prior to potentially moving into a clinical phase of development.

Interest Income

Interest income decreased by $11,043 for the year ended August 31, 2010 compared to the prior fiscal year due to the reduction of interest rates.

Interest Expense

Interest expense for the years ended August 31, 2010 and 2009 were nominal.

Foreign Currency Transaction Loss

Foreign currency transaction loss increased by $457 for the year ended August 31, 2010 compared to the prior fiscal year due to the addition of a Euro-denominated bank account and subsidiary in fiscal 2010 resulting from the creation of a European subsidiary to manage our European clinical trials.

Adjustment to the Fair Value of Common Stock Warrants

Adjustment to the fair value of common stock warrants increased by $5.9 million resulting in an increase to our net loss for the year ended August 31, 2010 compared to the prior fiscal year due to the fact that there was no warrant liability recorded in the prior fiscal year.

Years ended August 31, 2009 and 2008

General and Administrative

General and administrative expenses for the year ended August 31, 2009 increased by $450,000 compared to the prior fiscal year. The increase was primarily due to:

Reason for Variance	Variance in $ Thousands
Legal costs accrued related to 2009 Merger	290
Salaries, bonuses, benefits and other employment-related costs due to employee raises that occurred in July 2008, milestone-related bonus paid in October 2008, recruiting fees related to the hiring of our Director of Program Management in October 2008 and our Chief Medical Officer in April 2009 offset by fiscal year 2008 performance bonuses not repeated in the fiscal year 2009	170
General and administrative consulting due to retention of strategic business advisor in May 2008, investor relations consultants in February 2009 and for the redesign of our website in November 2008	200
Board fees and expenses due to the addition of a new Board member in July 2008	80
Decrease in depreciation related to fully depreciated assets	(50)
Decrease in travel expenses due to reduction in attendance at tradeshows and conferences	(50)
Increase in support services allocated to research and development	(190)
General and Administrative variance year ended August 31, 2009 vs. August 31, 2008	450

Research and Development

Research and development expenses for the year ended August 31, 2009 increased by $1.0 million over the prior fiscal year primarily due to:

Reason for Variance	Variance in $ Thousands
Formulation and manufacturing costs related to our proprietary formulation of DR Cysteamine in preparation for our clinical trials in cystinosis	1,210
Increase in research and development expenses in preparation for our pre-IND meeting with the FDA and in preparation for our IND submission	340
Increase in salaries and benefits due to the hiring of our director of Program Management in November 2008 and our Chief Medical Officer in April 2009	250
Increase in milestone payments for the commencement of the NASH trial in October 2008 and cystinosis trial in June 2009	250
Increase in clinical trial costs for our NASH indication	230
Increase in allocated support services to research and development	190
Decrease in tradeshows and conferences expenses due to reduction in attendance at conferences	(20)
Decrease in preclinical studies due to the reduction of resources allocated to preclinical programs	(100)
Decrease in lab collaboration fees due to the lapse of the Stanford collaboration on NeuroTrans	(240)
Decrease in preclinical manufacturing of HepTide conjugates made in fiscal 2008 not repeated in fiscal 2009	(270)
Decrease in lab personnel expenses due to a collaboration reimbursement	(300)
Decrease in clinical trial costs due to the Convivia trial that occurred in fiscal 2008 that did not repeat in fiscal 2009	(540)
Research and Development variance year ended August 31, 2009 vs. August 31, 2008	1,000

Research and development expenses include the following: (in $ millions)

Major Program (stage of development)	Cumulative Through August 31, 2009	FYE August 31, 2009	FYE August 31, 2008
DR Cysteamine – All Indications (clinical)	5.0	4.0	1.0
Convivia™ (clinical)	2.1	0.4	1.7
HepTide™ (preclinical)	1.6	0.4	0.7
NeuroTrans™ (preclinical)	0.3	(0.3)	0.3
WntTide™ (preclinical)	0.3	0.1	0.2
Minor or Inactive Programs	0.7	0.1	0.2
R & D Personnel and Other Costs Not Allocated to Programs	4.9	1.9	1.5
Total Research & Development Expenses	14.9	6.6	5.6

Major Program expenses recorded as general and administrative expenses: (in $ millions)

Major Program (stage of development)	Cumulative Through August 31, 2009	FYE August 31, 2009	FYE August 31, 2008
DR Cysteamine – All Indications (clinical)	0.20	0.12	0.08
Convivia™ (clinical)	0.09	0.05	0.04
HepTide™ (preclinical)	0.17	0.07	0.05
NeuroTrans™ (preclinical)	0.15	0.05	0.05
WntTide™ (preclinical)	0.06	0.01	0.02

Additional major program expenses include patent fees and patent expenses which were recorded as general and administrative expenses as these fees are to support patent applications (not issued patents).

Any of our major programs could be partnered for further development and/or could be accelerated, slowed or ceased due to scientific results or challenges in obtaining funding. The timing and costs of development of our programs beyond the next 12 months is highly uncertain and difficult to estimate. See Item 1A titled Risk Factors for further discussion about the risks and uncertainties pertaining to drug development.

In-Process Research and Development Expenses

In-process research and development expenses decreased by $0.24 million over the year ended August 31, 2008 due to the recording of the purchase of our Convivia™ program during the year ended August 31, 2008. No such expense was incurred in the year ended August 31, 2009. In-process research and development expenses were calculated based on the value of our stock issued in connection with the purchase of certain intellectual property rights to develop Convivia™ (4-MP) for the treatment of acetaldehyde toxicity.

Interest Income

Interest income decreased by $0.041 million during the year ended August 31, 2009 over the year ended August 31, 2008 due to the significant decrease in annual money market interest rates from an average of 2% in 2008 to an average of less than 1% in 2009.

Interest Expense

Interest expense decreased by $0.10 million in the year ended August 31, 2009 over the year ended August 31, 2008 due to the capitalized finder's fee of 46,625 shares of our common stock valued at $102,000 (which was paid in connection with a convertible loan), which was amortized as interest expense from August 2007 to April 2008, the term of the convertible loan. No draws were made on the convertible loan prior to its expiration.

Liquidity and Capital Resources

Capital Resource Requirements

As of August 31, 2010, we had approximately $17.0 million in cash, approximately $17.6 million in current liabilities (of which $15.8 million represented the non-cash common stock warrant liability) and approximately ($0.3) million of net working capital deficit. Our forecasted average monthly cash expenditures for the next twelve months are approximately $1.2 million.

We believe our cash and cash equivalents as of November 5, 2010 of $14.5 million will be sufficient to meet our obligations into December 2011. We are currently in the process of negotiating strategic partnerships, collaborations and potential equity sales to supplement the funding of our preclinical and clinical programs beyond December 2011.. If we are unable to obtain such additional capital when needed, we may be forced to scale down our expenditures.

Our recurring losses from operations and our accumulated deficit raise substantial doubt about our ability to continue as a going concern and, as a result, our independent registered public accounting firm included an explanatory paragraph in its report on our consolidated financial statements for the year ended August 31, 2010 with respect to this uncertainty. We may need to generate significant revenue or raise additional capital to continue to operate as a going concern beyond December 2011. In addition, the perception that we may not be able to continue as a going concern may cause others to choose not to deal with us due to concerns about our ability to meet our contractual obligations and may adversely affect our ability to raise additional capital.

The sale of additional securities is likely to result in additional dilution to our stockholders. Additional financing may not be available when needed in amounts or on terms satisfactory to us or at all. We may be unable to raise additional financing due to a variety of factors, including our financial condition, the status of our research and development programs, and the general condition of the financial markets. If we fail to raise additional financing when needed, we may have to delay or terminate some or all of our research and development programs, our financial condition and operating results may be adversely affected and we may have to scale back our operations.

In August 2009, Raptor Pharmaceuticals Corp. entered into a Securities Purchase Agreement with four investors for the private placement of units at a purchase price of $1.37 per unit. Each unit was comprised of one share of our common stock, par value $0.001 per share and one warrant to purchase one half of one share of our common stock. At the closing, Raptor Pharmaceuticals Corp. sold an aggregate of 1,738,226 units to the investors, comprised of an aggregate of 1,738,226 shares of our common stock and warrants to purchase up to in the aggregate, 869,113 shares of our common stock, for aggregate gross proceeds of $2,386,000. The investor warrants, exercisable for two years from the closing, had an exercise price of $2.57 per share during the first year and $3.22 per share during the second year, depending on when such investor warrants were exercised, if at all. To-date, warrants to purchase 233,124 shares were exercised for aggregate gross proceeds of $599,129. The balance of warrants to purchase 635,990 of our common stock remain outstanding as of November 5, 2010.

In December 2009, we entered into a definitive securities purchase agreement, or the Direct Offering Purchase Agreement, dated as of December 17, 2009, with 33 investors (collectively, the Direct Offering Investors) with respect to the sale of units, whereby, on an aggregate basis, the investors agreed to purchase 3,747,558 Units for a negotiated purchase price of $2.00 per unit for aggregate gross proceeds of approximately $7.5 million. Each unit consists of one share of our common stock, one Series A Warrant exercisable for 0.5 of a share of our common stock and one Series B Warrant exercisable for 0.5 of a share of our common stock. The shares of our common stock and the warrants were issued separately. The Series A Warrants exercisable for an aggregate 1,873,779 shares of our common stock were exercisable commencing on June 20, 2010 and ending December 22, 2014. The Series B Warrants exercisable for an aggregate 1,873,779 shares of our common stock were exercisable commencing on June 20, 2010 and ending June 22, 2011. The investor warrants have a per share exercise price of $2.45. In connection with this offering we paid a placement agent cash compensation equal to 6.5% of the gross proceeds or $487,183 plus a five-year warrant at an exercise price of $2.50 per share for the purchase of up to 74,951 shares of our common stock. To-date Series B warrants to purchase 68,808 shares of our common stock were exercised for aggregate gross proceeds of $168,580. As of November 5, 2010, there were Series A warrants to purchase 1,868,750 shares of our common stock and Series B warrants to purchase 1,810,000 shares of our common stock outstanding.

In April 2010, we entered into a $15 million equity line facility with LPC, which allows us to sell shares of our common stock every two days if our selling price to the investor is over $1.50 per share. Cumulatively, as of November 5, 2010, we have sold approximately 2.2 million shares under the equity line raising approximately $4.9 million. We may direct LPC to purchase up to an additional $10.1 million of shares of our common stock under the LPC Purchase Agreement over the next 20 months, generally in amounts of up to $100,000 every 2 business days. However, LPC does not have the right nor the obligation to purchase any shares of our common stock on any business day that the purchase price of our common stock is less than $1.50 per share. Although we have the right to sell additional shares of our common stock to LPC under the LPC Purchase Agreement, we are restricted from making such sale under the 2010 Private Placement Purchase Agreement until November 10, 2010.

On August 9, 2010, we entered into the 2010 Private Placement Purchase Agreements with the 2010 Private Placement Investors for the private placement of our common stock and warrants to purchase our common stock, at a purchase price of $3.075 per unit, with each unit comprised of one share of common stock and a warrant to purchase one share of common stock. We issued and sold an aggregate of 4,897,614 units, comprised of an aggregate of 4,897,614 shares of common stock and warrants to purchase up to 4,897,614 shares of our common stock for gross proceeds of approximately $15.1 million. Each warrant, exercisable for 5 years from August 12, 2010, has an exercise price of $3.075 per share. As the placement agent for the 2010 Private Placement, the Placement Agent was issued one warrant to purchase 97,952 shares of our common stock at an exercise price of $3.075 per share, paid a cash commission of $978,911 and reimbursed for certain of its expenses incurred in connection with the 2010 Private Placement.

There can be no assurance that we will be able to obtain funds required for our continued operation. There can be no assurance that additional financing will be available to us or, if available, that it can be obtained on commercially reasonable terms. If we are not able to obtain financing on a timely basis, we will not be able to meet our obligations as they become due and we will be forced to scale down or perhaps even cease the operation of our business. This also may be the case if we become insolvent or if we breach our asset purchase agreement with BioMarin or our licensing agreements with Washington University and UCSD due to non-payment (and we do not cure our non-payment within the stated cure period). If this happens, we would lose all rights to the RAP technology assigned to us by BioMarin and/or the rights to Mesd licensed to us by Washington University and/or the rights to DR Cysteamine licensed to us by UCSD, depending on which agreement is breached. If we lose our rights to the intellectual property related to the RAP technology purchased by us from BioMarin, our agreement with Roche would likely be terminated and any milestone or royalty payments from Roche to us would thereafter cease to accrue.

For the next 12 months we intend to expend a total of approximately $14.5 million to implement our operating plan of researching and developing our DR Cysteamine clinical programs, our RAP based platform, our licensed technologies, as well as continuing business development efforts for our other clinical-stage product candidates. Specifically, we estimate our operating expenses and working capital requirements for the next 12 months to be as follows:

Estimated spending for the next 12 months:	In millions
Research and development activities	$ 10.1
Research and development compensation and benefits	1.8
General and administrative activities	1.7
General and administrative compensation and benefits	0.9
Capital expenditures	-
Total estimated spending for the next 12 months	$ 14.5

We anticipate that we will not be able to generate revenues from the sale of products until we further develop our drug product candidates and obtain the necessary regulatory approvals to market our future drug product candidates, which could take several years or more, if we are able to do so at all. Accordingly, our cash flow projections are subject to numerous contingencies and risk factors beyond our control, including successfully developing our drug product candidates, market acceptance of our drug product candidates, competition from well-funded competitors, and our ability to manage our expected growth. It is likely that for many years, we will not be able to generate internal positive cash flow from the sales of our drug product candidates sufficient to meet our operating and capital expenditure requirements.

There is substantial doubt about our ability to continue as a going concern as the continuation of our business is dependent upon obtaining further long-term financing, the successful development of our drug product candidates and related technologies, the successful and sufficient market acceptance of any product offerings that we may introduce and, finally, the achievement of a profitable level of operations. The issuance of additional equity securities by us is likely to result in a significant dilution in the equity interests of our current stockholders. Obtaining commercial loans, assuming those loans would be available, including on acceptable terms, will increase our liabilities and future cash commitments.

Research and Development Activities

We plan to conduct further research and development, seek to support several clinical trials for DR Cysteamine, improve upon our RAP-based and in-licensed technology and continue business development efforts for our other clinical-stage product candidates in the next 12 months. We plan to conduct research and development activities by our own laboratory staff and also by engaging contract research organizations, clinical research organizations and contract manufacturing organizations. We also plan to incur costs for the production of our clinical study drug candidate, DR Cysteamine, clinical trials, clinical and medical advisors and consulting and collaboration fees. We anticipate our research and development costs for the next 12 months, excluding in-house research and development compensation, will be approximately $10.1 million.

Officer and Employee Compensation

We have five executive officers, one permanent scientific staff member, three permanent clinical development staff members and one permanent finance staff member. We anticipate spending up to approximately $2.6 million in officer and employee compensation during the next 12 months, of which $1.7 million is allocated to research and development expenses and $0.9 million is allocated to general and administrative expenses.

General and Administrative

We anticipate spending approximately $1.7 million on general and administrative costs in the next 12 months. These costs will consist primarily of legal and accounting fees, patent legal fees, investor relations expenses, board fees and expenses, insurance, rent and facility support expenses, excluding finance and administrative compensation.

Capital Expenditures

We anticipate spending approximately $20,000 in the next 12 months on capital expenditures for lab equipment and office furniture.

Contractual Obligations with BioMarin

Pursuant to the terms of the asset purchase agreement we entered into with BioMarin for the purchase of intellectual property related to our RAP based technology (including NeuroTrans™), we are obligated to make the following milestone payments to BioMarin upon the achievement of the following events:

- $50,000 (paid by us in June 2006) within 30 days after we receive total aggregate debt or equity financing of at least $2,500,000;

- $100,000 (paid by us in June 2006) within 30 days after we receive total aggregate debt or equity financing of at least $5,000,000;

- $500,000 upon our filing and acceptance of an investigational new drug application for a drug product candidate based on our NeuroTrans™ product candidate;

- $2,500,000 upon our successful completion of a Phase 2 human clinical trial for a drug product candidate based on our NeuroTrans™ product candidate;

- $5,000,000 upon our successful completion of a Phase 3 human clinical trial for a drug product candidate based on our NeuroTrans™ product candidate;

- $12,000,000 within 90 days of our obtaining marketing approval from the FDA or other similar regulatory agencies for a drug product candidate based on our NeuroTrans™ product candidate;

- $5,000,000 within 90 days of our obtaining marketing approval from the FDA or other similar regulatory agencies for a second drug product candidate based on our NeuroTrans™ product candidate;

- $5,000,000 within 60 days after the end of the first calendar year in which our aggregated revenues derived from drug product candidates based on our NeuroTrans™ product candidate exceed $100,000,000; and

- $20,000,000 within 60 days after the end of the first calendar year in which our aggregated revenues derived from drug product candidates based on our NeuroTrans™ product candidate exceed $500,000,000.

In addition to these milestone payments, we are also obligated to pay BioMarin a royalty at a percentage of our aggregated revenues derived from drug product candidates based on our NeuroTrans™ product candidate. On June 9, 2006, we made a milestone payment in the amount of $150,000 to BioMarin because we raised $5,000,000 in our May 25, 2006 private placement financing. If we become insolvent or if we breach our asset purchase agreement with BioMarin due to non-payment and we do not cure our non-payment within the stated cure period, all of our rights to RAP technology (including NeuroTrans™) will revert back to BioMarin.

Contractual Obligations with Thomas E. Daley (assignee of the dissolved Convivia, Inc.)

Pursuant to the terms of the asset purchase agreement, or the Asset Purchase Agreement, that we entered into with Convivia, Inc. and Thomas E. Daley, pursuant to which we purchased intellectual property related to our 4-MP product candidate program, Mr. Daley will be entitled to receive the following, if at all, in such amounts and only to the extent certain future milestones are accomplished by us, as set forth below:

- 23,312 shares of our restricted, unregistered common stock within fifteen (15) days after we enter into a manufacturing license or other agreement to produce any product that is predominantly based upon or derived from any assets purchased from Convivia, or Purchased Assets, in quantity, referred to as Product, if such license agreement is executed within one (1) year of execution of the Asset Purchase Agreement or, if thereafter, 11,656 shares of our restricted, unregistered common stock. Should we obtain a second such license or agreement for a Product, Mr. Daley will be entitled to receive 11,656 shares of our restricted, unregistered common stock within 30 days of execution of such second license or other agreement. In January 2008, Mr. Daley earned a $30,000 cash bonus pursuant to his employment agreement for executing the Patheon formulation agreement for manufacturing Convivia™. On March 31, 2008, Raptor Pharmaceuticals Corp. issued 23,312 shares of our common stock valued at $56,000 to Mr. Daley pursuant to this milestone reflecting the execution of an agreement to supply the active pharmaceutical ingredient for Convivia™, combined with the execution of a formulation agreement to produce the oral formulation of Convivia™. In July 2010, we issued 11,656 shares of our restricted common stock valued at $35,551 and paid a $10,000 cash bonus to Mr. Daley as result of the execution of the license agreement with Uni Pharma for the development of Convivia™ in Taiwan.

- 23,312 shares of our restricted, unregistered common stock within fifteen (15) days after we receive our first patent allowance on any patents which constitute part of the Purchased Assets in any one of certain predetermined countries, or a Major Market.

- 11,656 shares of our restricted, unregistered common stock within fifteen (15) days after we receive our second patent allowance on any patents which constitute part of the Purchased Assets different from the patent referenced in the immediately preceding bullet point above in a Major Market.

- 23,312 shares of our restricted, unregistered common stock within fifteen (15) days of completion of predetermined benchmarks in a Major Market by us or our licensee of the first phase 2 human clinical trial for a Product, or Successful Completion if such Successful Completion occurs within one (1) year of execution of the Asset Purchase Agreement or, if thereafter, 11,656 shares of our restricted, unregistered common stock within thirty (30) days of such Successful Completion. In October 2008, Raptor Pharmaceuticals Corp. issued 23,312 shares of our common stock valued at $27,000 and a $30,000 cash bonus (pursuant to Mr. Daley's employment agreement) to Mr. Daley pursuant to the fulfillment of this milestone.

- 11,656 shares of our restricted, unregistered common stock within fifteen (15) days of a Successful Completion in a Major Market by us or our licensee of the second phase 2 human clinical trial for a Product (other than the Product for which a distribution is made under the immediately preceding bullet point above).

- 23,312 shares of our restricted, unregistered common stock within fifteen (15) days after we or our licensee applies for approval to market and sell a Product in a Major Market for the indications for which approval is sought, or Marketing Approval.

- 11,656 shares of our restricted, unregistered common stock within fifteen (15) days after we or our licensee applies for Marketing Approval in a Major Market (other than the Major Market for which a distribution is made under the immediately preceding bullet point above).

- 46,625 shares of our restricted, unregistered common stock within fifteen (15) days after we or our licensee obtains the first Marketing Approval for a Product from the applicable regulatory agency in a Major Market.

- 23,312 shares of our restricted, unregistered common stock within fifteen (15) days after we or our licensee obtains Marketing Approval for a Product from the applicable regulatory agency in a Major Market (other than the Major Market for which a distribution is made under the immediately preceding bullet point above).

As discussed above, in aggregate, we issued to Mr. Daley, 58,281 shares of our common stock valued at $118,551 and paid $70,000 in cash bonuses related to Convivia™ milestones along with another $20,000 in cash bonuses related to employment milestones pursuant to Mr. Daley's employment agreement.

Contractual Obligations with Former Encode Securityholders

Pursuant to the terms of the merger agreement, or the Encode Merger Agreement, that we entered into with Encode Pharmaceuticals, Inc. and Nicholas Stergis in December 2007, former Encode securityholders will be entitled to receive the following, if at all, in such amounts and only to the extent certain future milestones are accomplished by us, as set forth below:

- Restricted, unregistered common stock, stock options to purchase our common stock, and warrants to purchase our common stock in an amount equal to, in the aggregate, 116,562 shares of our common stock upon the receipt by it at any time prior to the fifth-year anniversary of the Encode Merger Agreement of approval to market and sell a product for the treatment of cystinosis predominantly based upon and derived from the assets acquired from Encode, or Cystinosis Product, from the applicable regulatory agency (e.g., FDA and European Agency for the Evaluation of European Medical Products, or EMA) in a given major market in the world.

- Restricted, unregistered common stock, stock options to purchase our common stock, and warrants to purchase our common stock in an amount equal to 442,934 shares of our common stock upon the receipt by us at any time prior to the fifth anniversary of the Encode Merger Agreement of approval to market and sell a product, other than a Cystinosis Product, predominantly based upon and derived from the assets acquired from Encode, from the applicable regulatory agency (e.g., FDA and EMA) in a given major market in the world.

If within five years from the date of the Encode Merger Agreement, there occurs a transaction or series of related transactions that results in the sale of all or substantially all of the assets acquired from Encode other than to our affiliate in such case where such assets are valued at no less than $2.5 million, the former Encode stockholders will be entitled to receive, in the aggregate, restricted, unregistered common stock, stock options to purchase our common stock, and warrants to purchase our common stock in an amount equal to 559,496 shares of common stock, less the aggregate of all milestone payments previously made or owing, if any.

Pursuant to the terms of the Encode Merger Agreement, an Encode stockholder was granted the right to demand the registration of its portion of the initial restricted, unregistered common stock issued to it in connection with the execution of the Encode Merger Agreement at any time following 140 days from the closing date of the merger with Encode and prior to the expiration of the fourth anniversary of the Encode Merger Agreement. To the extent that future milestones as described above are accomplished by us within five years from the effective time of the merger with Encode, we will be obligated to file a registration statement within 90 days covering such Encode stockholder's portion of such respective future restricted, unregistered common stock issued relating to such milestone payment.

Contractual Obligations with UCSD

As a result of the merger of our clinical subsidiary and Encode, we received the exclusive worldwide license to DR Cysteamine, or License Agreement for use in the field of human therapeutics for metabolic and neurologic disorders, developed by clinical scientists at the UCSD, School of Medicine. DR Cysteamine is a proprietary, delayed-release, enteric-coated microbead formulation of cysteamine bitartrate, a cystine depleting agent currently approved by the FDA. Cysteamine bitartrate is

prescribed for the management of the genetic disorder known as cystinosis, a lysosomal storage disease. The active ingredient in DR Cysteamine has also demonstrated potential in studies as a treatment for other metabolic and neurodegenerative diseases, such as HD and NASH.

In consideration of the grant of the license, prior to the merger, Encode paid an initial license fee and we will be obligated to pay an annual maintenance fee of $15,000 until we begin commercial sales of any products developed pursuant to the License Agreement. In addition to the maintenance fee, we will be obligated to pay during the life of the License Agreement: milestone payments ranging from $20,000 to $750,000 for orphan indications and from $80,000 to $1,500,000 for non-orphan indications upon the occurrence of certain events, if ever; royalties on commercial net sales from products developed pursuant to the License Agreement ranging from 1.75% to 5.5%; a percentage of sublicense fees ranging from 25% to 50%; a percentage of sublicense royalties; and a minimum annual royalty commencing the year we begin commercially selling any products pursuant to the License Agreement, if ever. Under the License Agreement, we are obligated to fulfill predetermined milestones within a specified number of years ranging from 0.75 to 6 years from the effective date of the License Agreement, depending on the indication. In addition, we are obligated to, among other things, annually spend at least $200,000 for the development of products—which, as of August 31, 2010 and 2009, we had spent approximately $6.2 million and $4.1 million, respectively, on such programs—pursuant to the License Agreement. To-date, we have accrued $470,000 in milestone payments to UCSD based upon the initiation of clinical trials in cystinosis and in NASH. To the extent that we fail to perform any of our obligations under the License Agreement, UCSD may terminate the license or otherwise cause the license to become non-exclusive.

Contractual Obligations to TPTX, Inc. Employees

Pursuant to the documents related to the 2009 Merger, including amended employment agreements with the TPTX, Inc. employees, who were former executives of TorreyPines prior to the 2009 Merger, we were obligated to pay such former executives their salaries, benefits and other obligations through February 28, 2010, which obligations were extended through mid-April 2010. As of April 1, 2010, we had no remaining obligations to such former executives and they received their final compensation in mid-April 2010.

Off-Balance Sheet Arrangements

We do not have any outstanding derivative financial instruments, off-balance sheet guarantees, interest rate swap transactions or foreign currency contracts. We do not engage in trading activities involving non-exchange traded contracts.

Reverse Acquisition

We have treated the 2009 Merger as a reverse acquisition and the reverse acquisition is accounted for as a recapitalization.

For accounting purposes, Raptor Pharmaceuticals Corp. is considered the accounting acquirer in the reverse acquisition. The historical financial statements reported in this Annual Report on Form 10-K and in future periods are and will be those of Raptor Pharmaceuticals Corp. consolidated with its subsidiaries and with us, its parent, Raptor Pharmaceutical Corp. (formerly TorreyPines Therapeutics, Inc.). Earnings per share for periods prior to the reverse merger have been restated to reflect the number of equivalent shares received by former stockholders.

Going Concern

Due to the uncertainty of our ability to meet our current operating and capital expenses, in their reports on our audited financial statements for the years ended August 31, 2010, 2009, 2008, 2007 and for the period September 8, 2005 (inception) to August 31, 2006, our independent registered public accounting firm, Burr Pilger Mayer, Inc., included an explanatory paragraph regarding substantial doubt about our ability to continue as a going concern. Our financial statements contain additional note disclosures describing the circumstances that led to this disclosure by our independent registered public accounting firm.

New Accounting Pronouncements

In December 2007, the EITF reached a consensus on ASC Topic 808, *Collaborative Agreement,* or ASC 808 (previously EITF 07-01, *Accounting for Collaborative Arrangements*). ASC 808 discusses the appropriate income statement presentation and classification for the activities and payments between the participants in arrangements related to the development and commercialization of intellectual property. The sufficiency of disclosure related to these arrangements is also specified. ASC 808 is effective for fiscal years beginning after

December 15, 2008. As a result, ASC 808 is effective for us as of September 1, 2009. Based upon the nature of our business, ASC 808 could have a material impact on our financial position and consolidated results of operations in future years, but had no material impact for the year ended August 31, 2010.

In December 2007, the FASB, issued ASC Topic 805, *Business Combinations*, or ASC 805 (previously SFAS 141(R) and FASB ASC Topic 810, *Consolidation*, or ASC 810 (previously SFAS 160, *Noncontrolling Interests in Consolidated Financial Statements, an amendment of ARB No. 51*). These statements will significantly change the financial accounting and reporting of business combination transactions and non-controlling (or minority) interests in consolidated financial statements. ASC 805 requires companies to: (i) recognize, with certain exceptions, 100% of the fair values of assets acquired, liabilities assumed, and non-controlling interests in acquisitions of less than a 100% controlling interest when the acquisition constitutes a change in control of the acquired entity; (ii) measure acquirer shares issued in consideration for a business combination at fair value on the acquisition date; (iii) recognize contingent consideration arrangements at their acquisition-date fair values, with subsequent changes in fair value generally reflected in earnings; (iv) with certain exceptions, recognize pre-acquisition loss and gain contingencies at their acquisition-date fair values; (v) capitalize in-process research and development assets acquired; (vi) expense, as incurred, acquisition-related transaction costs; (vii) capitalize acquisition-related restructuring costs only if the criteria in ASC Topic 420, *Exit and Disposal Cost Obligations*, (previously SFAS No. 146, *Accounting for Costs Associated with Exit or Disposal Activities)*, are met as of the acquisition date; and (viii) recognize changes that result from a business combination transaction in an acquirer's existing income tax valuation allowances and tax uncertainty accruals as adjustments to income tax expense. ASC 805 is required to be adopted concurrently with ASC 810 and is effective for business combination transactions for which the acquisition date is on or after the beginning of the first annual reporting period beginning on or after December 15, 2008 (our fiscal 2010). Early adoption of these statements is prohibited. We believe the adoption of these statements will have a material impact on significant acquisitions completed after September 1, 2009. See Note 10 of our consolidated financial statements as of August 31, 2010, which reflect the accounting treatment of our 2009 Merger utilizing these provisions.

In May 2008, the FASB released ASC Topic 470, *Debt*, or ASC 470 (previously FSP APB 14-1 *Accounting For Convertible Debt Instruments That May Be Settled in Cash Upon Conversion (Including Partial Cash Settlement*), which alters the accounting treatment for convertible debt instruments that allow for either mandatory or optional cash settlements. ASC 470 specifies that issuers of such instruments should separately account for the liability and equity components in a manner that will reflect the entity's nonconvertible debt borrowing rate when interest cost is recognized in subsequent periods. Furthermore, it would require recognizing interest expense in prior periods pursuant to retrospective accounting treatment. ASC 470 is effective for financial statements issued for fiscal years beginning after December 15, 2008; therefore, we adopted ASC 470 as of September 1, 2009. We have determined that ASC 470 had no material impact on our consolidated financial statements for the year ended August 31, 2010.

In April 2008, the FASB issued ASC Topic 350, *Intangibles – Goodwill and Other*, or ASC 350 (previously FSP SFAS No. 142-3, *Determination of the Useful Life of Intangible Assets*). ASC 350 provides guidance with respect to estimating the useful lives of recognized intangible assets acquired on or after the effective date and requires additional disclosure related to the renewal or extension of the terms of recognized intangible assets. ASC 350 is effective for fiscal years and interim periods beginning after December 15, 2008. We adopted ASC 350 as of September 1, 2009 and have determined that ASC 350 had no material impact on our consolidated financial statements for the year ended August 31, 2010.

In May 2009, the FASB issued ASC Topic 855, *Subsequent Events*, or ASC 855 (previously SFAS No. 165, *Subsequent Events*). ASC 855 establishes general standards of accounting for and disclosure of events that occur after the balance sheet date but before financial statements are issued or are available to be issued. ASC 855 defines the period after the balance sheet date during which management of a reporting entity should evaluate events or transactions that may occur for potential recognition or disclosure in the financial statements, and the circumstances under which an entity should recognize events or transactions occurring after the balance sheet date in its financial statements. ASC 855 is effective for fiscal years and interim periods ending after June 15, 2009. We adopted ASC 855 as of August 31, 2009 and anticipate that the adoption will impact the accounting and disclosure of future transactions. Our management has evaluated and disclosed subsequent events from the balance sheet date of August 31, 2010 through the date the consolidated financial statements located elsewhere in this Annual Report on Form 10-K were available to be issued.

ASC Topic 825, *Financial Instruments*, or ASC 825 (previously FSP FAS 107-1 and APB 28-1 amends FASB Statement No. 107, *Disclosures about Fair Value of Financial Instruments*), to require disclosures about the fair value of financial instruments for interim reporting periods of publicly traded companies as well as in annual financial statements. This ASC 825 also amends APB Opinion No. 28, Interim Financial Reporting, to require those disclosures in summarized financial information at interim reporting periods. The adoption of ASC 825 did not have a material impact on our consolidated financial statements for the year ended August 31, 2010.

In June 2009, the FASB issued SFAS No. 167, *Amendments to FASB Interpretation No. 46(R),* or SFAS 167, which has not yet been codified in the ASC. The amendments include: (i) the elimination of the exemption for qualifying special purpose entities, (ii) a new approach for determining who should consolidate a variable-interest entity, and (iii) changes to when it is necessary to reassess who should consolidate a variable-interest entity. This statement is effective for fiscal years beginning after November 15, 2009, and for interim periods within that first annual reporting period. We are currently evaluating the impact of this standard, however, we do not expect SFAS 167 will have a material impact on our consolidated financial statements.

In June 2009, the FASB issued ASC Topic 105, Generally Accepted Accounting Standards, or ASC 105 (previously SFAS No. 168, The FASB Accounting Standards Codification™ and the Hierarchy of Generally Accepted Accounting Principles, a replacement of FASB Statement No. 162), or the Codification. The Codification, which was launched on July 1, 2009, became the single source of authoritative nongovernmental U.S. GAAP, superseding existing FASB, American Institute of Certified Public Accountants, EITF and related literature. The Codification eliminates the GAAP hierarchy contained in ASC 105 and establishes one level of authoritative GAAP. All other literature is considered non-authoritative. ASC 105 is effective for financial statements issued for interim and annual periods ending after September 15, 2009. We adopted ASC 105 as of September 1, 2009 however, references to both current GAAP and the Codification are included in this filing. We have determined that this provision had no material impact on our consolidated financial statements for the year ended August 31, 2010.

In June 2009, the FASB issued ASC Topic 860**,** Transfers and Servicing (Statement No. 166, Accounting for Transfers of Financial Assets — an amendment of FASB Statement No. 140), or ASC 860. The guidance removes the concept of a qualifying special purpose entity and changes the requirements for derecognizing financial assets. Many types of transferred financial assets that would have been derecognized previously are no longer eligible for derecognition. The guidance is effective for financial statements issued for fiscal years and interim periods beginning after November 15, 2009, and early adoption is prohibited. The guidance applies prospectively to transfers of financial assets occurring on or after the effective date. We are currently assessing the impact of ASC 860 and do not expect the adoption of this guidance to have a material impact on our consolidated financial statements.

In October 2009, the FASB issued ASU Update No. 2009-13**,** *Revenue Recognition (Topic 605), Multiple Deliverable Revenue Arrangements*. This guidance eliminates the residual method of allocation and requires the relative selling price method when allocating deliverables of a multiple-deliverable revenue arrangement. The determination of the selling price for each deliverable requires the use of a hierarchy designed to maximize the use of available objective evidence, including: vendor specific objective evidence, third party evidence of selling price, or estimated selling price. The guidance is effective prospectively for revenue arrangements entered into or materially modified in fiscal years beginning on or after June 15, 2010, and must be adopted in the same period using the same transition method. If adoption is elected in a period other than the beginning of a fiscal year, the amendments in these standards must be applied retrospectively to the beginning of the fiscal year. Full retrospective application of these amendments to prior fiscal years is optional. Early adoption of these standards may be elected. We will adopt these standards on September 1, 2010 and are currently reviewing the impact on our consolidated financial statements.

In January 2010, the FASB issued Accounting Standards Update, or ASU, 2010-06, *Fair Value Measurements and Disclosures (Topic 820): Improving Disclosures about Fair Value Measurements*, or ASU 2010-6. The ASU amends Subtopic 820-10 with new disclosure requirements and clarification of existing disclosure requirements. New disclosures required include the amount of significant transfers in and out of levels 1 and 2 fair value measurements and the reasons for the transfers. In addition, the reconciliation for level 3 activity will be required on a gross rather than net basis. The ASU provides additional guidance related to the level of disaggregation in determining classes of assets and liabilities and disclosures about inputs and valuation techniques. The amendments are effective for annual or interim reporting periods beginning after December 15, 2009, except for the requirement to provide the reconciliation for level 3 activity on a gross basis, which will be effective for fiscal years beginning after December 15, 2010. We are currently assessing the impact of ASU 2010-6 and do not expect the adoption of this guidance to have a material impact on our consolidated financial statements.

In April 2010, the FASB issued ASU 2010-17*, Revenue Recognition – Milestone Method (Topic 605): Milestone Method of Revenue Recognition* ("ASU 2010-17"). ASU 2010-17 provides guidance on defining a milestone and determining when it may be appropriate to apply the milestone method of revenue recognition for research or development transactions. Consideration that is contingent on achievement of a milestone in its entirety may be recognized as revenue in the period in which the milestone is achieved only if the milestone is judged to meet certain criteria to be considered substantive. Milestones should be considered substantive in their entirety and may not be bifurcated. An arrangement may contain both substantive and nonsubstantive milestones, and each milestone should be evaluated individually to determine if it is substantive. ASU 2010-17 is effective on a prospective basis for milestones achieved in fiscal years, and interim periods within those years, beginning on or after June 15, 2010, with early adoption permitted. We will adopt ASU 2010-17 as of September 1, 2010 and do not expect the adoption of this guidance to have a material impact on our consolidated financial statements.

ITEM 7A: QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

Per Item 305(e) of Regulation S-K, information is not required.

ITEM 8: FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

The information required to be filed in this item appears on pages F-1 to F-41 of this Annual Report on Form 10-K.

Documents filed as part of this annual report on Form 10-K:

Financial Statements

PART I – FINANCIAL INFORMATION

ITEM 9: CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

ITEM 9A: CONTROLS AND PROCEDURES

As of August 31, 2010, we performed an evaluation of the effectiveness of our disclosure controls and procedures that are designed to ensure that the information required to be disclosed in the reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by us in the reports that we file or submit under the Exchange Act, is accumulated and communicated to the our management, including our principal executive and principal financial officers, or persons performing similar functions, as appropriate to allow timely decisions regarding required disclosure. Based on our evaluation, our management, including our Chief Executive Officer and Chief Financial Officer, has concluded that our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) of the Securities Exchange Act of 1934, as amended) as of August 31, 2010, are effective at a reasonable assurance level.

Our management, under the supervision of our Chief Executive Officer and Chief Financial Officer, is responsible for establishing and maintaining adequate internal control over our financial reporting, as defined in Rules 13a-15(f) and 15d-15(f) of the Exchange Act. The Company's internal control over financial reporting is defined as a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. Internal control over financial reporting includes policies and procedures that: (i) pertain to the maintenance of records that in reasonable detail accurately and fairly reflect our transactions and asset dispositions; (ii) provide reasonable assurance that transactions are recorded as necessary to permit the preparation of our financial statements in accordance with generally accepted accounting principles, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and (iii) provide reasonable assurance regarding the prevention or timely detection of unauthorized acquisition, use or disposition of assets that could have a material effect on our financial statements.

Due to its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, we conducted an evaluation of the effectiveness of our internal control over financial reporting based on the framework in Internal Control —Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on our evaluation under the framework in Internal Control—Integrated Framework, our management concluded that our internal control over financial reporting was effective as of August 31, 2010.

This Annual Report on Form 10-K does not include an attestation report of our registered public accounting firm regarding internal control over financial reporting. Management's report was not subject to attestation by our registered public accounting firm pursuant recent Federal legislation that permits us to provide only management's report in this Annual Report.

Changes in Internal Control Over Financial Reporting

During the most recent fiscal quarter, there have not been any changes in our internal control over financial reporting or in other factors that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION

None.

PART III

ITEM 10: DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

Directors

The following table sets forth the name, age and position of each of our directors as of November 5, 2010.

Name	Age	Position(s) Held with the Company
Christopher M. Starr, Ph.D.	58	Chief Executive Officer and Director
Raymond W. Anderson (1)(2)(3)	68	Director
Erich Sager	52	Director
Richard L. Franklin, M.D., Ph.D. (1)(2)	65	Director
Llew Keltner, M.D., Ph.D. (1)(2)(3)	60	Director

(1) Member of the Corporate Governance and Nominating Committee.
(2) Member of the Audit Committee.
(3) Member of the Compensation Committee.

All of the current members of our board of directors were appointed in connection with the consummation of the 2009 Merger. Prior to the 2009 Merger, Drs. Starr and Franklin, and Messrs. Anderson and Sager served on the board of directors of RPC. Each of the current members of our board of directors has been elected to serve until our next annual meeting of stockholders or until their respective successors are duly elected and qualified.

Business Experience and Directorships

The following describes the background of our directors.

Christopher M. Starr, Ph.D., Chief Executive Officer. Dr. Starr has served as the Chief Executive Officer and a director of Raptor Pharmaceutical Corp. since September 2009. Dr. Starr was a co-founder of RPC and has served as the Chief Executive Officer, President and director thereof since its inception in 2006. Dr. Starr has served as Chief Executive Officer of our wholly owned subsidiary, Raptor Pharmaceutical Inc., since its inception in September 2005. Dr. Starr co-founded BioMarin Pharmaceutical Inc., or BioMarin, in 1997 where he last served as Senior Vice President and Chief Scientific Officer prior to joining the Company in 2006. As Senior Vice President at BioMarin, Dr. Starr was responsible for managing a Scientific Operations team of 181 research, process development, manufacturing and quality personnel through the successful development of commercial manufacturing processes for its enzyme replacement products, and supervised the cGMP design, construction and licensing of BioMarin's proprietary biological manufacturing facility. From 1991 to 1998, Dr. Starr supervised research and commercial programs at BioMarin's predecessor company, Glyko, Inc., where he served as Vice President of Research and Development. Prior to his tenure at Glyko, Inc., Dr. Starr was a National Research Council Associate at the National Institutes of Health. Dr. Starr earned a B.S. from Syracuse University and a Ph.D. in Biochemistry and Molecular Biology from the State University of New York Health Science Center, in Syracuse, New York. We nominated Dr. Starr to the Board of Directors due to his extensive experience at BioMarin Pharmaceutical where he was directly involved in the successful approval of two drugs for orphan indications.

Raymond W. Anderson. Mr. Anderson has served as a director of Raptor Pharmaceutical Corp. since September 2009 and as a director of RPC since May 2006. Mr. Anderson worked at Dow Pharmaceutical Sciences, Inc. (a wholly owned subsidiary of Valeant Pharmaceuticals International) from 2003 until he retired in June 2010,

had been its Managing Director since August 2009 and was previously its Chief Financial Officer and Vice President, Finance and Administration. Mr. Anderson has more than 30 years of healthcare industry experience, primarily focused in financial management within the biopharmaceutical sector. Prior to joining Dow in 2003, he was Chief Financial Officer for Transurgical, Inc., a private medical technology company.

Prior to that, Mr. Anderson served as Chief Operating Officer and Chief Financial Officer at BioMarin from June 1998 to January 2002.Prior to June 1998, Mr. Anderson held similar executive-level positions with other biopharmaceutical companies including Syntex, Chiron, Glycomed and Fusion Medical Technologies. Mr. Anderson holds an M.B.A. from Harvard University, an M.S. in Administration from George Washington University and a B.S. in Engineering from the United States Military Academy. We nominated Mr. Anderson to the Board of Directors due to his 30 years of healthcare experience in the areas of operations and finance.

Erich Sager. Mr. Sager has served as a director of Raptor Pharmaceutical Corp. since September 2009 and as a director of RPC since May 2006. He is a founding partner of Limetree Capital SA, a Swiss-based investment banking boutique. Mr. Sager also serves as Chairman and member of the board of directors at Calltrade Carrier Services AG, a European wholesale phone operator, and has held such position since 2004. He is also a current board member of Zecotek Medical Systems Inc. and Pulse Capital Corp. Mr. Sager served on the board of directors of BioMarin from November 1997 to March 2006 and as Chairman of LaMont Asset Management SA, a private investment management firm, from September 1996 until August 2004. Mr. Sager has held the position of Senior Vice President, Head of the Private Banking for Dresdner Bank (Switzerland) Ltd., Vice President, Private Banking, Head of the German Desk for Deutsche Bank (Switzerland) Ltd., and various positions at banks in Switzerland. Mr. Sager received a business degree from the School of Economics and Business Administration, Zurich, Switzerland. We nominated Mr. Sager to the Board of Directors due to his knowledge of healthcare fundraising in Europe including through his experience at BioMarin Pharmaceutical.

Richard L. Franklin, M.D., Ph.D. Dr. Franklin has served as a director of Raptor Pharmaceutical Corp. since September 2009 and as a director of RPC since July 2008. Dr. Franklin has served as Chairman of the board of directors of SyntheMed, Inc., a biomaterials company engaged in the development and commercialization of medical devices, since June 2003 and as a director of SyntheMed, Inc., since December 2000. Since September 2002, Dr. Franklin has been Chairman of DMS Data Systems, an internet-based information services company. Dr. Franklin has served as the Chief Executive Officer and Director of Tarix Pharmaceuticals, a drug development company, since 2004 and as Chairman of Pathfinder, LLC, a regenerative medicine company, since 2009. From May 1996 to September 2002, Dr. Franklin had been Chief Executive of Phairson, Ltd., a medical product development company. From January 1991 to May 1996, Dr. Franklin was founder and principal of Richard Franklin & Associates and from January 1988 to December 1990, Dr. Franklin was with Boston Capital Group, both of which are consulting firms to the healthcare industry. From July 1986 to December 1987, Dr. Franklin was head of Healthcare Corporate Finance at Tucker Anthony, an investment banking firm. Dr. Franklin received an M.A. in Mathematics from University of Wisconsin, a Ph.D. in Mathematics from Brandeis University and an M.D. from Boston University School of Medicine. We nominated Dr. Franklin to the Board of Directors due to his experience as a CEO and Chairman of various healthcare companies.

Llew Keltner, M.D., Ph.D. Dr. Keltner has served as a director of Raptor Pharmaceutical Corp. since September 2009. Dr. Keltner was Chief Executive Officer and President of Light Sciences Oncology, a privately-held biotechnology company developing a late stage, light-activated therapy for hepatocellular cancer and other solid tumors from 2001 to 2010. He is also Chief Executive Officer of EPISTAT, an international healthcare technology transfer, corporate risk management and healthcare strategy company that he founded in 1972. From 1997 to 2004, Dr. Keltner was Chief Executive Officer of Metastat, a development-stage biotech company focused on cancer metastasis. Dr. Keltner holds positions on the boards of Infostat, Oregon Life Sciences, and Goodwell Technologies. He is a previous director on the boards of Light Sciences Corporation, Vital Choice, Thesis Technologies, Oread Companies, and MannKind Corporation. He has also been a scientific advisory board member at Lifetime Corporation, ASB Meditest, Oread Laboratories, Hall-Kimbrell, and aai Pharma. He is currently a member of the American Society of Clinical Oncology, American Medical Association, International Association of Tumor Marker Oncology, American Association of Clinical Chemistry, and Drug Information Association.

Dr. Keltner received an M.S. in Epidemiology and Biostatistics; Ph.D. in Biomedical Informatics and M.D. from Case Western Reserve University in Cleveland, Ohio. Dr. Keltner has also authored several research publications.

We nominated Dr. Keltner to the Board of Directors due to his practical experience as a current CEO of a private life sciences company and due to his medical knowledge and network within the biotechnology industry.

Audit Committee

The audit committee of our board of directors, herein referred to as the Audit Committee, has been established in accordance with Section 3(a)(58)(A) of the Exchange Act. The Audit Committee is responsible for overseeing our accounting and financial reporting processes. In such capacity, our Audit Committee (a) has sole authority to appoint, replace and compensate our independent registered public accounting firm and is directly responsible for oversight of its work; (b) approves all audit fees and terms, as well as any permitted non-audit services performed by our independent registered public accounting firm; (c) meets and discusses directly with our independent registered public accounting firm its audit work and related matters; (d) oversees and performs investigations with respect to our internal and external auditing procedures, including the receipt, retention and treatment of complaints received by us regarding accounting, internal accounting controls or auditing matters and the confidential and anonymous submission by employees of concerns regarding questionable accounting or auditing matters and (e) undertakes such other activities as the Audit Committee deems necessary or advisable and as may be required by applicable law.

Mr. Anderson has been designated as the "audit committee financial expert" as defined by the regulations promulgated by the SEC. Our board of directors has determined that each member of the Audit Committee is independent as defined by NASDAQ and SEC rules applicable to audit committee members.

Section 16(a) Beneficial Ownership Reporting Compliance

Section 16(a) of the Exchange Act requires our directors, executive officers and holders of more than ten percent of a registered class of our equity securities, or 10% Stockholders, to file reports of ownership and reports of changes in ownership of our common stock and other equity securities with the SEC. Directors, executive officers and 10% Stockholders are required to furnish us with copies of all Section 16(a) forms they file. To our knowledge, based on a review of the copies of such reports furnished to us, we believe that during the fiscal year ended August 31, 2010, our directors, executive officers and 10% Stockholders timely filed all Section 16(a) reports applicable to them. During the fiscal year ended August 31, 2010, the following Form 4s were filed late: Dr. Rioux filed a Form 4 on July 9, 2010, which was seven business days late, reporting the receipt of a stock option grant in fulfillment of a milestone; Mr. Daley filed a Form 4 on July 9, 2010, which was eight business days late, reporting the receipt of restricted common stock in fulfillment of a milestone; and Dr. Franklin filed a Form 4 on March 12, 2010, which was one day late, reporting the receipt of a stock option grant for compensation for his services as a director.

Code of Ethics

We have adopted a Code of Business Conduct and Ethics, which is applicable to our directors and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller or persons performing similar functions. Our Code of Business Conduct and Ethics is posted on the "Investors & Media–Corporate Governance" section of our website at www.raptorpharma.com. If we make any substantive amendments to our Code of Business Conduct and Ethics or grant any waiver from a provision of the Code of Business Conduct and Ethics to any executive officer or director, we will promptly disclose the nature of the amendment or waiver in the "Investors & Media—Corporate Governance" section of our website at www.raptorpharma.com and/or in our public filings with the SEC.

Executive Officers

The following table sets forth the name, age, date first appointed to serve as an executive officer, and position held by each of our executive officers as of November 5, 2010. Our executive officers are elected by our board of directors on an annual basis and serve at the discretion of our board of directors or until their successors have been duly elected and qualified.

Name	Age	Position(s) Heldwith the Company
Christopher M. Starr, Ph.D.	58	Chief Executive Officer and Director
Todd C. Zankel, Ph.D.	47	Chief Scientific Officer
Thomas (Ted) E. Daley	47	President, Raptor Therapeutics Inc.
Patrice P. Rioux, M.D., Ph.D.	59	Chief Medical Officer, Raptor Therapeutics Inc.
Kim R. Tsuchimoto	47	Chief Financial Officer, Treasurer and Secretary

The following describes the background of our executive officers except for Dr. Starr, whose background is described above under the heading “Business Experience and Directorships.”

Todd C. Zankel Ph.D. As of September 29, 2009, Dr. Zankel was appointed our Chief Scientific Officer. Prior to that, Dr. Zankel was a co-founder and has been Chief Scientific Officer of our wholly owned subsidiaries, Raptor Pharmaceutical Inc. and Raptor Pharmaceuticals Corp., since their inception in 2006. From 1997 to 2005, Dr. Zankel served as a Senior Director of Research at BioMarin. Prior to 1997, Dr. Zankel was a fellow for the National Institutes of Health at the Plant Gene Expression Center in Berkeley, California and at the Swiss Institute of Technology in Zurich, Switzerland. Dr. Zankel has been the author of a number of peer-reviewed articles in a variety of scientific areas. Dr. Zankel earned a B.A. from Reed College in Portland, Oregon and a Ph.D. from Columbia University.

Thomas (Ted) E. Daley. As of September 29, 2009, Mr. Daley joined us as President and a board member of Raptor Therapeutics Inc., a wholly-owned indirect subsidiary acquired in the 2009 Merger. Mr. Daley joined Raptor Therapeutics Inc. following the acquisition by it of Convivia, Inc., which Mr. Daley founded. Mr. Daley was co-founder, VP business development and chief operating officer of Instill Corporation, a leading electronic commerce services provider to the US foodservice industry. Between 1993 and 2001 Mr. Daley helped raise over $50 million in venture capital and build Instill to a 150+ person operation with a nationwide customer base. After leaving Instill, from 2001 and 2007, Mr. Daley served in executive and consulting roles to a number of technology startup companies including MetricStream, Inc., PartsRiver and Certicom Security. Prior to that time, Mr. Daley worked in operations management for Anheuser-Busch, Inc., and consulted to Gordon Biersch Brewing Company and Lion Breweries (New Zealand). Mr. Daley received a BS in Fermentation Science from University of California at Davis, and an MBA from Stanford University.

Patrice P. Rioux, M.D., Ph.D. As of September 29, 2009, Dr. Rioux joined us as Chief Medical Officer of Raptor Therapeutics Inc., a wholly-owned indirect clinical subsidiary acquired in the 2009 Merger. Prior to joining Raptor Therapeutics Inc. in April 2009, from November 2008 until March 2009, Dr. Rioux served as Chief Medical Officer of FerroKin Biosciences, an early-stage developer of iron chelator for treatment of anemias. From May 2005 to October 2008, he was Chief Medical Officer and Vice President Clinical/Regulatory for Edison Pharmaceuticals, which focused on developing drugs to treat inherited and acquired energy impairment diseases. From January 2004 through March 2006, Dr. Rioux was an independent clinical operations consultant. Dr. Rioux’ three-decade career includes positions at Repligen Corp., Arrow International, Variagenics, Inc., Biogen and GRP (Groupement de Recherche en Pharmacologie). From 1975 to 1995, Dr. Rioux was a researcher in Clinical Research and Epidemiology at INSERM (Institut National de la Sante et de la Recherche Medicale), a French organization that supports national research in the medical field. Educated in France, Dr. Rioux has an M.D., a Ph.D. in Mathematical Statistics, and a Masters degree in Pharmacology.

Kim R. Tsuchimoto. As of September 29, 2009, Ms. Tsuchimoto was appointed our Chief Financial Officer, Treasurer and Secretary. Prior to that Ms. Tsuchimoto has served as the Chief Financial Officer, Treasurer and Secretary of our wholly owned subsidiaries, Raptor Pharmaceutical Inc. and Raptor Pharmaceuticals Corp., since their respective inceptions in 2006. Prior to this, Ms. Tsuchimoto served as Interim Controller at International Microcomputer Software, Inc., a software and Internet content company, from October 2005 to March 2006. From June 2005 to August 2005, Ms. Tsuchimoto served as Assistant Vice President, Controller at SpatiaLight Inc., a high technology company.

From February 1997 to June 2005, Ms. Tsuchimoto served at BioMarin and its predecessor company, Glyko, Inc., most recently as Vice President, Treasurer for two years, Vice President, Controller for two years and prior to that, as Controller. Prior to her employment at BioMarin, Ms. Tsuchimoto served as Controller of a marketing consulting firm and an international venture

capital firm and worked as a staff accountant in a local public accounting firm. Ms. Tsuchimoto is an inactive licensed California Certified Public Accountant and holds a B.S. in Business Administration with an emphasis in Accounting from San Francisco State University.

Relationships Among Executive Officers and Directors

There are no family relationships among any of our directors or executive officers.

ITEM 11: EXECUTIVE COMPENSATION

Stock Option and Equity Incentive Programs

Stock Options. Stock options granted by us have an exercise price equal to the fair market value of our common stock on the day prior to grant, typically vest over a four-year period with 6/48ths vesting six months after the vesting commencement date and the remainder vesting ratably each month thereafter based upon continued employment, and generally expire ten years after the date of grant. Incentive stock options also include certain other terms necessary to assure compliance with the Code.

The options that were granted to named executive officers are set forth in the "Grants of Plan-Based Awards" table below. All options granted to named executive officers are intended to be qualified incentive stock options as defined under Section 422 of the Code to the extent possible. Pursuant to Dr. Rioux's offer letter executed in April 2009, Dr. Rioux is eligible to receive separate grants of bonus stock options exercisable for up to 11,656 shares of our common stock on achievement during his employment of the following milestones: achievement of a successful pilot clinical trial of DR Cysteamine in cystinosis; first patient dosed in a pivotal clinical trial of DR Cysteamine in cystinosis; filing of a New Drug Application for DR Cysteamine in cystinosis; and marketing approval of DR Cysteamine in cystinosis. In March 2010, Dr. Rioux was granted options to purchase 11,656 of our common stock for the issuance of a final clinical study report of our pilot clinical trial of DR Cysteamine. Such stock options vested immediately with an exercise price of $1.66 per share and expire in 10 years from grant. In June 2010, Dr. Rioux was granted options to purchase 11,656 of our common stock for the commencement of our pivotal Phase 3 clinical trial of DR Cysteamine. Such stock options vested immediately with an exercise price of $3.05 per share and expire in 10 years from grant. In November 2010, Dr. Rioux agreed to accept a cash bonus of $25,000 in lieu of cancelling the potential milestone stock option grants for filing for marketing approval of DR Cysteamine for cystinosis and for the potential resultant marketing approval.

In March 2010, the Compensation Committee hired an outside consultant to benchmark our salaries and bonuses against a well-established industry salary survey for life science companies in the San Francisco Bay Area with less than 50 employees. The Compensation Committee also reviewed the progress we had achieved to-date. Along with the cash bonuses and salary review, the Compensation Committee recommended and the full Board approved the following stock option grants to officers at an exercise price of $2.02 per share, vesting commencing September 1, 2009 with a six month cliff vest and 1/48th per month thereafter with a 10 year expiry from grant date: Dr. Starr 46,750; and Mr. Daley 18,900.

Named Executive Officer Compensation

Summary Compensation Table

Name and Principal Position	Fiscal Year (ending August 31)	Salary ($)(1)	Bonus ($)*	Stock Awards (1)($)	Option Awards (2)($)	Non-Equity Incentive Plan Compensation ($)	NQDC Earnings ($)	All Other Compensation ($)(3)	Total ($)
Christopher M. Starr, Ph.D.	2010	277,200	68,280	—	8,827	—	—	1,266	355,573
Chief Executive Officer and Director	2009	213,610	—	—	27,883	—	—	6,399	247,892
Ted Daley,	2010	240,800	78,100	35,551	25,992	—	—	1,234	381,677
President, Raptor Therapeutics Inc.	2009	208,401	40,000	27,000	22,077	—	—	7,806	305,284
Patrice P. Rioux, M.D., PhD.	2010	283,208	25,000	—	47,074	—	—	1,678	356,960
Chief Medical Officer, Raptor Therapeutics Inc	2009	94,759	—	—	1,696	—	—	419	96,874

* Cash bonuses for 2010 include accruals of bonuses paid in October 2010 based upon milestones achieved by us for the period March 1, 2010 through August 31, 2010 as follows: Dr. Starr, $41,580; Mr. Daley $30,100; and Dr. Rioux $25,000.

(1) Dr. Starr's full time employment commenced on May 1, 2006 at an annual base salary of $150,000. Dr. Starr's salary increased to $213,610 in July 2008 and to $277,200 effective on September 1, 2009.. Mr. Daley's full-time employment commenced on September 10, 2007 at an annual base salary of $150,000, which increased to $208,401 in July 2008 and to $240,800 effective September 1, 2009. Dr. Rioux's full time employment commenced on April 15, 2009 at an annual base salary of $280,000, which increased to $287,000 effective April 15, 2010.

(2) This column represents the dollar amount recognized for financial statement reporting purposes with respect to the fiscal years ended August 31, 2010 and 2009 for the fair value of the stock options granted to each of named executive officers since inception, in accordance with ASC Topic 718. The amounts shown exclude the impact of estimated forfeitures related to service-based vesting conditions. For additional information on the valuation assumptions with respect to the fiscal years ended August 31, 2010 and 2009, please refer to the notes in our consolidated financial statements included elsewhere in this Annual Report on Form 10-K. These amounts reflect our accounting expense for these awards, and do not correspond to the actual value that will be recognized by the named executive officers.

(3) All Other Compensation includes 401(k) matching funded by us through March 28, 2009, at which time such matching was discontinued, and life insurance premiums paid by us where the executive is the beneficiary.

Employment Agreements

Drs. Starr and Zankel and Ms. Tsuchimoto entered into employment agreements with our wholly owned subsidiaries, Raptor Pharmaceutical Inc. and RPC, in May 2006. The employment agreements described below remained operative following the consummation of the 2009 Merger and are currently still in effect.

Each employment agreement had an initial term of three years commencing on May 1, 2006 in the case of Dr. Starr and Ms. Tsuchimoto and May 15, 2006 in the case of Dr. Zankel, and automatically renews for additional one year periods unless either party under such agreement notifies the other that the term will not be extended. Under their agreements, each officer is entitled to an annual salary ($150,000 each for Drs. Starr and Zankel and $160,000 for Ms. Tsuchimoto), the amount of which may be increased from time to time in the discretion of our board of directors, and stock options to purchase 58,281 shares of our common stock, which vested over three years with a six month cliff vest. Dr. Starr's, Dr. Zankel's and Ms. Tsuchimoto's annual salaries are subject to annual review and potential increase by our board of directors. In addition, they are each eligible to receive annual bonuses in cash or stock options as awarded by our

board of directors, at its discretion. Information regarding Dr. Starr's annual salary and bonus received during the year ended August 31, 2010 are described above under the heading "Named Executive Officer Compensation."

On September 7, 2007, our wholly-owned subsidiary, Raptor Therapeutics Inc., entered into an employment agreement with Ted Daley for a term of 18 months which automatically renews for additional one year periods unless either party under such agreement notifies the other that the term will not be extended. Under Mr. Daley's agreement, Mr. Daley is entitled to an annual salary of $150,000 and stock options to purchase 34,969 shares of our common stock at an exercise price of $2.23 per share, which vest over four years with a six month cliff vest. In August 2008, RPC's compensation committee recommended, and its full

board of directors approved, a stock option grant to Mr. Daley for the purchase of 23,313 shares of our common stock at an exercise price of $1.88 per share, which vests 6/48ths upon the six-month anniversary of the grant date and 1/48th per month thereafter and expires ten years from the grant date. Mr. Daley's 2008 stock options were granted in order to increase his initial employment stock option grant to be equal to the stock option grants of our other executive officers. Mr. Daley's annual salary is subject to annual review and potential increase by our board of directors. In addition, Mr. Daley is eligible to receive certain bonuses in cash and stock options based on triggering events related to the successful development of our Convivia™ product development program. Information regarding Mr. Daley's annual salary and bonuses received during the year ended August 31, 2010 are described above under the heading "Named Executive Officer Compensation."

Each of Drs. Starr's and Zankel's, Ms. Tsuchimoto's and Mr. Daley's respective employment agreements were amended effective as of January 1, 2009 for purposes of bringing such employment agreements into compliance with the applicable provisions of Section 409A of the Code and the Treasury Regulations and interpretive guidance issued thereunder.

In April 2009, RPC executed an employment offer to Dr. Rioux with an annual base salary of $280,000. Dr. Rioux's annual salary is subject to annual review and potential increase by our board of directors. In addition, Dr. Rioux is eligible to receive certain bonuses in cash and stock options based on triggering events related to the successful development of DR Cysteamine. Information regarding Dr. Rioux's annual salary and bonuses received during the year ended August 31, 2010 are described above under the heading "Named Executive Officer Compensation."

Except for Dr. Rioux and Mr. Daley, if any officer's employment is constructively terminated or terminated by us without cause, including in the event of a change of control, then such officer will be entitled to continue to receive his or her base salary, bonuses and other benefits for a period of 12 months from the date of termination. If Dr. Rioux's or Mr. Daley's employment is constructively terminated or terminated by us without cause, including in the event of a change of control, then he will be entitled to continue to receive his base salary and other certain benefits for a period of six months from the date of termination.

Except for Dr. Rioux, if any officer's employment is terminated for cause, by death or due to a voluntary termination, we shall pay to such officer, or in the case of termination due to death, his or her estate, the compensation and benefits payable through the date of termination.

Except for Dr. Rioux, if any officer's employment is terminated due to disability, we shall pay to such officer the compensation and benefits payable through the date of termination and shall continue to pay such officer salary and a prorated bonus for three months following such termination, at the end of which time such officer may be entitled to receive short-term and eventually long-term disability benefits, subject to the terms of and pursuant to our then current disability insurance plans.

Stock Option Grants and Exercises During the Fiscal Year Ended August 31, 2010

Grants of Plan-Based Awards Table

The following table sets forth information concerning stock option grants made during the fiscal year ended August 31, 2010 to our executive officers named in the "Summary Compensation Table" above. The fair value information in the far right column is for illustration purposes only and is not intended to predict the future price of our common stock. The actual future value of such stock options will depend on the market value of our common stock.

		Estimated Future Payouts Under Non-Equity Incentive Plan Awards			Estimated Future Payouts Under Equity Incentive Plan Awards			All Other Stock Awards: Number of Shares of Stock	All Other Option Awards: Number of Securities Underlying	Exercise or Base Price of Option Awards	Grant Date Fair Value of Stock and Option
Name	Grant Date	Thres-hold ($)	Target ($)	Maximum ($)	Threshold ($)	Target ($)	Maximum ($)	Or Units (#)	Options (#) (1)	($/Sh)	Awards ($) (2)
Christopher M. Starr, Ph.D.	3/9/10	—	—	—	—	—	—	—	46,750	2.02	8,827
Ted Daley	3/9/10	—	—	—	—	—	—	—	18,900	2.02	3,569
Patrice P. Rioux, M.D., Ph.D.	3/30/10	—	—	—	—	—	—	—	11,656	1.66	13,969
	6/28/10	—	—	—	—	—	—	—	11,656	3.05	25,636

(1) These stock options vest 6/48ths on the six-month anniversary of the grant date and 1/48th per month thereafter. The options expire 10 years from grant date.

(2) This column represents the dollar amount recognized for financial statement reporting purposes with respect to our year ended August 31, 2010 for the fair value of the stock options granted to each of the named executive officers in the fiscal year ended August 31, 2010 in accordance with ASC Topic 718. The amounts shown exclude the impact of estimated forfeitures related to service-based vesting conditions. These amounts reflect our accounting expense for these awards, and do not correspond to the actual value that will be recognized by the named executive officers.

Outstanding Equity Awards at August 31, 2010

The following table sets forth certain information with respect to outstanding stock option awards of our executive officers for the fiscal year ended August 31, 2010.

	Option Awards				
Name	Number of Securities Underlying Unexercised Options (#) Exercisable	Number of Securities Underlying Unexercised Options (#) Unexercisable	Equity Incentive Plan Awards: Number of Securities Underlying Unexercised Unearned Options (#)	Option Exercise Price ($)	Option Expiration Date
Christopher M. Starr, Ph.D.	58,281 (1)	—	—	2.83	5/26/2016
	10,719(3)	36,031	—	2.02	3/9/2020
Ted Daley	25,497 (2)	9,472	—	2.23	9/10/2017
	11,656 (2)	11,657	—	1.88	8/12/2018
	4,333 (3)	14,567	—	2.02	3/9/2020
Patrice P. Rioux, M.D., Ph.D.	11,656 (2)	23,313	—	0.85	4/16/2019
	11,656 (4)	—	—	1.66	3/30/2020
	11,656 (4)	—	—	3.05	6/28/2020

(1) Stock options vest 6/36ths on the six month anniversary of grant date and 1/36th per month thereafter.
(2) Stock options vest 6/48ths on the six month anniversary of grant date and 1/48th per month thereafter.
(3) Stock options vest 6/48ths on grant date and1/48th per month thereafter.
(4) Stock options vest 100% upon grant date.

Option Exercises

There were no option exercises by our executive officers during the fiscal year ended August 31, 2010.

Executive Payments Upon Termination

Change in control arrangements are designed to retain executives and provide continuity of management in the event of a change in control. These agreements are described in more detail elsewhere in this Annual Report on Form 10-K, including the sections titled “Employment Agreements” and “Named Executive Officer Compensation.”

The following table quantifies the amounts that we would owe each of our executive officers upon each of the termination triggers discussed above under “Employment Agreements,” assuming a termination date of August 31, 2010:

Christopher M. Starr, Ph.D.
Chief Executive Officer, President and Director

Executive Benefits and Payments Upon Termination	Disability	Death	Termination Without Cause or Constructive Termination	CIC Whether or Not Services are Terminated
Base Salary	$ 69,300(3)	—	$ 277,200(2)	$ 277,200(2)
Short-Term Incentive	$ —(4)	$ —(4)	$ —(5)	$ —(5)
Value of Unvested Equity Awards and Accelerated Vesting Stock	—	—	—	55,564 (6)
Total	$ 69,300	$ —	$ 277,200	$ 332,764

(1) "CIC" means change in control, as defined in the officer's employment agreement.
(2) 12 months base salary.
(3) 3 months base salary.
(4) Pro rata bonus.
(5) Full cash bonus otherwise payable.
(6) Vesting of all stock options granted in accordance with ASC Topic 718. The amount shown excludes the impact of estimated forfeitures related to service-based vesting conditions. This amount reflects our accounting expense for these awards, and does not correspond to the actual value that will be recognized by the officer

Todd C. Zankel, Ph.D.
Chief Scientific Officer

Executive Benefits and Payments Upon Termination	Disability	Death	Termination Without Cause or Constructive Termination	CIC Whether or Not Services are Terminated (1)
Base Salary	$ 49,275(3)	$ —	$ 197,100(2)	$ 197,100(2)
Short-Term Incentive	—(4)	—(4)	—(5)	—(5)
Value of Unvested Equity Awards and Accelerated Vesting Stock Options	—	—	—	23,644(6)
Total	**$ 49,275**	**$ —**	**$ 197,100**	$ **220,744**

(1) "CIC" means change in control, as defined in the officer's employment agreement.
(2) 12 months base salary.
(3) 3 months base salary.
(4) Pro rata bonus.
(5) Full cash bonus otherwise payable.
(6) Vesting of all stock options granted in accordance with ASC Topic 718. The amount shown excludes the impact of estimated forfeitures related to service-based vesting conditions. This amount reflects our accounting expense for these awards, and does not correspond to the actual value that will be recognized by the officer.

Kim R. Tsuchimoto
Chief Financial Officer, Secretary and Treasurer

Executive Benefits and Payments Upon Termination	Disability	Death	Termination Without Cause or Constructive Termination	CIC Whether or Not Services are Terminated (1)
Base Salary	$ 60,200(3)	$ —	$ 240,800(2)	$ 240,800(2)
Short-Term Incentive	—(4)	—(4)	—(5)	—(5)
Value of Unvested Equity Awards and Accelerated Vesting Stock Options	—	—	—	29,060(6)
Total	**$ 60,200**	**$ —**	**$ 240,800**	$ **269,860**

(1) "CIC" means change in control, as defined in the officer's employment agreement.
(2) 12 months base salary.
(3) 3 months base salary.
(4) Pro rata bonus.
(5) Full cash bonus otherwise payable.
(6) Vesting of all stock options granted in accordance with ASC Topic 718. The amount shown excludes the impact of estimated forfeitures related to service-based vesting conditions. This amount reflects our accounting expense for these awards, and does not correspond to the actual value that will be recognized by the officer

Ted Daley
President, Raptor Therapeutics Inc.

Executive Benefits and Payments Upon Termination	Disability	Death	Termination Without Cause or Constructive Termination	CIC Whether or Not Services are Terminated (1)
Base Salary	$ 60,200(3)	$ —	$ 120,400(2)	$ 120,400(2)
Short-Term Incentive	—(4)	—(4)	—(5)	—(5)
Value of Unvested Equity Awards and Accelerated Vesting Stock Options	—	—	—	53,176(6)
Total	**$ 60,200**	**$ —**	**$ 120,400**	$ **173,576**

(1) "CIC" means change in control, as defined in the officer's employment agreement.
(2) 6 months base salary.
(3) 3 months base salary.
(4) Pro rata bonus.
(5) Full cash bonus otherwise payable.
(6) Vesting of all stock options granted in accordance with ASC Topic 718. The amount shown excludes the impact of estimated forfeitures related to service-based vesting conditions. This amount reflects our accounting expense for these awards, and does not correspond to the actual value that will be recognized by the officer.

Patrice P. Rioux, M.D., Ph.D.
Chief Medical Officer, Raptor Therapeutics Inc.

Executive Benefits and Payments Upon Termination	Disability	Death	Termination Without Cause or Constructive Termination	CIC Whether or Not Services are Terminated (1)
Base Salary	$ —	$ —	$ 143,500(2)	$ 143,500(2)
Short-Term Incentive	—	—	—	—
Value of Unvested Equity Awards and Accelerated Vesting Stock Options	—	—	—	19,648(3)
Total	**$ —**	**$ —**	**$ 143,500**	$ **163,148**

(1) "CIC" means change in control, as defined in the officer's employment agreement.
(2) 6 months base salary.
(3) Vesting of all stock options granted in accordance with ASC Topic 718. The amount shown excludes the impact of estimated forfeitures related to service-based vesting conditions. This amount reflects our accounting expense for these awards, and does not correspond to the actual value that will be recognized by the officer.

Equity Compensation Plan Information

The following table provides certain information with respect to all of our equity compensation plans in effect as of August 31, 2010:

Plan Category	Number of securities to be issued upon exercise of outstanding options, warrants and rights	Weighted average exercise price of outstanding options, warrants and rights	Number of securities remaining available for future issuance under equity compensation plans
Equity compensation plans approved by stockholders	1,391,288	14.25	2,697,228
Equity compensation plans not approved by stockholders	-	-	-
Total	1,391,288	14.25	2,697,228

Director Compensation

Effective October 1, 2009, our non-employee directors receive the following compensation: $60,000 cash compensation annually paid quarterly in arrears to the Chairman of the board and $40,000 cash compensation annually paid quarterly in arrears to all other non-employee directors. Effective September 1, 2010, the Chairman will received $68,000 annually and $48,000 for all other non-employee directors. No cash compensation is paid to our Chief Executive Officer for his services as a member of our board of directors. No formal plan exists regarding non-cash compensation to our non-employee directors at this time, but it is anticipated that a plan will be implemented over the next 12 months.

Upon joining RPC's board of directors on May 26, 2006, Mr. Anderson and Mr. Sager were granted stock options to purchase 116,562 shares and 233,124 shares, respectively, of our common stock at respective exercise prices of $2.57 per share. Such stock options vested 6/36ths on the six month anniversary of such grant and 1/36th per month thereafter and expire ten years from grant date. Upon joining the board of directors of RPC on July 10, 2008, Dr. Franklin was granted stock options to purchase 34,969 shares of our common stock at an exercise price of $2.23 per share, which vests 6/48ths on the six-month anniversary of such grant and 1/48th per month thereafter and expires ten years from grant date.

In addition, at the discretion of the stock option committee of RPC's board of directors, each non-employee director of RPC was entitled to receive options to purchase 23,313 shares of our common stock for each subsequent year of service on the company's board of directors. Such options were generally granted at fair market value one day preceding the grant date, vest 6/48ths on the six month

anniversary of the grant date and 1/48th per month thereafter and expire ten years from grant date. RPC made these grants to Mr. Anderson and Mr. Sager with respect to its fiscal year ended August 31, 2007, on June 14, 2007 at a per share exercise price of $2.57. No such annual grants were approved for the fiscal year ended August 31, 2010 or the fiscal year ended August 31, 2009.

Dr. Keltner was appointed to our board of directors immediately following the 2009 Merger on September 30, 2009 and was granted stock options to purchase up to 34,968 shares of our common stock at an exercise price of $3.30 per share, which vests 6/48ths on March 30, 2010 and 1/48th per month thereafter, with an expiry of ten years. Dr. Keltner's annual compensation for his services as a director was $40,000. Dr. Starr, who is our employee, did not receive additional compensation for his service as a director. On March 9, 2010, non-employee directors were granted options to purchase up to 15,000 shares of our common stock at an exercise price of $2.02 per share for their services for the fiscal year ended August 31, 2010. Such options vest commencing on September 1, 2009 over four years, with an expiry of ten years from the date of grant. The following table sets forth the total compensation paid by us to each of our non-employee directors during our fiscal year ended August 31, 2010.

Name	Fees Earned or Paid in Cash ($)	Option Awards($)(1)	Total($)
Raymond W. Anderson (2)	40,000	13,331	53,331
Erich Sager (3)	60,000	13,331	73,331
Richard L. Franklin, M.D. Ph.D. (4)	40,000	17,584	57,584
Llew Keltner, M.D., Ph.D. (5)	30,000	24,227	54,227

(1) Amounts shown do not reflect compensation actually received by a director, but reflect the dollar amount compensation cost recognized by us for financial statement reporting purposes (disregarding an estimate of forfeitures related to service-based vesting conditions) for the fiscal year ended August 31, 2010, in accordance with Financial Accounting Standards Board Accounting Standards Codification Topic 718, Compensation—Stock Compensation, herein referred to as ASC Topic 718, and thus may include amounts from awards granted in and prior to the fiscal year ended August 31, 2010. The assumptions underlying the calculations pursuant to ASC Topic 718 are set forth under Note 8 of the Notes to Consolidated Financial Statements, beginning on page F-23 of our Consolidated Financial Statements.

(2) Mr. Anderson had 154,875 options outstanding as of August 31, 2010, of which 138,456were exercisable.
(3) Mr. Sager had 271,437 options outstanding as of August 31, 2010, of which 255,018 were exercisable.
(4) Dr. Franklin had 48,969 options outstanding as of August 31, 2010, of which 21,651 were exercisable.
(5) Dr. Keltner had 49,968 options outstanding as of August 31, 2010, of which 11,452 were exercisable.

On October 12, 2010, each non-employee director was granted options to purchase up to 30,000 shares of our common stock at an exercise price of $2.97 per share for his services as a director for the fiscal year ending August 31, 2011. Such options commenced vesting on September 1, 2010, and vests 6/48ths on March 1, 2011 and 1/48th per month thereafter and expire 10 years from the grant date.

Defined Contribution Plan

We maintain a qualified retirement plan pursuant to Code Sections 401(a) and 401(k) covering substantially all employees, subject to certain minimum age and service requirements, herein referred to as our 401(k) Plan. Our 401(k) Plan allows such employees to make voluntary contributions. The assets of the 401(k) plan are held in trust for participants and generally are distributable upon the retirement, disability, death or other termination of employment of the participant.

Employees who participate in our 401(k) Plan may contribute to their 401(k) account up to the maximum amount that varies annually in accordance with the Code. We also make available to 401(k) plan participants the ability to direct the investment of their 401(k) accounts in a well-balanced spectrum of various investment funds.

At our discretion, we provide for a 401(k) matching in the amount of 100% of the first 3% of employee deferral and 50% of the next 2% of employee deferral, in compliance with the Internal Revenue Service's Safe Harbor rules. As of March 28, 2009, in order to preserve cash, we discontinued 401(k) matching for all of our employees. In October 2010, we re-implemented our 401(k) matching program for all employees.

ITEM 12: SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The following table sets forth, as of November 5, 2010, each beneficial owner (or group of affiliated beneficial owners) of more than five percent (5%) of any class of voting securities of Raptor Pharmaceutical Corp., each of our named executive officers as of the end of the fiscal year ended August 31, 2010, each our directors and all of our executive officers and directors as a group. Except as otherwise indicated, each listed stockholder directly owned his or her shares and had sole voting and investment power. Unless otherwise noted, the address for each person listed below is Raptor Pharmaceutical Corp., 9 Commercial Blvd., Suite 200, Novato, CA 94949.

Name of Beneficial Owner and Address	Number of Shares Of Common Stock Beneficially Owned	Number of Shares Subject to Options/ Options and Warrants (1)	Percentage of Outstanding Shares of Common Stock (2)
Entities affiliated with Deerfield Management Company, LP (3)	3,085,514	1,951,220	9.6%
Entities affiliated with Ayer Capital Management, LP (4)	2,977,429	1,172,760	9.5%
Aran Asset Management SA (5)	2,200,491	1,156,399	7.0%
Entities affiliated with Straus Capital Management, L.L.C. (6)	1,648,300	750,000	5.3%
Christopher M. Starr, Ph.D.	772,264	72,895	2.5%
Todd C. Zankel, Ph.D.	763,870	64,501	2.5%
Erich Sager	493,665	258,211	1.6%
Ted Daley	152,822	47,918	*
Kim R. Tsuchimoto	80,506	79,924	*
Patrice P. Rioux, M.D, Ph.D.	37,882	37,882	*
Raymond W. Anderson	141,649	141,649	*
Richard L. Franklin, M.D., Ph.D.	25,815	25,815	*
Llew Keltner, M.D., Ph.D.	15,616	15,616	*
All executive officers and directors as a group (8 persons)	2,484,089	744,411	8.2%

* Less than one percent.

(1) Beneficial ownership is determined in accordance with SEC rules and generally includes voting or investment power with respect to securities. Shares of common stock subject to options, warrants and convertible preferred stock currently exercisable or convertible, or exercisable or convertible within sixty (60) days of November 5, 2010, are counted as outstanding for computing the percentage held by each person holding such options or warrants but are not counted as outstanding for computing the percentage of any other person.

(2) Based on 30,213,378 shares outstanding as of November 5, 2010.

(3) Includes 429,024 shares and warrants to purchase 741,464 shares held by Deerfield Special Situations Fund, LP, and 705,270 shares and warrants to purchase 1,209,756 shares held by Deerfield Special Situations Fund International, Limited. Deerfield Special Situations Fund, LP and Deerfield Special Situations Fund International, Limited, (or collectively, the "Deerfield Funds") are affiliated with Deerfield Management Company, LP. The Deerfield Funds were issued warrants to purchase an aggregate of 1,951,220 shares of common stock in the 2010 Private Placement. However, these warrants are exercisable only to the extent that the number of shares beneficially held by the entities affiliated with Deerfield Management Company, LP does not exceed 9.999% of our outstanding stock and therefore, a portion of those warrants have not been counted as outstanding for purposes of computing the percentage held by the entities affiliated with Deerfield Capital Management, LP. The principal business address of each of the Deerfield Funds is 780 3rd Avenue, 37th Floor, New York, NY 10017.

(4) Includes (i) 144,570 shares and warrants to purchase 117,863 shares held by Epworth- Ayer Capital, (ii) 52,722 shares and warrants to purchase 28,077 shares held by Ayer Capital Partners Krestrel Fund, LP and (iii) 1,607,377 shares and warrants to purchase 1,026,820 shares held by Ayer Capital Partners Master Fund, LP (or collectively with Epworth-Ayer Capital and Ayer Capital Partners Krestrel Fund, LP, the "Ayer Capital Funds"). Each of the Ayer Capital Funds is affiliated with Ayer Capital Management, LP. The address for each of the Ayer Capital Funds is 230 California Street, Suite 600, San Francisco, CA 94111.

(5) The address for this entity is Bahnhofplatz, P.O. Box 4010, 6304 Zug, Switzerland. Aran Asset Management disclaims beneficial ownership of the shares registered in its name on behalf of its clients. The Chairman and CEO of Aran Asset Management SA is Michael C. Thalmann who disclaims beneficial ownership of these shares except to the extent of his pecuniary interest therein.

(6) Includes (i) 464,060 shares and warrants to purchase 403,060 shares held by Straus Partners, L.P. and (ii) 434,240 shares and warrants to purchase 346,820 shares held by Straus Healthcare Partners, L.P. (or collectively with Straus Partners, L.P., the "Straus Funds"). Each of the Straus Funds is affiliated with Straus Capital Management, L.L.C. The address for each of the Straus Funds is 767 Third Avenue, 21st Floor, New York, NY 10017.

ITEM 13: CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

Review, Approval or Ratification of Transactions with Related Persons

Since September 1, 2009, there has not been nor is there currently proposed any transaction or series of similar transactions to which we were or are to be a party in which the amount involved exceeds $120,000 and in which any of our directors, executive officers, persons who we know hold more than 5% of our common stock, or any member of the immediate family of any of the foregoing persons had or will have a direct or indirect material interest other than: (i) compensation agreements and other arrangements, which are described elsewhere in this Annual Report on Form 10-K, and (ii) the transactions described below.

We have entered into indemnity agreements with certain of our officers and directors which provide, among other things, that we will indemnify such officer or director, under the circumstances and to the extent provided for therein, for expenses, damages, judgments, fines and settlements he or she may be required to pay in actions or proceedings which he or she is or may be made a party by reason of his or her position as a director, officer or other agent of us, and otherwise to the fullest extent permitted under Delaware law and our Bylaws.

Pursuant to the terms of an asset purchase agreement, we and our wholly-owned subsidiary, Raptor Therapeutics Inc. purchased certain assets of Convivia, Inc., which was as of such time wholly-owned by Ted Daley (currently the President of Raptor Therapeutics Inc.). To date, in aggregate Mr. Daley has received 104,904 shares of our common stock and $90,000 in cash bonuses and may receive additional common stock and cash bonuses based on the successful development of our Convivia™ development program. Mr. Daley was hired to develop the Convivia™ product candidate along with other clinical-stage programs at Raptor Therapeutics Inc.

In the ordinary course of business, our officers have loaned money to us by paying travel expenses and equipment and other costs from their personal funds on our behalf. We have promptly reimbursed the officers for such expenses and costs.

Independence of Our Board of Directors

Our board of directors has determined that all current members of our board of directors are independent (as independence is currently defined in Rule 5605(a)(2) of the NASDAQ listing standards), except for Dr. Starr and Mr. Sager. Our board of directors has also determined that each member of our Audit Committee, Compensation Committee and Corporate Governance and Nominating Committee is independent as defined by the SEC and NASDAQ rules.

ITEM 14: PRINCIPAL ACCOUNTING FEES AND SERVICES

Independent Registered Public Accounting Firm

Since June 15, 2006, Burr Pilger Mayer, Inc. has served as our independent registered public accounting firm.

The following is a summary of the fees and services provided for our years ended August 31 2010 and 2009.

Description of Services Provided by Burr Pilger Mayer, Inc.	Year Ended August 31, 2010	Year Ended August 31, 2009
Audit Fees*	$ 128,081	$ 115,440
Audit Related Fees: These services relate to assurance and related services reasonably related to the performance of the audit or review of financial statements not included above.	133,036	66,271
Tax Compliance Fees: These services relate to the preparation of federal, state and foreign tax returns and other filings.	39,151	16,130
Tax Consulting and Advisory Services: These services primarily relate to the area of tax strategy and minimizing Federal, state, local and foreign taxes.	-	-
All Other Fees	-	-

* Audit Fees for August 31, 2010 includes unbilled audit fees for the year ended August 31, 2010, which is estimated to be $78,775.

As provided in the Audit Committee charter, the Audit Committee pre-approves all of the services provided by our independent registered public accounting firm. 100% of the above services and estimates of the expected fees were reviewed and approved by the Audit Committee before the respective services were rendered.

The Audit Committee has considered the nature and amount of the fees billed by Burr Pilger Mayer, Inc. and believes that the provision of the services for activities unrelated to the audit is compatible with maintaining Burr Pilger Mayer, Inc’s independence.

PART IV

ITEM 15: EXHIBITS, FINANCIAL STATEMENT SCHEDULES

The information required to be filed in this item appears on pages F-1 to F-41 of this Annual Report on Form 10-K.

Documents filed as part of this annual report on Form 10-K:

Exhibits

The following exhibits are filed as part of, or incorporated by reference into this Annual Report on Form 10-K:

Exhibit Index

2.1	Agreement and Plan of Merger and Reorganization, dated as of June 7, 2006, by and among Axonyx Inc., Autobahn Acquisition, Inc. and TorreyPines Therapeutics, Inc. (incorporated by reference to Annex A to Registration Statement No. 333-136018 filed on July 25, 2006).
2.2	Amendment No. 1 to Agreement and Plan of Merger and Reorganization, dated as of August 25, 2006, by and among Axonyx Inc., Autobahn Acquisition, Inc. and TorreyPines Therapeutics, Inc. (incorporated by reference to Annex A to Amendment No. 1 to Registration Statement No. 333-136018 filed on August 25, 2006).
2.3	Agreement and Plan of Merger and Reorganization, dated July 27, 2009, by and among Raptor Pharmaceuticals Corp., TorreyPines Therapeutics, Inc., a Delaware corporation, and ECP Acquisition, Inc., a Delaware corporation (incorporated by reference to Exhibit 2.3 to the Registrant's Current Report on Form 8-K, filed on July 28, 2009).
2.4	Form of Voting Agreement between TorreyPines Therapeutics, Inc. and certain stockholders of Raptor Pharmaceuticals Corp. (incorporated by reference to Exhibit 99.3 to the Registrant's Current Report on Form 8-K, filed on July 28, 2009).
2.5	Form of Voting Agreement between Raptor Pharmaceuticals Corp. and certain stockholders of TorreyPines Therapeutics, Inc. (incorporated by reference to Exhibit 99.2 to the Registrant's Current Report on Form 8-K, filed on July 28, 2009).
3.1	Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K, filed on October 10, 2006).
3.2	Bylaws of the Registrant (incorporated by reference to Exhibit 3.2 to the Registrant's Current Report on Form 8-K, filed on October 10, 2006).
3.3	Certificate of Amendment filed with the Secretary of State of the State of Nevada effecting an 8-for-1 reverse stock of the Registrant's common stock and changing the name of the Registrant from Axonyx Inc. to TorreyPines Therapeutics, Inc. (incorporated by reference to Exhibit 3.3 to the Registrant's Current Report on Form 8-K, filed on October 10, 2006).
3.4	Articles of Conversion filed with the Secretary of State of the State of Nevada changing the state of incorporation of the Registrant (incorporated by reference to Exhibit 3.4 to the Registrant's Current Report on Form 8-K, filed on October 10, 2006).
3.5	Certificate of Conversion filed with the Secretary of State of the State of Delaware (incorporated by reference to Exhibit 3.5 to the Registrant's Current Report on Form 8-K, filed on October 10, 2006).
3.6	Amendment to Bylaws of the Registrant (incorporated by reference to Exhibit 3.6 to the Registrant's Annual Report on Form 10-K, filed on March 29, 2007).
3.7	Charter Amendment for TorreyPines (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K, filed on October 9, 2009).
3.8	Certificate of Merger between Raptor Pharmaceuticals Corp., ECP Acquisition, Inc. and TorreyPines Therapeutics, Inc. (incorporated by reference to Exhibit 3.2 to the Registrant's Current Report on Form 8-K, filed on October 9, 2009).
4.1	Specimen common stock certificate of the Registrant (incorporated by reference to Exhibit 4.7 to the Registrant's Current Report on Form 8-K, filed on October 9, 2009).
4.2	Form of Warrant to Purchase Common Stock issued to previous holders of TPTX, Inc. redeemable convertible preferred stock in connection with the business combination between TorreyPines Therapeutics, Inc. and Axonyx, Inc. (incorporated by reference to Exhibit 4.2 to the Registrant's Annual Report on Form 10-K, filed on March 29, 2007).
4.3	Form of Registration Rights Agreement 1999 (incorporated by reference to Exhibit 4.4 to the Registrant's Annual Report on Form 10-KSB, filed on March 13, 2000).
4.4	Registration Rights Agreement dated as of January 8, 2004 between Axonyx Inc. and certain investors (incorporated by reference to Exhibit 4.2 to the Registrant's Current Report on Form 8-K, filed on January 12, 2004).
4.5	Registration Rights Agreement dated as of May 3, 2004, between Axonyx Inc. and certain investors (incorporated by reference to Exhibit 4.2 to the Registrant's Current Report on Form 8-K, filed on May 5, 2004).
4.6	Form of Warrant issued to Comerica Bank on July 1, 2003 (incorporated by reference to Exhibit 4.14 to the Registrant's Annual Report on Form 10-K, filed on March 29, 2007).
4.7	Form of Warrant issued to Silicon Valley Bank on December 8, 2000 (incorporated by reference to Exhibit 4.15 to the Registrant's Annual Report on Form 10-K, filed on March 29, 2007).

4.8	Form of Warrant issued to Oxford Financial and Silicon Valley Bank on September 27, 2005 (incorporated by reference to Exhibit 4.16 to the Registrant's Annual Report on Form 10-K, filed on March 29, 2007).
4.9	Rights Agreement, dated as of May 13, 2005, between the Registrant and The Nevada Agency and Trust Company, as Rights Agent (incorporated by reference to Exhibit 99.2 to the Registrant's Current Report on Form 8-K, filed on May 16, 2005).
4.10	Amendment to Rights Agreement, dated as of June 7, 2006, between the Registrant and The Nevada Agency and Trust Company, as Rights Agent (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K, filed on June 12, 2006).
4.11	Form of Warrant issued to Comerica Bank on June 11, 2008 (incorporated by reference to Exhibit 4.1 to the Registrant's Report on Form 8-K, filed on June 17, 2008).
4.12	Amendment to Rights Agreement, dated as of October 3, 2006, between the Registrant and The Nevada Agency and Trust Company, as Rights Agent (incorporated by reference to Exhibit 4.19 to the Registrant's Annual Report on Form 10-K, filed on March 29, 2007).
4.13	Rights Agreement Amendment, dated as of July 27, 2009, to the Rights Agreement dated May 13, 2005 between TorreyPines and American Stock Transfer and Trust Company (replacing The Nevada Agency and Trust Company) (incorporated by reference to Exhibit 2.3 to the Registrant's Current Report on Form 8-K, filed on July 28, 2009).
4.14	Amendment to Rights Agreement, dated August 6, 2010, by and between the Registrant and American Stock Transfer & Trust Company, LLC (incorporated by reference to Exhibit 4.2 to the Registrant's Current Report on Form 8-K, filed on August 10, 2010).
4.15 *	Warrant to purchase common stock dated December 14, 2007 issued to Flower Ventures, LLC (incorporated by reference to Exhibit 4.1 to Raptor Pharmaceuticals Corp.'s Quarterly Report on Form 10QSB/A, filed on April 15, 2008).
4.16 *	Warrant Agreement Amendment, dated December 17, 2009, between the Registrant and Flower Ventures, LLC (incorporated by reference to Exhibit 4.15 to Registrant's Quarterly Report on Form 10QSB, filed on April 9, 2010).
4.17 *	Warrant to purchase common stock dated December 14, 2007 issued to ICON Partners, LP (incorporated by reference to Exhibit 4.2 to Raptor Pharmaceuticals Corp.'s Quarterly Report on Form 10QSB/A, filed on April 15, 2008).
4.18 *	Form of Warrant to purchase common stock of Raptor Pharmaceuticals Corp. (incorporated by reference to Exhibit 4.1 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K, filed on May 22, 2008).
4.19 *	Form of Placement Agent Warrant to purchase common stock of Raptor Pharmaceuticals Corp. (incorporated by reference to Exhibit 4.2 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K/A, filed on May 28, 2008).
4.20 *	Form of Warrant to purchase common stock of Raptor Pharmaceuticals Corp. (incorporated by reference to Exhibit 4.1 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K, filed on August 25, 2009).
4.21*	Form of Placement Agent Warrant to purchase common stock of Raptor Pharmaceuticals Corp. (incorporated by reference to Exhibit 4.2 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K, filed on August 25, 2009).
4.22	Form of Senior Debt Indenture of the Registrant (incorporated by reference to Exhibit 4.10 to the Registrant's Registration Statement on Form S-3, filed on October 7, 2009).
4.23	Form of Subordinated Debt Indenture of the Registrant (incorporated by reference to Exhibit 4.11 to the Registrant's Registration Statement on Form S-3, filed on October 7, 2009).
4.24	Form of Investor Warrants (incorporated by reference to Exhibit 4.1 on Registrant's Current Report on Form 8-K filed on December 18, 2009).
4.25	Form of Investor Warrants (incorporated by reference to Exhibit 4.1 on Registrant's Current Report on Form 8-K filed on August 10, 2010).
4.26	Placement Agent Warrant (incorporated by reference to Exhibit 4.2 on Registrant's Current Report on Form 8-K filed on August 13, 2010).
4.27	Reference is made to Exhibits 3.1 through 3.8.
10.1#	TorreyPines Therapeutics, Inc. 2006 Equity Incentive Plan (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K, filed on October 4, 2006).
10.2#	Form of Stock Option Agreement under TorreyPines Therapeutics, Inc. 2006 Equity Incentive Plan (incorporated by reference to Exhibit 10.9 to the Registrant's Current Report on Form 8-K, filed on October 14, 2006).
10.3**	Development and License Agreement between TPTX, Inc. (formerly Neurogenetics, Inc.) and Eli Lilly and the Registrant, effective as of April 21, 2003 (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K, filed on October 10, 2006).

10.4**	Research and License Agreement by and between TPTX, Inc. and Life Science Research Israel Ltd. dated as of May 10, 2004 (incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K, filed on October 10, 2006).
10.5**	License Agreement by and between TPTX, Inc. and University of Iowa Research Foundation dated as of May 10, 2006 (incorporated by reference to Exhibit 10.5 to the Registrant's Current Report on Form 8-K, filed on October 10, 2006).
10.6	Lease Agreement by and between TPTX, Inc. and Slough TPSP LLC dated as of July 18, 2005, which became effective February 10, 2006 (incorporated by reference to Exhibit 10.10 to the Registrant's Current Report on Form 8-K, filed on October 10, 2006).
10.7	Form of Indemnity Agreement (incorporated by reference to Exhibit 10.13 to the Registrant's Current Report on Form 8-K, filed on October 10, 2006).
10.8#	Employment Agreement by and between Evelyn Graham and TorreyPines Therapeutics, Inc. dated December 14, 2006 (incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K, filed on December 20, 2006).
10.9#	Employment Agreement by and between Craig Johnson and TorreyPines Therapeutics, Inc. dated December 14, 2006 (incorporated by reference to Exhibit 10.3 to the Registrant's Current Report on Form 8-K, filed on December 20, 2006).
10.10#	Form of Restricted Stock Unit Award Agreement under TorreyPines Therapeutics, Inc. 2006 Equity Incentive Plan (incorporated by reference to Exhibit 10.17 to the Registrant's Annual Report on Form 10-K, filed on March 29, 2007).
10.11#	Employment Agreement between Raptor Pharmaceuticals Corp. and Dr. Christopher Starr dated May 1, 2006 (incorporated by reference to Exhibit 10.5 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K, filed on May 26, 2006).
10.12#	First Amendment to the Employment Agreement between Raptor Pharmaceuticals Corp. and Dr. Christopher Starr dated January 1, 2009 (incorporated by reference to Exhibit 10.1 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K, filed on January 5, 2009).
10.13#	Employment Agreement between Raptor Pharmaceuticals Corp. and Dr. Todd Zankel dated May 15, 2006 (incorporated by reference to Exhibit 10.6 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K filed on May 26, 2006).
10.14#	First Amendment to the Employment Agreement between Raptor Pharmaceuticals Corp. and Dr. Todd Zankel dated January 1, 2009 (incorporated by reference to Exhibit 10.3 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K, filed on January 5, 2009).
10.15#	Employment Agreement between Raptor Pharmaceuticals Corp. and Ms. Kim Tsuchimoto dated May 1, 2006 (incorporated by reference to Exhibit 10.7 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K filed on May 26, 2006).
10.16#	First Amendment to the Employment Agreement between Raptor Pharmaceuticals Corp. and Ms. Kim Tsuchimoto dated January 1, 2009 (incorporated by reference to Exhibit 10.2 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K, filed on January 5, 2009).
10.17#	Employment Agreement between Raptor Therapeutics Inc. and Thomas E. Daley dated September 7, 2007 (incorporated by reference to Exhibit 10.1 to Raptor Pharmaceuticals Corp.'s Quarterly Report on Form 10-QSB filed on January 14, 2008).
10.18#	First Amendment to the Employment Agreement between Raptor Pharmaceuticals Corp. and Thomas E. Daley dated January 1, 2009 (incorporated by reference to Exhibit 10.4 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K, filed on January 5, 2009).
10.19#	Offer Letter from Raptor Therapeutics Inc. dated April 8, 2009 for Dr. Patrice Rioux (incorporated by reference to Exhibit 10.1 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K filed on April 14, 2008).
10.20#	2006 Equity Incentive Plan of Raptor Pharmaceuticals Corp., as amended (incorporated by reference to Exhibit 4.3 to Raptor Pharmaceuticals Corp.'s Registration Statement on Form S-8 filed on February 28, 2007).
10.21#	2008 Plan Amendment to 2006 Equity Incentive Plan of Raptor Pharmaceuticals Corp. (incorporated by reference to Exhibit 10.5 to Raptor Pharmaceuticals Corp.'s Annual Report on Form 10-K/A filed on December 23, 2008).
10.22	Asset Purchase Agreement between Raptor Therapeutics, Inc., Raptor Pharmaceuticals Corp. and Convivia, Inc. dated October 17, 2007 (incorporated by reference to Exhibit 10.3 to Raptor Pharmaceuticals Corp.'s Quarterly Report on Form 10QSB filed on January 14, 2008).
10.23	Merger agreement between Raptor Therapeutics, Inc., Raptor Pharmaceuticals Corp. and Encode Pharmaceuticals, Inc. dated December 14, 2007 (incorporated by reference to Exhibit 10.1 to Raptor Pharmaceuticals Corp.'s Quarterly Report on Form 10QSB/A filed on April 15, 2008).

10.24**	Pharmaceutical development services agreement between Raptor Therapeutics Inc. and Patheon Pharmaceuticals Inc. dated January 7, 2008 (incorporated by reference to Exhibit 10.2 to Raptor Pharmaceuticals Corp.'s Quarterly Report on Form 10QSB/A filed on April 15, 2008).
10.25**	License agreement between Raptor Therapeutics Inc. and Regents of the University of California dated October 31, 2007 (incorporated by reference to Exhibit 10.3 to Raptor Pharmaceuticals Corp.'s Quarterly Report on Form 10QSB/A filed on April 15, 2008).
10.26**	Amendment No. 1 to License agreement between Raptor Therapeutics Inc. and Regents of the University of California dated February 29, 2008 (incorporated by reference to Exhibit 10.4 to Raptor Pharmaceuticals Corp.'s Quarterly Report on Form 10QSB/A filed on April 15, 2008).
10.27	Securities Purchase Agreement, dated as of May 21, 2008, by and among Raptor Pharmaceuticals Corp. and the investors listed on the signature pages thereto (incorporated by reference to Exhibit 10.1 to Raptor Pharmaceuticals Corp.'s Quarterly Report on Form 10QSB filed on July 9, 2008).
10.28	Amendment to Securities Purchase Agreement, dated as of May 21, 2008, by and among Raptor Pharmaceuticals Corp. and the investors listed on the signature pages thereto (incorporated by reference to Exhibit 10.2 to Raptor Pharmaceuticals Corp.'s Quarterly Report on Form 10QSB filed on July 9, 2008).
10.29**	Collaboration and License Agreement, effective June 3, 2009, among Hoffmann-La Roche Ltd,, Hoffmann-La Roche Inc. and the Registrant (incorporated by reference to Exhibit 10.19 on Raptor Pharmaceuticals Corp.'s Annual Report on Form 10-K filed on October 28, 2009)
10.30	First Amendment dated January 7, 2009 to Lease by and between TorreyPines Therapeutics, Inc. and HCP TPSP LLC dated July 18, 2005 (incorporated by reference to Exhibit 10.15 to the Registrant's Annual Report on Form 10-K, filed on March 27, 2009).
10.31**	Amendment dated November 21, 2008 to Development and License Agreement by and between TPTX, Inc. and Eli Lilly and the Registrant, effective as of April 21, 2003 (incorporated by reference to Exhibit 10.16 to the Registrant's Annual Report on Form 10-K, filed on March 27, 2009).
10.32#	Amended and Restated Employment Agreement by and between Evelyn Graham and TorreyPines Therapeutics, Inc. dated September 1, 2008 (incorporated by reference to Exhibit 10.17 to the Registrant's Annual Report on Form 10-K, filed on March 27, 2009).
10.33#	Amendment dated February 3, 2009 to Amended Employment Agreement by and between Evelyn Graham and TorreyPines Therapeutics, Inc. dated September 1, 2008 (incorporated by reference to Exhibit 10.18 to the Registrant's Annual Report on Form 10-K, filed on March 27, 2009).
10.34#	Amended and Restated Employment Agreement by and between Craig Johnson and TorreyPines Therapeutics, Inc. dated November 12, 2008 (incorporated by reference to Exhibit 10.19 to the Registrant's Annual Report on Form 10-K, filed on March 27, 2009).
10.35#	Amendment dated February 3, 2009 to Amended Employment Agreement by and between Craig Johnson and TorreyPines Therapeutics, Inc. dated November 12, 2008 (incorporated by reference to Exhibit 10.20 to the Registrant's Annual Report on Form 10-K, filed on March 27, 2009).
10.36#	Amended and Restated Employment Agreement by and between Paul Schneider and TorreyPines Therapeutics, Inc. dated November 12, 2008 (incorporated by reference to Exhibit 10.21 to the Registrant's Annual Report on Form 10-K, filed on March 27, 2009).
10.37#	Amendment dated February 3, 2009 to Amended Employment Agreement by and between Paul Schneider and TorreyPines Therapeutics, Inc. dated November 12, 2008 (incorporated by reference to Exhibit 10.22 to the Registrant's Annual Report on Form 10-K, filed on March 27, 2009).
10.38**	Supply Agreement, effective July 20, 2009, between Raptor Therapeutics Inc. and Mylan Pharmaceutical Inc. (incorporated by reference to Exhibit 10.20 on Raptor Pharmaceuticals Corp.'s Annual Report on Form 10-K filed on October 28, 2009).
10.39#	Second Amended and Restated Employment by and between Evelyn Graham and TPTX, Inc. dated July 27, 2009 (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K, filed on July 28, 2009).
10.40#	Second Amended and Restated Employment by and between Craig Johnson and TPTX, Inc. dated July 27, 2009 (incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K, filed on July 28, 2009).
10.41#	Second Amended and Restated Employment by and between Paul Schneider and TPTX, Inc. dated July 27, 2009 (incorporated by reference to Exhibit 10.3 to the Registrant's Current Report on Form 8-K, filed on July 28, 2009).
10.42	Securities Purchase Agreement, dated as of August 21, 2009, by and among Raptor Pharmaceuticals Corp. and the investors listed on the signature pages thereto (incorporated by reference to Exhibit 10.19 on Raptor Pharmaceuticals Corp.'s Annual Report on Form 10-K filed on October 28, 2009).

10.43	Raptor Form Indemnity Agreement dated on December 9, 2009 (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on December 15, 2009).
10.44	Placement Agent Agreement by and between the Registrant and Ladenburg Thalmann & Co. Inc. dated December 17, 2009 (incorporated by reference to Exhibit 1.1 on Registrant's Current Report on Form 8-K filed on December 18, 2009).
10.45	Securities Purchase Agreement, dated December 17, 2009, by and between the Registrant and the investors signatories thereto (incorporated by reference to Exhibit 10.1 on Registrant's Current Report on Form 8-K filed on December 18, 2009).
10.46#	Raptor Pharmaceutical Corp. 2010 Stock Incentive Plan (incorporated by reference to Appendix A to the Registrant's Revised Definitive Proxy Statement, filed on February 5, 2010).
10.47	Purchase Agreement, dated April 16, 2010, between the Registrant and Lincoln Park Capital Fund, LLC (incorporated by reference to Exhibit 10.1 on Registrant's Current Report on Form 8-K, filed on April 22, 2010).
10.48	Registration Rights Agreement, dated April 16, 2010, between the Registrant and Lincoln Park Capital Fund, LLC (incorporated by reference to Exhibit 10.2 on Registrant's Current Report on Form 8-K, filed on April 22, 2010).
10.49#	Form of Award Agreement under the Raptor Pharmaceutical Corp. 2010 Stock Incentive Plan (incorporated by reference to Exhibit 4.13 to the Registrant's Registration Statement on Form S-8 (File No. 33-166813), filed on May 14, 2010).
10.50	Securities Purchase Agreement, dated August 9, 2010, by and among the Registrant and the Investors signatories thereto (incorporated by reference to Exhibit 10.1 on Registrant's Current Report on Form 8-K, filed on August 10, 2010).
10.51	Securities Purchase Agreement, dated August 9, 2010, by and among the Registrant and the Investor signatory thereto (incorporated by reference to Exhibit 10.2 of the Registrant's Current Report on Form 8-K filed on August 10, 2010).
10.52	Registration Rights Agreement, dated August 12, 2010, by and among the Registrant and the signatories thereto (incorporated by reference to Exhibit 10.3 of the Registrant's Current Report on Form 8-K, filed on August 13, 2010).
21.1†	Subsidiaries of the Registrant.
23.1†	Consent of Burr Pilger Mayer, Inc. Independent Registered Public Accounting Firm to the Registrant
24.1†	Power of Attorney (included in the signature page hereto).
31.1†	Certification of Christopher M. Starr, Ph.D., Chief Executive Officer and Director
31.2†	Certification of Kim R. Tsuchimoto, Chief Financial Officer, Secretary and Treasurer
32.1†	Certification of Christopher M. Starr, Ph.D., Chief Executive Officer and Director, and of Kim R. Tsuchimoto, Chief Financial Officer, Secretary and Treasurer
*	The Raptor Pharmaceuticals Corp. warrants set forth in Exhibits 4.15 - 4.21 have been converted into warrants of the Registrant and the exercise price of such warrants and number of shares of common stock issuable thereunder have been converted as described in Item 1.01 (under the section titled, "Background") of the Registrant's Current Report on Form 8-K, filed on October 5, 2009.
**	Certain information omitted pursuant to a request for confidential treatment filed separately with and granted by the SEC.
#	Indicates a management contract or compensatory plan or arrangement.
†	Filed herewith.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

RAPTOR PHARMACEUTICALS CORP.

Dated: November 22, 2010

By:/s/ Kim R. Tsuchimoto

Kim R. Tsuchimoto

Chief Financial Officer, Secretary and Treasurer

(Principal Financial Officer and Principal Accounting Officer)

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Christopher M. Starr, Ph.D. and Kim R. Tsuchimoto, his or her attorney-in-fact, with the power of substitution, for him or her in any and all capacities, to sign any amendments to the Annual Report on Form 10-K and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, hereby ratifying and confirming all that each of said attorneys-in-fact, or his or her substitute or substitutes, may do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated:

Signatures	Title	Date
/s/ Christopher M. Starr Christopher M. Starr, Ph.D.	Chief Executive Officer and Director (Principal Executive Officer)	November 22, 2010
/s/ Kim R. Tsuchimoto Kim R. Tsuchimoto	Chief Financial Officer, Secretary and Treasurer (Principal Financial Officer and Principal Accounting Officer)	November 22, 2010
/s/ Erich Sager Erich Sager	Director	November 22, 2010
/s/ Raymond William Anderson Raymond William Anderson	Director	November 22, 2010
/s/ Richard L. Franklin Richard L. Franklin, M.D., Ph.D.	Director	November 22, 2010
/s/ Llew Keltner Llew Keltner, M.D., Ph.D.	Director	November 22, 2010

Financial Statements

The following consolidated financial statements of Raptor Pharmaceuticals Corp. and the Independent Registered Public Accounting Firm's Report issued thereon, are incorporated by reference in Part II, Item 8 of this Annual Report on Form 10-K:

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Board of Directors and Stockholders of

Raptor Pharmaceutical Corp.

We have audited the accompanying consolidated balance sheets of Raptor Pharmaceutical Corp. and its subsidiaries (the "Company") (a development stage enterprise) as of August 31, 2010 and 2009 and the related consolidated statements of operations, stockholders' equity and cash flows for the years ended August 31, 2010 and 2009 and the cumulative amounts from September 8, 2005 (inception) to August 31, 2010. These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these consolidated financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. The Company is not required to have, nor were we engaged to perform an audit of the Company's internal control over financial reporting. Our audit included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the consolidated financial statements, assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the consolidated financial position of Raptor Pharmaceutical Corp. and its subsidiaries as of August 31, 2010 and 2009 and the consolidated results of their operations and cash flows for the years ended August 31, 2010 and 2009 and the cumulative amounts from September 8, 2005 (inception) to August 31, 2010 in conformity with accounting principles generally accepted in the United States of America.

The accompanying consolidated financial statements have been prepared assuming that the Company will continue as a going concern. As discussed in Note 2 to the consolidated financial statements, the Company is in the development stage and has not generated any revenue to date. These factors raise substantial doubt about the Company's ability to continue as a going concern. Management's plans in regard to these matters are also described in Note 2. The financial statements do not include any adjustments relating to the recoverability and classification of asset carrying amounts or the amount and classification of liabilities that might result should the Company be unable to continue as a going concern.

As discussed in Note 1 to the consolidated financial statements, effective September 29, 2009, the Company completed a reverse merger with TorreyPines Therapeutics, Inc. The combined company is called Raptor Pharmaceutical Corp.

/s/ Burr Pilger Mayer, Inc.

San Francisco, California

November 22, 2010

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Raptor Pharmaceutical Corp.
(A Development Stage Company)
Consolidated Balance Sheets

	August 31,	
ASSETS	2010	2009
Current assets:		
Cash and cash equivalents	$ 16,953,524	$ 3,701,787
Prepaid expenses and other	285,898	107,054
Total current assets	17,239,422	3,808,841
Intangible assets, net	3,512,542	2,524,792
Goodwill	3,275,403	-
Fixed assets, net	93,249	144,735
Deposits	102,906	100,206
Deferred offering costs	166,015	-
Total assets	$ 24,389,537	$ 6,578,574
LIABILITIES AND STOCKHOLDERS' EQUITY		
Liabilities		
Current liabilities:		
Accounts payable	$ 637,321	$ 613,577
Accrued liabilities	1,129,810	451,243
Common stock warrant liability	15,780,216	-
Deferred rent	2,673	-
Capital lease liability – current	4,865	4,117
Total current liabilities	17,554,885	1,068,937
Capital lease liability - long-term	1,811	6,676
Total liabilities	17,556,696	1,075,613
Commitments and contingencies		
Stockholders' equity:		
Preferred stock, $0.001 par value, 15,000,000 shares authorized, zero shares issued and outstanding	-	-
Common stock, $0.001 par value, 150,000,000 shares authorized 30,076,758 and 17,857,555 shares issued and outstanding as at August 31, 2010 and 2009, respectively	30,077	17,858
Additional paid-in capital	47,617,449	27,364,286
Accumulated other comprehensive loss	(7,854)	-
Deficit accumulated during development stage	(40,806,831)	(21,879,183)
Total stockholders' equity	6,832,841	5,502,961
Total liabilities and stockholders' equity	$ 24,389,537	$ 6,578,574

The accompanying notes are an integral part of these consolidated financial statements.

Raptor Pharmaceutical Corp.
(A Development Stage Company)
Consolidated Statements of Operations

	For the year ended August 31,		For the cumulative period from September 8, 2005 (inception) to August 31,
	2010	**2009**	**2010**
Revenues:	$ -	$ -	$ -
Operating expenses:			
General and administrative	3,720,148	2,687,993	10,676,388
Research and development	9,334,080	6,570,119	24,208,364
In-process research and dev.		-	240,625
Total operating expenses	13,054,228	9,258,112	35,125,377
Loss from operations	(13,054,228)	(9,258,112)	(35,125,377)
Interest income	25,701	36,744	327,604
Interest expense	(3,950)	(2,526)	(113,887)
Foreign currency transaction loss	(457)	-	(457)
Adjustment to fair value of common stock warrants	(5,894,714)	-	(5,894,714)
Net loss	$ (18,927,648)	$ (9,223,894)	$ (40,806,831)
Loss per share from operations:			
Basic and diluted	$ (0.59)	$ (0.64)	
Net loss per share:			
Basic and diluted	$ (0.85)	$ (0.64)	
Weighted average shares outstanding used to compute:			
Basic and diluted	22,227,198	14,440,254	

The accompanying notes are an integral part of these consolidated financial statements.

Raptor Pharmaceutical Corp.

(A Development Stage Company)

Consolidated Statements of Stockholders' Equity

For the period from September 8, 2005 (inception) to August 31, 2006

	Common stock		Additional paid-in	Receivable from	Deficit accumulated during the development	
	Shares	Amount	Capital	stockholders	stage	Total
Balance at September 8, 2005, issuance of common stock to founders at $0.004 per share, net of retirement of common stock upon reverse merger	1,398,740	$ 1,399	$ 8,601	$ (10,000)	$ —	$ —
Common stock issued in May 2006 at $0.43 per share pursuant to a stock purchase agreement dated February 2006	233,123	233	99,767	(100,000)	—	—
Common stock issued in May 2006 at $0.86 per share pursuant to a stock purchase agreement dated February 2006	233,123	233	199,767	—	—	200,000
Common stock issued on May 25, 2006 at $2.57 per share, net of fundraising costs of $217,534	1,942,695	1,943	4,780,523	—	—	4,782,466
Common stock and warrants issued for a placement fee in connection with May 25, 2006 financing	186,499	186	(186)	—	—	—
Common stock issued in connection with reverse merger in May 2006	2,914,042	2,914	(2,914)	—	—	—
Warrant subscribed pursuant to a consulting agreement dated September 2005	—	—	60	—	—	60
Consultant stock-based compensation expense	—	—	23,500	—	—	23,500
Repayment of receivable from stockholders	—	—	—	110,000	—	110,000
Net loss	—	—	—	—	(969,250)	(969,250)
Balance at August 31, 2006	6,908,222	$ 6,908	$ 5,109,118	$ —	$ (969,250)	$ 4,146,776

The accompanying notes are an integral part of these consolidated financial statements.

Raptor Pharmaceutical Corp.

(A Development Stage Company)

Consolidated Statements of Stockholders' Equity

For the year ended August 31, 2007

	Common stock		Additional paid-in	Deficit accumulated during the development	
	Shares	Amount	Capital	stage	Total
Balance at September 1, 2006	6,908,222	$ 6,908	$ 5,109,118	$ (969,250)	$ 4,146,776
Exercise of common stock warrants	765,422	766	1,969,234	—	1,970,000
Exercise of common stock options	3,380	3	8,697		8,700
Consultant stock-based compensation expense	—	—	95,731	—	95,731
Employee stock-based compensation expense	—	—	368,978	—	368,978
Net loss	—	—	—	(3,632,076)	(3,632,076)
Balance at August 31, 2007	7,677,024	$ 7,677	$ 7,551,758	$ (4,601,326)	$ 2,958,109

The accompanying notes are an integral part of these consolidated financial statements.

Raptor Pharmaceutical Corp.

(A Development Stage Company)

Consolidated Statements of Stockholders' Equity

For the year ended August 31, 2008

	Common stock		Additional paid-in capital	Deficit accumulated during the development stage	Total
	Shares	Amount			
Balance at September 1, 2007	7,677,024	$ 7,677	$ 7,551,758	$ (4,601,326)	$ 2,958,109
Exercise of common stock warrants	747,938	748	1,924,252	—	1,925,000
Consultant stock-based compensation expense	2,040	2	240,227	—	240,229
Employee stock-based compensation expense	23,312	23	491,532	—	491,555
Issuance of common stock for loan placement fee	46,625	47	101,953	—	102,000
Issuance of common stock for the purchase of Convivia, Inc. assets	101,992	102	240,523	—	240,625
Issuance of common stock for the merger with Encode Pharmaceuticals, Inc.	802,946	803	2,657,197	—	2,658,000
Issuance of common stock and warrants for the sale of units in a private placement at $2.14 per unit, including placement agent warrants, net of fundraising costs of $944,065	4,662,468	4,662	9,051,273	—	9,055,935
Net loss	—	—	—	(8,053,963)	(8,053,963)
Balance at August 31, 2008	14,064,345	$ 14,064	$ 22,258,715	$ (12,655,289)	$ 9,617,490

The accompanying notes are an integral part of these consolidated financial statements.

Raptor Pharmaceutical Corp.

(A Development Stage Company)

Consolidated Statements of Stockholders' Equity

For the year ended August 31, 2009

	Common stock		Additional paid-in	Deficit accumulated during the development	
	Shares	Amount	Capital	stage	Total
Balance at August 31, 2008	14,064,345	$ 14,064	$ 22,258,715	$ (12,655,289)	$ 9,617,490
Exercise of common stock warrants	2,031,671	2,032	2,612,468	—	2,614,500
Consultant stock-based compensation expense		—	48,094	—	48,094
Employee stock-based compensation expense	23,312	23	354,471	—	354,494
Issuance of common stock and warrants for the sale of units in a private placement at $1.37 per unit, including placement agent warrants, net of fundraising costs of $293,724	1,738,227	1,739	2,090,538	—	2,092,277
Net loss	—	—	—	(9,223,894)	(9,223,894)
Balance at August 31, 2009	17,857,555	$ 17,858	$ 27,364,286	$ (21,879,183)	$ 5,502,961

The accompanying notes are an integral part of these consolidated financial statements.

Raptor Pharmaceutical Corp.
(A Development Stage Company)

Consolidated Statements of Stockholders' Equity
For the year ended August 31, 2010

	Common stock		Additional paid-in capital	Accumulated other comprehensive loss	Deficit accumulated during development stage	Total
	Shares	Amount				
Balance at August 31, 2009	17,857,555	$ 17,858	$ 27,364,286	$ —	$(21,879,183)	$ 5,502,961
Exercise of common stock warrants	196,736	197	474,822	—	—	475,019
Exercise of common stock options	37,881	38	63,984	—	—	64,022
Consultant stock-based compensation expense	—	—	78,327	—	—	78,327
Employee stock-based compensation expense	11,656	12	216,719	—	—	216,731
Common stock issued and warrants/options assumed with 2009 Merger	940,863	940	4,416,106	—	—	4,417,046
Issuance of common stock to LPC pursuant to an equity line facility at a $2.26 average per share purchase price, net of fundraising costs and commitment shares totaling $533,294	2,386,895	2,387	4,839,407	—	—	4,841,794
Issuance of common stock and warrants in a registered direct financing at $2.00 per unit, including placement agent warrants, net of fundraising costs of $1,246,658	3,747,558	3,748	6,243,062	—	—	6,246,810
Initial value of warrants issued in a	—	—	(1,863,615)	—	—	(1,863,615)

registered direct financing						
Issuance of common stock and warrants for the sale of units in a private placement at $3.075 per unit, including placement agent warrants, net of fundraising costs of $1,457,687	4,897,614	4,897	13,597,578	—	—	13,602,475
Initial value of warrants issued in 2010 private placement	—	—	(7,813,227)	—	—	(7,813,227)
Foreign currency translation loss	—	—	—	(7,854)	—	(7,854)
Net loss	—	—	—	—	(18,927,648)	(18,927,648)
Balance at August 31, 2010	30,076,758	$ 30,077	$ 47,617,449	$ (7,854)	$ (40,806,831)	$ 6,832,841

The accompanying notes are an integral part of these consolidated financial statements.

Raptor Pharmaceutical Corp.
(A Development Stage Company)
Consolidated Statements of Cash Flows

	For the year ended August 31,		For the cumulative period from September 8, 2005 (inception) to August 31,
	2010	2009	2010
Cash flows from operating activities:			
Net loss	$ (18,927,648)	$ (9,223,894)	$ (40,806,831)
Adjustments to reconcile net loss to net cash used in operating activities:			
Employee stock-based compensation expense	216,731	354,494	1,431,758
Consultant stock-based compensation expense	78,327	48,094	485,941
Fair value adjustment of common stock warrants	5,894,714	-	5,894,714
Amortization of intangible assets	152,250	138,499	397,458
Depreciation of fixed assets	72,241	84,693	423,181
In-process research and development	-	-	240,625
Amortization of capitalized finder's fee	-	-	102,000
Capitalized acquisition costs previously expensed	-	-	38,000
Changes in assets and liabilities:			
Prepaid expenses and other	(79,407)	8,540	(186,460)
Intangible assets	-	-	(150,000)
Deposits	(2,700)	-	(102,907)
Accounts payable	23,744	47,984	637,321
Accrued liabilities	(2,264)	18,809	449,084
Deferred rent	2,673	(2,951)	2,568
Net cash used in operating activities	(12,571,339)	(8,525,732)	(31,143,548)
Cash flows from investing activities:			
Purchase of fixed assets	(20,756)	(22,734)	(497,106)
Cash acquired in 2009 Merger	581,391	-	581,391
Net cash provided by (used in) investing activities	560,635	(22,734)	84,285
Cash flows from financing activities:			
Proceeds from the sale of common stock	22,555,278	2,386,000	39,941,278
Proceeds from the sale of common stock under an equity line	4,899,951	-	4,899,951
Proceeds from the exercise of common stock warrants	475,019	2,614,500	6,984,519
Proceeds from the exercise of common stock options	64,022	-	72,721
Fundraising costs	(2,719,857)	(293,724)	(4,175,181)
Proceeds from the sale of common stock to initial investors	-	-	310,000
Proceeds from bridge loan	-	-	200,000
Repayment of bridge loan	-	-	(200,000)
Principal payments on capital lease	(4,118)	(3,435)	(12,647)
Net cash provided by financing activities	25,270,295	4,703,341	48,020641
Foreign currency translation loss	(7,854)	-	(7,854)
Net increase (decrease) in cash and cash equivalents	13,251,737	(3,845,125)	16,953,524
Cash and cash equivalents, beginning of period	3,701,787	7,546,912	-
Cash and cash equivalents, end of period	$ 16,953,524	$ 3,701,787	$ 16,953,524
Supplemental cash flow information:			
Interest paid	$ 3,949	$ 2,526	$ 11,886
Supplemental disclosure of non-cash financing activities:			
Warrants issued in connection with financings	$ 9,676,842	$ -	$ 16,310,414

Initial fair value of warrants issued to placement agents in connection with financings	$ 208,660	$ -	$ 208,660
Common stock and warrants issued in connection with reverse merger	$ 4,417,046	$ -	$ 4,417,046
Common stock issued as fee for equity line	$ 475,137	$ -	$ 475,137
Acquisition of equipment in exchange for capital lease	$ -	$ 14,006	$ 21,403
Notes receivable issued in exchange for common stock	$ -	$ -	$ 110,000
Common stock issued for a finder's fee	$ -	$ -	$ 102,000
Common stock issued in asset purchase	$ -	$ -	$ 2,898,624

The accompanying notes are an integral part of these consolidated financial statements.

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

(1) NATURE OF OPERATIONS AND BUSINESS RISKS

The accompanying consolidated financial statements reflect the results of operations of Raptor Pharmaceutical Corp. (the "Company" or "Raptor") and have been prepared in accordance with the accounting principles generally accepted in the United States of America. The Company's fiscal year end is August 31.

On July 28, 2009, the Company and ECP Acquisition, Inc., a Delaware corporation, the Company's then-wholly-owned subsidiary("merger sub"), entered into an Agreement and Plan of Merger and Reorganization (the "2009 Merger Agreement"), with Raptor Pharmaceuticals Corp., a Delaware corporation ("RPC"). On September 29, 2009, on the terms and subject to the conditions set forth in the 2009 Merger Agreement, pursuant to a stock-for-stock reverse triangular merger (the "2009 Merger"), merger sub was merged with and into RPC and RPC survived the 2009 Merger as a wholly-owned subsidiary of the Company. Immediately prior to the 2009 Merger and in connection therewith, the Company effected a 1-for-17 reverse stock split of its common stock and changed its corporate name from "TorreyPines Therapeutics, Inc." to "Raptor Pharmaceutical Corp."

As a result of the 2009 Merger and in accordance with the 2009 Merger Agreement, each share of RPC's common stock outstanding immediately prior to the effective time of the 2009 Merger was converted into the right to receive 0.2331234 shares of the Company's common stock, on a post 1-for-17 reverse-split basis. Each option and warrant to purchase RPC's common stock outstanding immediately prior to the effective time of the 2009 Merger was assumed by the Company at the effective time of the 2009 Merger, with each share of such common stock underlying such options and warrants being converted into the right to receive 0.2331234 shares of the Company's common stock, on a post 1-for-17 reverse split basis, rounded down to the nearest whole share of the Company's common stock. Following the 2009 Merger, each such option or warrant has an exercise price per share of the Company's common stock equal to the quotient obtained by dividing the per share exercise price of such common stock subject to such option or warrant by 0.2331234, rounded up to the nearest whole cent.

Immediately following the effective time of the 2009 Merger, RPC's stockholders (as of immediately prior to the 2009 Merger) owned approximately 95% of the Company's outstanding common stock and the Company's stockholders (as of immediately prior to the 2009 Merger) owned approximately 5% of the Company's outstanding common stock.

RPC, the Company's wholly-owned subsidiary, was the "accounting acquirer," and for accounting purposes, the Company was deemed as having been "acquired" in the 2009 Merger. The board of directors and officers that managed and operated RPC immediately prior to the effective time of the 2009 Merger became the Company's board of directors and officers. Additionally, following the effective time of the 2009 Merger, the business conducted by RPC immediately prior to the effective time of the 2009 Merger became primarily the business conducted by the Company.

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The following reflects the Company's current, post-2009 Merger corporate structure (State of Incorporation):

Raptor Pharmaceutical Corp., formerly TorreyPines Therapeutics, Inc. (Delaware)
|
Raptor Pharmaceuticals Corp. (Delaware)
| |
Raptor Therapeutics Inc. (Delaware) Raptor Discoveries Inc. (Delaware)
(f/k/a Bennu Pharmaceuticals Inc.) (f/k/a Raptor Pharmaceutical Inc.)
(merged with TPTX, Inc. on August 30, 2010)

Raptor is a publicly-traded biotechnology company dedicated to speeding the delivery of new treatment options to patients by enhancing existing therapeutics through the application of highly specialized drug targeting platforms and formulation expertise. The Company focuses on underserved patient populations where it can have the greatest potential impact. Raptor's clinical division advances clinical-stage product candidates towards marketing approval and commercialization. Raptor's clinical programs include DR Cysteamine for the potential treatment of nephropathic cystinosis, non-alcoholic steatohepatitis ("NASH"), and Huntington's Disease. Raptor also has two clinical stage product candidates for which it is seeking to out-license or form a development partnership: Convivia™ for the potential treatment of aldehyde dehydrogenase ("ALDH2") deficiency; and Tezampanel and NGX426, a non-opioid solution designed to treat chronic pain.

Raptor's preclinical division bioengineers novel drug candidates and drug-targeting platforms derived from the human receptor-associated protein ("RAP") and related proteins. Raptor's preclinical programs target cancer, neurodegenerative disorders and infectious diseases. HepTide™ is designed to utilize engineered RAP-based peptides conjugated to drugs to target delivery to the liver to potentially treat primary liver cancer and hepatitis. NeuroTrans™ represents engineered RAP peptides created to target receptors in the brain and are currently, in collaboration with Roche, undergoing preclinical evaluation for their ability to enhance the transport of therapeutics across the blood-brain barrier. WntTide™ is based upon Mesd and Mesd peptides that the Company is studying in a preclinical breast cancer model for WntTide™'s potential inhibition of Wnt signaling through LRP5, which may block cancers dependent on signaling through LRP5 or LRP6. Raptor is also examining Tezampanel and NGX426, for the treatment of thrombotic disorder.

The Company is subject to a number of risks, including: the need to raise capital through equity and/or debt financings; the uncertainty whether the Company's research and development efforts will result in successful commercial products; competition from larger organizations; reliance on licensing proprietary technology of others; dependence on key personnel; uncertain patent protection; and dependence on corporate partners and collaborators. See the section titled "Risk Factors" included elsewhere in this Annual Report on Form 10-K.

(2) SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

(a) Basis of Presentation

The Company's consolidated financial statements include the accounts of the Company's wholly owned subsidiaries, Raptor Pharmaceuticals Corp., Raptor Discoveries Inc., and Raptor Therapeutics Inc., such subsidiaries incorporated in Delaware on May 5, 2006, September 8, 2005 (date of inception), and August 1, 2007, respectively. All inter-company accounts have been eliminated. The Company's

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consolidated financial statements have been prepared on a going concern basis, which contemplates the realization of assets and the settlement of liabilities and commitments in the normal course of business. Through August 31, 2010, the Company had accumulated losses of approximately $40.8 million. Management expects to incur further losses for the foreseeable future. Management believes that the Company's cash and cash equivalents at August 31, 2010 will be sufficient to meet the Company's obligations into December 2011. The Company plans to continue to review strategic partnerships, collaborations and potential equity sales as a potential means to fund its preclinical and clinical programs beyond December 2011. Until the Company can generate sufficient levels of cash from its operations, the Company expects to continue to finance future cash needs primarily through proceeds from equity or debt financings, loans and collaborative agreements with corporate partners or through a business combination with a company that has such financing in order to be able to sustain its operations until the Company can achieve profitability and positive cash flows, if ever.

On September 29, 2009, upon the closing of the merger with RPC (as discussed further in the Note 10, Issuance of Common Stock), RPC's stockholders exchanged each share of RPC's common stock into .2331234 shares of the post-merger company and the exercise prices and stock prices were divided by .2331234 to reflect the post-merger equivalent stock prices and exercise prices. Therefore, all shares of common stock and exercise prices of common stock options and warrants are reported in these consolidated financial statements on a post-merger basis.

The Company's independent registered public accounting firm has audited the Company's consolidated financial statements for the years ended August 31, 2010 and 2009. The November 22, 2010 audit opinion included a paragraph indicating substantial doubt as to the Company's ability to continue as a going concern due to the fact that the Company is in the development stage and has not generated any revenue to date.

Management plans to seek additional debt and/or equity financing for the Company through private or public offerings or through a business combination or strategic partnership, but it cannot assure that such financing or transaction will be available on acceptable terms, or at all. The uncertainty of this situation raises substantial doubt about the Company's ability to continue as a going concern. The accompanying consolidated financial statements do not include any adjustments that might result from the failure to continue as a going concern.

(b) Use of Estimates

The preparation of financial statements in conformity with United States generally accepted accounting principles requires management to make certain estimates and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent assets and liabilities as of the dates of the consolidated financial statements and the reported amounts of revenues and expenses during the reporting period. Actual results could differ from those estimates.

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(c) Fair Value of Financial Instruments

The carrying amounts of certain of the Company's financial instruments including cash and cash equivalents, prepaid expenses, accounts payable, accrued liabilities and capital lease liability approximate fair value due either to length of maturity or interest rates that approximate prevailing market rates unless otherwise disclosed in these consolidated financial statements.

(d) Segment Reporting

The Company has determined that it operates in two operating segments, preclinical development and clinical development. Operating segments are components of an enterprise for which separate financial information is available and are evaluated regularly by the Company in deciding how to allocate resources and in assessing performance. The Company's chief executive officer assesses the Company's performance and allocates its resources. Below is a break-down of the Company's net loss and total assets by operating segment:

	For the years ended August 31,					
	2010			2009		
	Preclinical	Clinical	Total	Preclinical	Clinical	Total
Net loss	$ (4,015,814)	$ (14,911,834)	$ (18,927,648)	$ (2,920,598)	$ (6,303,295)	$ (9,223,894)
Total assets	2,413,600	21,975,937	24,389,537	683,828	5,894,746	6,578,574

(e) Cash and Cash Equivalents

The Company considers all highly liquid investments with original maturities of three months or less, when purchased, to be cash equivalents. The Company maintains cash and cash equivalents, which consist principally of money market funds with high credit quality financial institutions. Such amounts exceed Federal Deposit Insurance Corporation insurance limits. The Company has not experienced any losses on these investments.

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(f) Intangible Assets

Intangible assets include the intellectual property and other rights relating to DR Cysteamine, to the RAP technology and to the out-license and the rights to NGX 426 acquired in the 2009 Merger. The intangible assets related to DR Cysteamine and the RAP technology are amortized using the straight-line method over the estimated useful life of 20 years, which is the life of the intellectual property patents. The 20 year estimated useful life is also based upon the typical development, approval, marketing and life cycle management timelines of pharmaceutical drug products. The intangible assets related to the out-license will be amortized using the straight-line method over the estimated useful life of 16 years, which is the life of the intellectual property patents. The intangible assets related to NGX 426, which has been classified as in-process research and development, will not be amortized until development is completed.

(g) Goodwill

Goodwill represents the excess of the value of the purchase consideration over the identifiable assets acquired in the 2009 Merger. Goodwill is reviewed annually, or when an indication of impairment exists, to determine if any impairment analysis and resulting write-down in valuation is necessary.

(h) Fixed Assets

Fixed assets, which mainly consist of leasehold improvements, lab equipment, computer hardware and software and capital lease equipment, are stated at cost. Depreciation is computed using the straight-line method over the related estimated useful lives, except for leasehold improvements and capital lease equipment, which are depreciated over the shorter of the useful life of the asset or the lease term. Significant additions and improvements that have useful lives estimated at greater than one year are capitalized, while repairs and maintenance are charged to expense as incurred.

(i) Impairment of Long-Lived Assets

The Company evaluates its long-lived assets for indicators of possible impairment by comparison of the carrying amounts to future net undiscounted cash flows expected to be generated by such assets when events or changes in circumstances indicate the carrying amount of an asset may not be recoverable. Should an impairment exist, the impairment loss would be measured based on the excess carrying value of the asset over the asset's fair value or discounted estimates of future cash flows. The Company has not identified any such impairment losses to date.

(j) Common Stock Warrant Liabilities

The warrants issued by the Company in the a 2010 private placement contain a cash-out provision which may be triggered upon request by the warrant holders if the Company is acquired or upon the occurrence of certain other fundamental transactions involving the Company. This provision requires these warrants to be classified as liabilities and will be marked to market at each period-end commencing on August 31, 2010. The warrants issued by the Company in its December 2009 equity financing contain a conditional obligation that may require the Company to transfer assets to repurchase the warrants upon the occurrence of potential future events. Under the Financial Accounting Standards Board ("FASB") Accounting Standards Codification ("ASC") Topic 480, *Distinguishing Liabilities from Equity* ("ASC 480"), a financial instrument that

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may require the issuer to settle the obligation by transferring assets is classified as a liability. Therefore, the Company has classified the warrants as liabilities and will mark them to fair value at each period-end.

(k) Marked-to-Market

The common stock warrants issued in the Company's 2010 private placement and its December 2009 equity financing are classified as liabilities under ASC 480 and are, therefore, re-measured at the end of every reporting period with the change in value reported in its consolidated statements of operations.

(l) Income Taxes

Income taxes are recorded under the liability method, under which deferred tax assets and liabilities are determined based on the difference between the financial statement and tax bases of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to affect taxable income. Valuation allowances are established when necessary to reduce deferred tax assets to the amount expected to be realized.

(m) Research and Development

The Company is a development stage biotechnology company. Research and development costs are charged to expense as incurred. Research and development expenses include medical, clinical, regulatory and scientists' salaries and benefits, lab collaborations, preclinical studies, clinical trials, clinical trial materials, regulatory and clinical consultants, lab supplies, lab services, lab equipment maintenance and small equipment purchased to support the research laboratory, amortization of intangible assets and allocated executive, human resources and facilities expenses.

(n) In-Process Research and Development

Prior to September 1, 2009, the Company recorded in-process research and development expense for a product candidate acquisition where there is not more than one potential product or usage for the assets being acquired. Upon the adoption of the revised guidance on business combinations, effective September 1, 2009, the fair value of acquired in-process research and development is capitalized and tested for impairment at least annually. Upon completion of the research and development activities, the intangible asset is amortized into earnings over the related product's useful life. The Company reviews each product candidate acquisition to determine the existence of in-process research and development.

(o) Net Loss per Share

Net loss per share is calculated by dividing net loss by the weighted average shares of common stock outstanding during the period. Diluted net income per share is calculated by dividing net income by the weighted average shares of common stock outstanding and potential shares of common stock during the period. For all periods presented, potentially dilutive securities are excluded from the computation of fully diluted net loss per share as their effect is anti-dilutive. Potentially dilutive securities include:

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	August 31,	
	2010	**2009**
Warrants to purchase common stock	10,373,228	2,057,990
Options to purchase common stock	1,391,288	989,213
Total potentially dilutive securities	11,764,516	3,047,203

(p) Stock Option Plan

Effective September 1, 2006, the Company adopted the provisions of FASB ASC Topic 718, *Accounting for Compensation Arrangements*, ("ASC 718") (previously listed as Statement of Financial Accounting Standards ("SFAS") No. 123 (revised 2004), *Share-Based Payment)* in accounting for its stock option plans. Under ASC 718, compensation cost is measured at the grant date based on the fair value of the equity instruments awarded and is recognized over the period during which an employee is required to provide service in exchange for the award, or the requisite service period, which is usually the vesting period. The fair value of the equity award granted is estimated on the date of the grant. The Company previously applied Accounting Principles Board ("APB") Opinion No. 25, *Accounting for Stock Issued to Employees*, and related interpretations and provided the required pro forma disclosures required by SFAS No. 123, *Accounting for Stock-Based Compensation*. The Company accounts for stock options issued to third parties, including consultants, in accordance with the provisions of the FASB ASC Topic 505-50, *Equity-Based Payments to Non-Employees*, ("ASC 505-50") (previously listed as Emerging Issues Task Force ("EITF") Consensus No. 96-18, *Accounting for Equity Instruments That Are Issued to Other Than Employees for Acquiring, or in Conjunction with Selling Goods or Services*). See Note 8, Stock Option Plans, for further discussion of employee stock-based compensation.

(q) Recent Accounting Pronouncements

In December 2007, the EITF reached a consensus on ASC Topic 808, *Collaborative Agreement* ("ASC 808") (previously EITF 07-01, *Accounting for Collaborative Arrangements*). ASC 808 discusses the appropriate income statement presentation and classification for the activities and payments between the participants in arrangements related to the development and commercialization of intellectual property. The sufficiency of disclosure related to these arrangements is also specified. ASC 808 is effective for fiscal years beginning after December 15, 2008. As a result, ASC 808 is effective for the Company as of September 1, 2009. Based upon the nature of the Company's business, ASC 808 could have a material impact on the Company's financial position and consolidated results of operations in future years, but had no material impact for the year ended August 31, 2010.

In December 2007, the FASB issued ASC Topic 805, *Business Combinations*, ("ASC 805") (previously SFAS 141(R)) and FASB ASC Topic 810, *Consolidation* ("ASC 810") (previously SFAS 160, *Noncontrolling Interests in Consolidated Financial Statements, an amendment of ARB No. 51*). These statements will significantly change the financial accounting and reporting of business combination transactions and non-controlling (or minority) interests in consolidated financial statements. ASC 805 requires companies to: (i) recognize, with certain

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exceptions, 100% of the fair values of assets acquired, liabilities assumed, and non-controlling interests in acquisitions of less than a 100% controlling interest when the acquisition constitutes a change in control of the acquired entity; (ii) measure acquirer shares issued in consideration for a business combination at fair value on the acquisition date; (iii) recognize contingent consideration arrangements at their acquisition-date fair values, with subsequent changes in fair value generally reflected in earnings; (iv) with certain exceptions, recognize pre-acquisition loss and gain contingencies at their acquisition-date fair values; (v) capitalize in-process research and development assets acquired; (vi) expense, as incurred, acquisition-related transaction costs; (vii) capitalize acquisition-related restructuring costs only if the criteria in ASC Topic 420, *Exit and Disposal Cost Obligations* (previously SFAS No. 146, *Accounting for Costs Associated with Exit or Disposal Activities)*, are met as of the acquisition date; and (viii) recognize changes that result from a business combination transaction in an acquirer's existing income tax valuation allowances and tax uncertainty accruals as adjustments to income tax expense. ASC 805 is required to be adopted concurrently with ASC 810 and is effective for business combination transactions for which the acquisition date is on or after the beginning of the first annual reporting period beginning on or after December 15, 2008 (the Company's fiscal 2010). Early adoption of these statements is prohibited. The Company believes the adoption of these statements will have a material impact on significant acquisitions completed after September 1, 2009. See Note 10 which reflects the accounting treatment of the 2009 Merger utilizing these provisions.

In May 2008, the FASB released ASC Topic 470, *Debt* ("ASC 470") (previously FASB Staff Position APB 14-1 *Accounting For Convertible Debt Instruments That May Be Settled in Cash Upon Conversion (Including Partial Cash Settlement*), which alters the accounting treatment for convertible debt instruments that allow for either mandatory or optional cash settlements. ASC 470 specifies that issuers of such instruments should separately account for the liability and equity components in a manner that will reflect the entity's nonconvertible debt borrowing rate when interest cost is recognized in subsequent periods. Furthermore, it would require recognizing interest expense in prior periods pursuant to retrospective accounting treatment. ASC 470 is effective for financial statements issued for fiscal years beginning after December 15, 2008; therefore, the Company adopted ASC 470 as of September 1, 2009. The Company has determined that ASC 470 had no material impact on its consolidated financial statements for the year ended August 31, 2010.

In April 2008, the FASB issued ASC Topic 350, *Intangibles – Goodwill and Other* ("ASC 350") (previously FSP SFAS No. 142-3, *Determination of the Useful Life of Intangible Assets*). ASC 350 provides guidance with respect to estimating the useful lives of recognized intangible assets acquired on or after the effective date and requires additional disclosure related to the renewal or extension of the terms of recognized intangible assets. ASC 350 is effective for fiscal years and interim periods beginning after December 15, 2008. The Company adopted ASC 350 as of September 1, 2009 and has determined that ASC 350 had no material impact on the Company's consolidated financial statements for the year ended August 31, 2010.

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In May 2009, the FASB issued ASC Topic 855, *Subsequent Events* ("ASC 855") (previously SFAS No. 165, *Subsequent Events*). ASC 855 establishes general standards of accounting for and disclosure of events that occur after the balance sheet date but before financial statements are issued or are available to be issued. ASC 855 defines the period after the balance sheet date during which management of a reporting entity should evaluate events or transactions that may occur for potential recognition or disclosure in the financial statements, and the circumstances under which an entity should recognize events or transactions occurring after the balance sheet date in its financial statements. ASC 855 is effective for fiscal years and interim periods ending after June 15, 2009. The Company adopted ASC 855 as of August 31, 2009 and anticipates that the adoption will impact the accounting and disclosure of future transactions. The Company's management has evaluated and disclosed subsequent events from the balance sheet date of August 31, 2010 through the date these consolidated financial statements were available to be issued.

ASC Topic 825, *Financial Instruments*, ("ASC 825") (previously FSP FAS 107-1 and APB 28-1 amends FASB Statement No. 107, *Disclosures about Fair Value of Financial Instruments*), to require disclosures about the fair value of financial instruments for interim reporting periods of publicly traded companies as well as in annual financial statements. ASC 825 also amends APB Opinion No. 28, Interim Financial Reporting, to require those disclosures in summarized financial information at interim reporting periods. The adoption of ASC 825 did not have a material impact on the Company's consolidated financial statements for the year ended August 31, 2010.

In June 2009, the FASB issued SFAS No. 167, *Amendments to FASB Interpretation No. 46(R)* ("SFAS 167"), which has not yet been codified in the ASC. The amendments include: (i) the elimination of the exemption for qualifying special purpose entities, (ii) a new approach for determining who should consolidate a variable-interest entity, and (iii) changes to when it is necessary to reassess who should consolidate a variable-interest entity. This statement is effective for fiscal years beginning after November 15, 2009, and for interim periods within that first annual reporting period. The Company is currently evaluating the impact of this standard, however, it does not expect SFAS 167 will have a material impact on its consolidated financial statements.

In June 2009, the FASB issued ASC Topic 860, Transfers and Servicing (Statement No. 166, Accounting for Transfers of Financial Assets — an amendment of FASB Statement No. 140) ("ASC 860"). The guidance removes the concept of a qualifying special purpose entity and changes the requirements for derecognizing financial assets. Many types of transferred financial assets that would have been derecognized previously are no longer eligible for derecognition. The guidance is effective for statements issued for fiscal years and interim periods beginning after November 15, 2009, and early adoption is prohibited. The guidance applies prospectively to transfers of financial assets occurring on or after the effective date. The Company is currently assessing the impact of ASC 860 and does not expect the adoption of this guidance to have a material impact on its consolidated financial statements.

In October 2009, the FASB issued ASU Update No. 2009-13**,** *Revenue Recognition (Topic 605), Multiple Deliverable Revenue Arrangements*. This guidance eliminates the residual method of allocation and requires the relative selling price method when allocating deliverables of a multiple-deliverable revenue arrangement. The determination of the selling price for each deliverable requires the use of a hierarchy designed to maximize the use of available objective evidence, including: vendor specific objective evidence, third party evidence of selling price, or estimated selling price. The guidance is effective prospectively for revenue arrangements entered into or materially modified in fiscal years beginning on or after June 15, 2010, and must be adopted in the same period using the same transition method. If adoption is elected in a period other than the beginning of a fiscal year, the amendments in these standards must be applied retrospectively to the beginning of the fiscal year. Full retrospective application of these amendments to prior fiscal years is optional. Early adoption of these standards may be elected. The Company will adopt these standards on September 1, 2010 and is currently reviewing the impact on its consolidated financial statements.

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In January 2010, the FASB issued Accounting Standards Update ("ASU") 2010-06, *Fair Value Measurements and Disclosures (Topic 820): Improving Disclosures about Fair Value Measurements* ("ASU 2010-6"). The ASU amends Subtopic 820-10 with new disclosure requirements and clarification of existing disclosure requirements. New disclosures required include the amount of significant transfers in and out of levels 1 and 2 fair value measurements and the reasons for the transfers. In addition, the reconciliation for level 3 activity will be required on a gross rather than net basis. The ASU provides additional guidance related to the level of disaggregation in determining classes of assets and liabilities and disclosures about inputs and valuation techniques. The amendments are effective for annual or interim reporting periods beginning after December 15, 2009, except for the requirement to provide the reconciliation for level 3 activity on a gross basis, which will be effective for fiscal years beginning after December 15, 2010. The Company is currently assessing the impact of ASU 2010-6 and does not expect the adoption of this guidance to have a material impact on its consolidated financial statements.

In April 2010, the FASB issued ASU 2010-17*, Revenue Recognition – Milestone Method (Topic 605): Milestone Method of Revenue Recognition* ("ASU 2010-17"). ASU 2010-17 provides guidance on defining a milestone and determining when it may be appropriate to apply the milestone method of revenue recognition for research or development transactions. Consideration that is contingent on achievement of a milestone in its entirety may be recognized as revenue in the period in which the milestone is achieved only if the milestone is judged to meet certain criteria to be considered substantive. Milestones should be considered substantive in their entirety and may not be bifurcated. An arrangement may contain both substantive and nonsubstantive milestones, and each milestone should be evaluated individually to determine if it is substantive. ASU 2010-17 is effective on a prospective basis for milestones achieved in fiscal years, and interim periods within those years, beginning on or after June 15, 2010, with early adoption permitted. The Company will adopt ASU 2010-17 as of September 1, 2010 and does not expect the adoption of this guidance to have a material impact on its consolidated financial statements.

(3) INTANGIBLE ASSETS AND GOODWILL

On January 27, 2006, BioMarin Pharmaceutical Inc. ("BioMarin") assigned the intellectual property and other rights relating to the RAP technology to the Company. As consideration for the assignment of the RAP technology, BioMarin will receive milestone payments based on certain financing and regulatory triggering events. No other consideration was paid for this assignment. The Company has recorded $150,000 of intangible assets on the consolidated balance sheets as of May 31, 2010 and August 31, 2009 based on the estimated fair value of its agreement with BioMarin.

On December 14, 2007, the Company acquired the intellectual property and other rights to develop DR Cysteamine to treat various clinical indications from the University of California at San Diego ("UCSD") by way of a merger with Encode Pharmaceuticals, Inc. ("Encode"), a privately held research and development company, which held the intellectual property license with UCSD. The intangible assets, recorded at approximately $2.6 million acquired in the merger with Encode, were primarily based on the value of the Company's common stock and warrants issued to the Encode stockholder.

Intangible assets recorded as a result of the 2009 Merger were approximately $1.1 million as discussed in Note 10 below.

Summary of intangibles acquired as discussed above:

Intangible asset (IP license) related to the Encode merger	$	2,620,000
Intangible asset related to NeuroTrans™ purchase from BioMarin		150,000
Intangible assets (out-license) related to the 2009 Merger		240,000
In-process research and development (IP license) related to the 2009 Merger		900,000
Total intangible assets		3,910,000

Less accumulated amortization	(397,458)
Intangible assets, net	$ 3,512,542

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The intangible assets related to DR Cysteamine and NeuroTrans™ are being amortized monthly over 20 years, which are the life of the intellectual property patents and the estimated useful life. The 20 year estimated useful life is also based upon the typical development, approval, marketing and life cycle management timelines of pharmaceutical drug products. The intangible assets related to the out-license will be amortized using the straight-line method over the estimated useful life of 16 years, which is the life of the intellectual property patents. The intangible assets related to NGX 426, which has been classified as in-process research and development, will not be amortized until the product is developed. During the years ended August 31, 2010 and 2009 and the cumulative period from September 8, 2005 (inception) to August 31, 2010, the Company amortized $152,250, $138,500 and $397,458, respectively, of intangible assets to research and development expense.

The following table summarizes the actual and estimated amortization expense for intangible assets for the periods indicated:

Amortization period	Amortization expense
September 8, 2005 (inception) to August 31, 2006 – actual	$ 4,375
Fiscal year ended August 31, 2007 – actual	7,500
Fiscal year ended August 31, 2008 – actual	94,833
Fiscal year ended August 31, 2009 – actual	138,500
Fiscal year ended August 31, 2010 – actual	152,250
Fiscal year ending August 31, 2011 – estimate	153,500
Fiscal year ending August 31, 2012 – estimate	153,500
Fiscal year ending August 31, 2013 – estimate	153,500
Fiscal year ending August 31, 2014 – estimate	153,500
Fiscal year ending August 31, 2015 – estimate	153,500

Goodwill of $3,275,403 represents the excess of total consideration recorded for the 2009 Merger over the value of the assets assumed. The Company has reviewed the carrying value of goodwill for impairment and has determined that there is no impairment.

(4) FIXED ASSETS

Fixed assets consisted of:

Category	August 31, 2010	August 31, 2009	Estimated useful lives
Leasehold improvements	$ 119,773	$ 113,422	Shorter of life of asset or lease term
Office furniture	3,188	3,188	7 years
Laboratory equipment	277,303	277,303	5 years
Computer hardware and software	94,842	80,437	3 years
Capital lease equipment	14,006	14,006	Shorter of life of asset or lease term
Total at cost	509,112	488,356	
Less: accumulated depreciation	(415,863)	(343,621)	
Total fixed assets, net	$ 93,249	$ 144,735	

Depreciation expense for the years ended August 31, 2010 and 2009 and the cumulative period from September 8, 2005 (inception) to August 31, 2010 was $72,241, $84,693 and $423,181, respectively. Accumulated depreciation on capital lease equipment was $8,260 and $3,951 as of August 31, 2010 and 2009, respectively.

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(5) FAIR VALUE MEASUREMENT

The Company uses a fair-value approach to value certain assets and liabilities. Fair value is the price that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. As such, fair value is a market-based measurement that should be determined based on assumptions that market participants would use in pricing an asset or liability. The Company uses a fair value hierarchy, which distinguishes between assumptions based on market data (observable inputs) and an entity's own assumptions (unobservable inputs). The hierarchy consists of three levels:

- Level one — Quoted market prices in active markets for identical assets or liabilities;
- Level two — Inputs other than level one inputs that are either directly or indirectly observable; and
- Level three — Unobservable inputs developed using estimates and assumptions, which are developed by the reporting entity and reflect those assumptions that a market participant would use.

Determining which category an asset or liability falls within the hierarchy requires significant judgment. The Company evaluates its hierarchy disclosures each quarter. Assets and liabilities measured at fair value on a recurring basis at August 31, 2010 and 2009 are summarized as follows:

Assets	Level 1	Level 2	Level 3	August 31, 2010
Fair value of cash equivalents	$16,509,186	$ —	$ —	$16,509,186
Total	$16,509,186	$ —	$ —	$16,509,186
Liabilities				
Fair value of common stock warrants	$ —	$ —	$15,780,216	$15,780,216
Total	$ —	$ —	$15,780,216	$15,780,216

Assets	Level 1	Level 2	Level 3	August 31, 2009
Fair value of cash equivalents	$ 3,515,353	$ —	$ —	$ 3,515,353
Total	$ 3,515,353	$ —	$ —	$ 3,515,353

Cash equivalents represent the fair value of the Company's investment in two money market accounts as of August 31, 2010 and 2009.

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Marked-to-Market

The common stock warrants issued in the Company's August 2010 private placement and the Company's December 2009 equity financing are classified as liabilities under ASC 480 and are, therefore, re-measured at the end of every reporting period with the change in value reported in its consolidated statements of operations.

For the year ended August 31, 2010, as a result of the marking-to-market of the warrant liability, the Company recorded a loss of $5.89 million, in the line item adjustment to fair value of common stock warrants in its consolidated statement of operations. See Note 11 for further discussion on the calculation of the fair value of the warrant liability.

	Warrant liability in $ millions
Fair value of warrants (including broker warrants) at issuance date on December 23, 2009	1.92
Adjustment to mark to market common stock warrants at August 31, 2010	3.91
December 2009 direct offering common stock warrant liability at fair value on August 31, 2010	5.83
Fair value of warrants (including broker warrants) at issuance date on August 12, 2010	7.97
Adjustment to mark to market common stock warrants at August 31, 2010	1.98
August 2010 private placement common stock warrant liability at fair value on August 31, 2010	9.95
Total warrant liability August 31, 2010	15.78

(6) ACCRUED LIABILITIES

Accrued liabilities consisted of:

	August 31,	
	2010	**2009**
Clinical trial costs	$ 280,918	$ -
Clinical milestone payment due to UCSD	200,000	-
Accrued bonuses	184,021	-
Legal fees	182,890	195,552
Salaries and wages	88,024	57,351
Accrued vacation	79,077	38,109
Clinical trial materials	50,000	-
Auditing and tax preparation fees	33,245	19,720
Consulting - general and administrative	19,304	-
Patent costs	8,956	10,500
Consulting - research and development	-	21,000
2009 Merger joint proxy/prospectus	-	109,011
Other	3,375	-
Total accrued liabilities	$ 1,129,810	$ 451,243

(7) IN-PROCESS RESEARCH AND DEVELOPMENT

On October 17, 2007, the Company purchased certain assets of Convivia, Inc. ("Convivia"), including intellectual property, know-how and research reports related to a product candidate targeting liver ALDH2 deficiency, a genetic metabolic disorder. The Company issued an aggregate of 101,991 shares of its restricted, unregistered common stock to the seller and other third parties in

settlement of the asset purchase. Pursuant to ASC Topic 730, *Research and Developmen*t (previously Financial Accounting Standard ("FAS") 2 Paragraph 11(c), *Intangibles Purchased From Others*), the Company has expensed the value of the common stock issued in connection with this asset purchase as in-process research and development expense. The amount expensed was based upon the closing price of Raptor's common stock on the date of the closing of the asset purchase transaction of $2.359 per share multiplied by the aggregate number of shares of Raptor common stock issued or 101,991 for a total expense of $240,625 recorded on Raptor's consolidated statement of operations during the year ended August 31, 2008.

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(8) STOCK OPTION PLANS

Effective September 1, 2006, the Company began recording compensation expense associated with stock options and other forms of equity compensation in accordance with ASC 718. Prior to September 1, 2006, the Company accounted for stock options according to the provisions of Accounting Principles Board ("APB") Opinion No. 25, *Accounting for Stock Issued to Employees*, and related interpretations, and therefore no related compensation expense was recorded for awards granted with no intrinsic value. The Company adopted the modified prospective transition method provided for under ASC 718, and consequently has not retroactively adjusted results from prior periods. Under this transition method, compensation cost associated with stock options now includes: (i) quarterly amortization related to the remaining unvested portion of all stock option awards granted prior to September 1, 2006, based on the grant date value estimated in accordance with the original provisions of ASC 718; and (ii) quarterly amortization related to all stock option awards granted subsequent to September 1, 2006, based on the grant date fair value estimated in accordance with the provisions of ASC 718. In addition, the Company records consulting expense over the vesting period of stock options granted to consultants. The compensation expense for stock- based compensation awards includes an estimate for forfeitures and is recognized over the requisite service period of the options, which is typically the period over which the options vest, using the straight-line method. Employee stock-based compensation expense for the years ended August 31, 2010 and 2009 and for the cumulative period from September 8, 2005 (inception) to August 31, 2010 was $216,732, $354,494 and $1,431,758, respectively, of which cumulatively $1,186,398 was included in general and administrative expense and $245,360 was included in research and development expense. No employee stock compensation costs were recognized for the period from September 8, 2005 (inception) to August 31, 2006, which was prior to the Company's adoption of ASC 718.

Stock-based compensation expense was based on the Black-Scholes option-pricing model assuming the following:

Period*	Risk-free interest rate	Expected life of stock option	Annual volatility	Annual turnover rate
September 8, 2005 (inception) to August 31, 2006**	5 %	10 years	100%	0%
Quarter ended November 30, 2006	5 %	8 years	100%	10%
Quarter ended February 28, 2007	5 %	8 years	100%	10%
Quarter ended May 31, 2007	5 %	8 years	100%	10%
Quarter ended August 31, 2007	4 %	8 years	100%	10%
Quarter ended November 30, 2007	3.75 %	8 years	109%	10%
Quarter ended February 29, 2008	2 %	8 years	119%	10%
Quarter ended May 31, 2008	2 %	8 years	121%	10%
Quarter ended August 31, 2008	2.5 %	8 years	128%	10%
Quarter ended November 30, 2008	1.5 %	7 years	170%	10%
Quarter ended February 28, 2009	2.0 %	7 years	220%	10%
Quarter ended May 31, 2009	2.6 %	7 years	233%	10%
Quarter ended August 31, 2009	3.2 %	7 years	240%	10%
Quarter ended November 30, 2009	3.0 %	7 years	245%	10%
Quarter ended February 28, 2010	3.1 %	7 years	55%	10%
Quarter ended May 31, 2010	3.1 %	7 years	77%	2.5%
Quarter ended August 31, 2010	2.07 %	6 years	85%	2.5%

* Dividend rate is 0% for all periods presented.

** Stock-based compensation expense was recorded on the consolidated statements of operations commencing on the effective date of ASC 718, September 1, 2006. Prior to September 1, 2006, stock based compensation was reflected only in the footnotes to the consolidated statements of operations, with no effect on the consolidated statements of operations, per the guidelines of APB Opinion No. 25. Consultant stock-based compensation expense has been recorded on the consolidated statements of operations since inception.

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If factors change and different assumptions are employed in the application of ASC 718, the compensation expense recorded in future periods may differ significantly from what was recorded in the current period.

During the quarter ended May 31, 2010, the Company changed its volatility calculation to reflect its historical trading commencing on September 30, 2009, which is the date that the 2009 Merger was consummated and the Company's common stock started trading on NASDAQ. The Company originally estimated volatility based upon historical volatility commencing in June 2006, when it first began trading on the Over-the-Counter Bulletin Board. The Company changed the volatility assumptions to better reflect its anticipated trading on NASDAQ. During the quarter ended May 31, 2010, the Company analyzed its actual turnover rate and concluded that 2.5% was a more accurate turnover rate on an annual basis.

The Company recognizes as an expense the fair value of options granted to persons who are neither employees nor directors. The fair value of expensed options was based on the Black-Scholes option-pricing model assuming the same factors shown in the stock-based compensation expense table above. Stock-based compensation expense for consultants for the years ended August 31, 2010 and 2009 and for the cumulative period from September 8, 2005 (inception) to August 31, 2010 was $78,327, $48,094 and $485,941, respectively, of which cumulatively $118,919 was included in general and administrative expense and $367,021 was included in research and development expense.

A summary of the activity in the 2010 Equity Incentive Plan, the 2006 Equity Compensation Plan, as amended and the Company's other stock option plans, is as follows:

	Option shares	Weighted-average exercise price	Exercisable	Weighted-average fair value of options granted
Outstanding at September 8, 2005	—	—	—	—
Granted	580,108	$ 2.64	—	$ 2.47
Exercised	—	—	—	—
Canceled	—	—	—	—
Outstanding at August 31, 2006	580,108	$ 2.64	4,010	$ 2.47
Granted	107,452	$ 2.56	—	$ 2.31
Exercised	(3,381)	$ 2.57	—	$ 2.40
Canceled	—	—	—	—
Outstanding at August 31, 2007	684,179	$ 2.63	273,236	$ 2.45
Granted	223,439	$ 2.27	—	$ 2.21
Exercised	—	—	—	—
Canceled	—	—	—	—
Outstanding at August 31, 2008	907,618	$ 2.54	600,837	$ 2.39
Granted	81,595	$ 1.13	—	$ 1.04
Exercised	—	—	—	—
Canceled	—	—	—	—
Outstanding at August 31, 2009	989,213	$ 2.42	826,303	$ 2.40
Granted	302,772	$ 2.29	160,605	$ 1.24
Assumed in the 2009 Merger	161,044	$ 114.12	158,475	$ 2.63
Exercised	(37,881)	$ 1.69	—	$ 1.49
Canceled	(23,860)	$ 142.42	—	$ 2.00
Outstanding at August 31, 2010	1,391,288	$ 14.25	1,089,248	$ 1.87

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The weighted average intrinsic values of stock options outstanding and expected to vest and stock options exercisable as of August 31, 2010 and 2009 were $526,891, $311,279, $66,937 and $11,364, respectively.

There were 2,697,228 options available for grant as of August 31, 2010 under the 2010 Equity Incentive Plan, which was approved by the Company's Board of Directors as of February 2, 2010 and approved by its stockholders on March 9, 2010. No further grants will be made under any previous or assumed stock option plans. As of August 31, 2010, the options outstanding under all of the Company's stock option plans consisted of the following:

Range of exercise prices	Options outstanding			Options exercisable	
	Number of options outstanding and expected to vest (#)	Weighted-average remaining contractual life (yrs.)	Weighted-average Exercise price ($)	Number of options exercisable (#)	Weighted-average exercise price ($)
$0 to $1.00	34,969	8.63	.85	11,656	0.85
$1.01 to $2.00	86,259	8.74	1.73	35,901	1.64
$2.01 to $3.00	1,050,147	6.84	2.46	851,504	2.55
$3.01 to $4.00	105,802	9.26	3.57	78,847	3.67
$4.01 to $5.00	62,104	9.13	4.57	59,333	4.59
$5.01 to $1,564	52,007	5.00	315.34	52,007	315.34
	1,391,288	7.15	14.25	1,089,248	17.62

At August 31, 2010, the total unrecognized compensation cost was approximately $471,000. The weighted average period over which it is expected to be recognized is 3 years.

(9) INCOME TAXES

The provision for income taxes differs from the amount estimated by applying the statutory federal income tax rate to income (loss) before taxes as follows:

	August 31,			
	2010		2009	
Federal tax (benefit) at statutory rate	$ (6,390,517)	-34.00%	$ (3,132,608)	-34.00%
State tax (benefit) at statutory rate, net of federal tax benefit	(953,473)	-5.07%	(629,304)	-6.83%
Change in valuation allowance	6,067,977	32.28%	5,069,715	55.02%
Research and development credits	(708,240)	-3.77%	(1,325,036)	-14.38%
Fair market value of warrants	2,004,203	10.66%	-	-%
Other	(19,950)	-0.10%	17,233	0.19%
Provision for income taxes	$ (0)	(0)	$ 0	0

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Deferred tax assets (liabilities) consist of the following (in thousands):

	August 31,	
	2010	2009
Deferred tax assets		
Net operating loss carryforwards	$ 9,154,868	$ 4,722,078
Capitalized start-up costs	3,487,300	1,615,625
Stock option expense	268,019	207,169
Research credit	3,513,229	2,223,767
Capital loss carryforwards	55,768	47,600
Basis difference for fixed assets and intangibles	216,556	277,941
Accruals	37,389	24,823
Valuation allowance	(16,733,129)	(9,119,003)
Gross deferred tax asset	$ 0	$ 0

As of August 31, 2010, the Company had net operating loss carryforwards for federal and state income tax purposes of approximately $22.6 million and $25.0 million respectively, which expire beginning after the year 2022 and 2015, respectively. As of August 31, 2010, the Company had federal and state research and development credits of $3.2 million and $.5 million respectively. The federal credits expire beginning after the year 2026 and the state credits have no expiration.

The valuation allowance increased approximately $7.6 million during the year ended August 31, 2010, primarily as a result of current year losses.

Utilization of the Company's net operating loss may be subject to substantial annual limitation due to the ownership change limitations provided by the Internal Revenue Code of 1986, as amended, or the Code, and similar state provisions. Such an annual limitation could result in the expiration of the net operating loss before utilization.

In July 2006, the FASB released Final Interpretation No. 48, *Accounting for Uncertainty in Income Taxes* ("FIN 48"). FIN 48 prescribes the minimum recognition threshold a tax position is required to meet before being recognized in the financial statements. This interpretation also provides guidance on the recognition of income tax assets and liabilities, classification of current and deferred income tax assets and liabilities, accounting for interest and penalties associated with tax positions, accounting for income taxes in interim periods, and income tax disclosures. FIN 48 also requires additional disclosure of the beginning and ending unrecognized tax benefits and details regarding the uncertainties that may cause the unrecognized benefits to increase or decrease within a twelve-month period. FIN 48 is effective for fiscal years beginning after December 15, 2006, with the cumulative effect of the change in accounting principle, if any, recorded as an adjustment to opening retained earnings.

On September 1, 2009, we adopted FASB Topic 740 - *Income Taxes* ("Topic 740") - an interpretation of FIN 48. As of September 1, 2009, no unrecognized tax benefits were recorded. Because of net operating loss and research credit carryforwards, substantially all of the Company's tax years, from 2001 through 2009, remain open to U.S. federal and state tax examinations. The Company did not record a change in its unrecorded tax benefits during the year ended August 31, 2010, and expects no change in its unrecorded tax benefits in the next 12 months. The Company's policy will be to recognize interest and penalties related to income taxes in income tax expense. The Company is not aware of any pending income tax audits. Significant components of the Company's deferred tax assets for income tax purposes are net operating loss carryforwards, capitalized start-up costs, stock-based compensation and research credits. Due to the Company's lack of earning history, any deferred assets recorded have been fully offset by a valuation allowance.

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(10) ISSUANCE OF COMMON STOCK

As of August 31, 2010, there were 30,076,758 shares of the Company's common stock outstanding.

ISSUANCE OF COMMON STOCK PURSUANT TO COMMON STOCK WARRANT EXERCISES AND STOCK OPTION EXERCISES

During the year ended August 31, 2010, the Company received $475,020 from the exercise of warrants in exchange for the issuance of 189,056 shares of the Company's common stock and the Company issued 7,680 shares of its common stock resulting from a cashless exercise of a warrant issued in 2007 in connection with the purchase of DR Cysteamine. During the cumulative period from September 8, 2005 (inception) through August 31, 2010, the Company received approximately $7.0 million from the exercise of warrants in exchange for the issuance of an aggregate of 3,741,767 shares.

During the year ended August 31, 2010, the Company received $64,022 from the exercise of stock options in exchange for 37,881 shares of the Company's common stock. For the cumulative period from September 8, 2005 (inception) through August 31, 2010, the Company received $72,718 from the exercise of stock options resulting in the issuance of 41,261 shares of common stock.

ISSUANCE OF COMMON STOCK PURSUANT TO AN ASSET PURCHASE AGREEMENT WITH CONVIVIA, INC.

On October 18, 2007, the Company purchased certain assets of Convivia, including intellectual property, know-how and research reports related to a product candidate targeting liver ALDH2 deficiency, a genetic metabolic disorder. The Company hired Convivia's chief executive officer and founder, Thomas E. (Ted) Daley, as President of its clinical division. In exchange for the assets related to the ALDH2 deficiency program, the Company issued to Convivia 46,625 shares of its restricted, unregistered common stock, an additional 46,625 shares of its restricted, unregistered common stock to a third party in settlement of a convertible loan between the third party and Convivia, and another 8,742 shares of restricted, unregistered common stock in settlement of other obligations of Convivia. Mr. Daley, as the former sole stockholder of Convivia (now dissolved), may earn additional shares of the Company based on certain triggering events or milestones related to the development of Convivia assets. In addition, Mr. Daley may earn cash bonuses based on the same triggering events pursuant to his employment agreement. In January 2008, Mr. Daley earned a $30,000 cash bonus pursuant to his employment agreement for executing the Patheon formulation agreement for manufacturing Convivia™. In March 2008, Mr. Daley earned a $10,000 cash bonus pursuant to his employment agreement and was issued 23,312 shares of common stock valued at $56,000 based on the execution of an agreement to supply the Company with the active pharmaceutical ingredient for

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Convivia™ pursuant to the asset purchase agreement. In October 2008, Mr. Daley was issued 23,312 shares of restricted common stock valued at $27,000 and earned a $30,000 cash bonus (pursuant to Mr. Daley's employment agreement) pursuant to the fulfillment of a clinical milestone. In July 2010, the Company issued 11,656 shares of its restricted common stock valued at $35,551and paid a $10,000 cash bonus to Mr. Daley as a result of the execution of the license agreement with Uni Pharma for the development of Convivia™ in Taiwan. Pursuant to ASC 730, the accounting guidelines for expensing research and development costs, the Company has expensed the value of the stock issued in connection with this asset purchase (except for milestone bonuses, which are expensed as compensation expense) as in-process research and development expense in the amount of $240,625 on its consolidated statement of operations for the year ended August 31, 2008.

MERGER OF RAPTOR'S CLINICAL DEVELOPMENT SUBSIDIARY AND ENCODE PHARMACEUTICALS, INC.

On December 14, 2007, the Company entered into a Merger Agreement (the "Encode Merger Agreement"), dated as of the same date, by and between the Company, its clinical development subsidiary and Encode Pharmaceuticals, Inc. ("Encode"), a privately held development stage company. Pursuant to the Encode Merger Agreement, a certificate of merger was filed with the Secretary of State of the State of Delaware and Encode was merged with and into the Company's clinical development subsidiary. The existence of Encode ceased as of the date of the Encode Merger Agreement. Pursuant to the Encode Merger Agreement and the certificate of merger, the Company's clinical development subsidiary, as the surviving corporation, continued as a wholly-owned subsidiary of the Company. Under the terms of and subject to the conditions set forth in the Encode Merger Agreement, the Company issued 802,946 shares of restricted, unregistered shares of the Company's common stock, par value $.001 per share (the "Common Stock") to the stockholders of Encode (the "Encode Stockholders"), options ("Company Options") to purchase 83,325 shares of Common Stock to the optionholders of Encode (the "Encode Optionholders"), and warrants ("Company Warrants") to purchase 256,034 restricted, unregistered shares of Common Stock to the warrantholders of Encode (the "Encode Warrantholders", and together with the Encode Stockholders and Encode Optionholders, the "Encode Securityholders"), as of the date of the Encode Merger Agreement. Such Common Stock, Company Options to purchase Common Stock, and Company Warrants to purchase Common Stock combine for an aggregate amount of 1,142,305 shares of Common Stock issuable to the Encode Securityholders as of the closing of the merger with Encode. The purchase price was valued at $2.6 million, which is reflected as intangible assets on the Company's consolidated balance sheet as of August 31, 2008, primarily based on the value of the Company's common stock and warrants issued to Encode stockholders. The Encode Securityholders are eligible to receive up to an additional 559,496 shares of Common Stock, Company Options and Company Warrants to purchase Common Stock in the aggregate based on certain triggering events related to regulatory approval of DR Cysteamine, an Encode product program described below, if completed within the five year anniversary date of the Encode Merger Agreement. The Company recorded this transaction as an asset purchase rather than a business combination, as Encode had not commenced planned principal operations at the time of the merger, such as generating revenues from its drug product candidate.

As a result of the merger with Encode, the Company received the exclusive worldwide license to DR Cysteamine ("License Agreement"), developed by clinical scientists at the UCSD, School of Medicine. DR Cysteamine is a proprietary enterically coated formulation of cysteamine bitartrate, a cystine depleting agent currently approved by the U.S. Food and Drug Administration ("FDA"). Cysteamine bitartrate is prescribed for the management of the genetic disorder known as nephropathic cystinosis ("cystinosis"), a lysosomal storage disease. The active ingredient in DR Cysteamine has also demonstrated potential in studies as a treatment for other metabolic and neurodegenerative diseases, such as Huntington's Disease and NASH.

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In consideration of the grant of the license, the Company will be obligated to pay an annual maintenance fee until it begins commercial sales of any products developed pursuant to the License Agreement. In addition to the maintenance fee, the Company will be obligated to pay during the life of the License Agreement: milestone payments ranging from $20,000 to $750,000 for orphan indications and from $80,000 to $1,500,000 for non-orphan indications upon the occurrence of certain events, if ever; royalties on commercial net sales from products developed pursuant to the License Agreement ranging from 1.75% to 5.5%; a percentage of sublicense fees ranging from 25% to 50%; a percentage of sublicense royalties; and a minimum annual royalty commencing the year the Company begins commercially selling any products pursuant to the License Agreement, if ever. Under the License Agreement, the Company is obligated to fulfill predetermined milestones within a specified number of years ranging from 0.75 to 6 years from the effective date of the License Agreement, depending on the indication. To the extent that the Company fails to perform any of the obligations, UCSD may terminate the license or otherwise cause the license to become non-exclusive. To-date, Raptor has accrued $470,000 in milestone payments to UCSD based upon the initiation of clinical trials in cystinosis and in NASH.

ISSUANCES OF COMMON STOCK AND WARRANTS IN CONNECTION WITH THE SALE OF UNITS IN A PRIVATE PLACEMENT

During the period from May 21, 2008 through June 27, 2008, Raptor entered into a Securities Purchase Agreement, as amended (the "2008 Private Placement Purchase Agreement"), with 11 investors for the private placement of units of the Company, each unit comprised of one share of Raptor's Common Stock and one warrant to purchase one half of one share of Raptor's Common Stock, at a purchase price of $2.14 per unit. Pursuant to the 2008 Private Placement Purchase Agreement, the Company sold an aggregate of 4,662,468 shares of Common Stock for aggregate gross proceeds of $10 million and issued to the investors warrants, exercisable for two years from the initial closing, which entitle the investors to purchase up to an aggregate of 2,331,234 shares of Common Stock of the Company and have an exercise price of either $3.22 or $3.86 per share, depending on when such warrants are exercised, if at all, and were valued at approximately $3 million (using the following Black-Scholes pricing model assumptions: risk-free interest rate 2%; expected term 2 years and annual volatility 121.45%).

In connection with the May / June 2008 private placement, the Company issued warrants and a cash fee to placement agents to compensate them for placing investors into the financing. Placement agents were issued warrants exercisable for 7% of Common Stock issued and issuable under the warrants issued to investors as part of the financing units and a cash fee based upon the proceeds of the sale of the units of the private placement. In connection with the sale of units, the Company issued placement agent warrants to purchase 489,559 shares of Raptor's Common Stock at an exercise price of $2.36 per share for a five year term (valued at approximately $960,000 using the following Black-Scholes pricing model assumptions: risk-free interest rate 2%; expected term 5 years and annual volatility 121.45%) and cash fees to placement agents totaling $700,000. Of the placement agents compensated, Limetree Capital was issued warrants to purchase 438,890 shares of Raptor's Common Stock and cash commission of $627,550. One of the Company's Board members serves on the board of Limetree Capital.

On April 29, 2009, in order to reflect current market prices, Raptor notified the holders of warrants purchased in the May/June 2008 private placement that the Company was offering, in exchange for such warrants, new warrants to purchase its common stock at an exercise price of $1.29 per share, but only to the extent such exchange of the original warrants and exercise of the new warrants, including the delivery of the exercise price, occurred on or prior to July 17, 2009. The new warrants were valued at approximately $2.3 million based on the following Black-Scholes pricing model assumptions: risk-free interest rate 0.55%; expected term 1 year and annual

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volatility 231.97%. The warrants that were not exchanged prior to or on July 17, 2009 retained their original exercise prices of $3.86 per share and original expiration date of May 21, 2010. The Company received $2,614,500 of proceeds from warrant exercises that resulted in the issuance of 2,031,670 shares of Raptor's common stock pursuant to the exchange described above.

On August 21, 2009, Raptor entered into a securities purchase agreement, with four investors for the private placement of units of the Company at a purchase price of $1.37 per unit, each unit comprised of one share of Raptor's common stock, par value $0.001 per share and one warrant to purchase one half of one share of Raptor's common stock. Pursuant to the securities purchase agreement, the Company sold an aggregate of 1,738,226 units to the investors for aggregate gross proceeds of $2,386,000. The 1,738,226 units are comprised of an aggregate of 1,738,226 shares of common stock and warrants to purchase up to 869,113 shares of Raptor's common stock valued at $1.0 million (using the following Black-Scholes pricing model assumptions: risk-free interest rate 1.11%; expected term 2 years and annual volatility 240.29%). The warrants, exercisable for two years from the closing, entitle the investors to purchase, in the aggregate, up to 869,113 shares of Raptor's common stock and have an exercise price of either $2.57 until the first anniversary of issuance or $3.22 per share after the first anniversary of issuance.

In connection with the August 2009 private placement, the Company issued warrants and a cash fee to Limetree Capital as its sole placement agent to compensate it for placing investors into the financing. Limetree Capital was issued warrants exercisable for 7% of common stock issued and issuable under the warrants issued to investors as part of the financing units and a 3.5% cash fee based upon the proceeds of the sale of the units of the August 2009 private placement. Limetree Capital was issued a five-year warrant to purchase 129,733 shares of Raptor's Common Stock at an exercise price of $1.50 per share (valued at approximately $171,000 using the following Black-Scholes pricing model assumptions: risk-free interest rate 2.58%; expected term 5 years and annual volatility 240.29%) and cash commission of $59,360.

2009 MERGER AND NASDAQ LISTING

On September 29, 2009, the Company, formerly known as TorreyPines Therapeutics, Inc. ("TorreyPines") and RPC completed a reverse merger. The Company changed its name to "Raptor Pharmaceutical Corp." and commenced trading on September 30, 2009 on the NASDAQ Capital Market under the ticker symbol "RPTP."

In connection with the exchange of shares in the merger, immediately after the effective time of such merger, RPC and the Company's stockholders owned 95% and 5% of the outstanding shares of the combined company, respectively. RPC stockholders received (as of immediately prior to such merger) 17,881,300 shares of the combined company's common stock in exchange for the 76,703,147 shares of RPC's common stock outstanding immediately prior to the closing of the merger. On September 29, 2009, immediately prior to the effective time of such merger, the Company's board of directors, with the consent of RPC's board of directors, acted to effect a reverse stock split of the issued and outstanding shares of the Company's common stock such that every 17 shares of the Company's common stock outstanding immediately prior to the effective time of the merger would represent one share of the Company's common stock. Due to the reverse stock split implemented by the Company, the 15,999,058 shares of the Company's common stock outstanding immediately prior to the closing of the merger became 940,863 shares of the combined company's common stock.

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In connection with the merger and subject to the same conversion factor as the RPC common stock (.2331234), the combined company assumed all of RPC's stock options and warrants outstanding at the time of the merger. The combined company also retained the Company's stock options and warrants outstanding at the merger, subject to the same adjustment factor as described above to give effect to the 1 for 17 reverse split.

The combined company is headquartered in Novato, California and is managed by Christopher M. Starr, Ph.D., as Chief Executive Officer and director, Todd C. Zankel, Ph.D., as Chief Scientific Officer, Kim R. Tsuchimoto as Chief Financial Officer, Ted Daley, as President of the clinical division and Patrice P. Rioux., M.D., Ph.D., as Chief Medical Officer of the clinical division.

There were a number of factors on which RPC's board of directors relied in approving the 2009 Merger. The primary reason for RPC's board of directors' decision to merge with TorreyPines was the benefit anticipated from the additional liquidity expected from having a NASDAQ trading market on which the combined company's common stock could be listed, in addition to having access to an expanded pipeline of product candidates and having development capabilities across a wider spectrum of diseases and markets.

The liquidity benefit is the primary factor behind the goodwill recognized in the transaction (see below). The goodwill has been assigned to the Company's clinical segment and is expected to be fully deductible for tax purposes. Below is a breakdown of the assets acquired and liabilities assumed in the merger described herein (in millions, except for %):

Asset Allocation	Value (millions)	%
Cash and equivalents	$ 0.58	13
Other current assets	0.10	2
Accrued liabilities	(0.68)	(15)
Intangible assets:		
In-process research & development	0.90	20
Licenses	0.24	6
Total identifiable assets	1.14	26
Plus Goodwill	3.28	74
Total net assets acquired	$ 4.42	100

Acquisition costs incurred by the Company related to the 2009 Merger were approximately $0.4 million and were expensed as incurred. If the 2009 Merger had occurred on September 1, 2008, the Company's revenues would have increased by approximately $1.5 million from fees earned by TorreyPines from the sale one of its programs in the quarter ended December 31, 2008, for total pro forma revenues of $1.5 million for the year ended August 31, 2009. Net loss would have increased by approximately $2.5 million due to an increase of revenues of $1.5 million described above offset by $3.1 million of loss on impairment of purchased patents recognized by TorreyPines during the period plus $0.9 million in transaction costs and costs associated with obligations owed to the TorreyPines employees for a pro forma net loss and net loss per share of $11.7 million or $0.81 per share for the year ended August 31, 2009. If the 2009 Merger had occurred on September 1, 2009, the Company's revenues would have remained zero and the Company's net loss and net loss per share for the year ended August 31, 2010 would have remained $18.9 million or $0.85 per share.

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ISSUANCES OF COMMON STOCK AND WARRANTS IN CONNECTION WITH THE SALE OF UNITS IN A REGISTERED DIRECT OFFERING

On December 17, 2009, the Company entered into a Placement Agent Agreement with Ladenburg Thalmann & Co. Inc. as placement agent (the "Placement Agent"), relating to the issuance and sale to the Direct Offering Investors (as defined below) pursuant to a registered direct offering (the "Offering") of up to 3,747,558 units (the "Units"), consisting of (i) 3,747,558 shares of the Company's common stock, (ii) warrants to purchase an aggregate of up to 1,873,779 shares of the Company's common stock (and the shares of common stock issuable from time to time upon exercise of such warrants) (the "Series A Warrants"), and (iii) warrants to purchase an aggregate of up to 1,873,779 shares of the Company's common stock (and the shares of common stock issuable from time to time upon exercise of such warrants) (the "Series B Warrants," and collectively with the Series A Warrants, the "Investor Warrants").

The Placement Agent for the Direct Offering received a placement fee equal to 6.5% of the gross cash proceeds to the Company from the Direct Offering of the Units or $487,183 (excluding any consideration that may be paid in the future upon exercise of the Warrants), a warrant to purchase up to an aggregate of 74,951 shares of the Company's common stock at $2.50 per share (valued at approximately $52,000 using the following Black-Scholes pricing model assumptions: risk-free interest rate 2.23%; expected term 5 years and annual volatility 49.28%) and $25,000 in out-of-pocket accountable expenses. The warrant issued to Ladenburg has the same terms and conditions as the Investor Warrants except that the exercise price is 125% of the public offering price per share or $2.50 per share, and the expiration date is five years from the effective date of the Registration Statement.

In connection with the Direct Offering, following execution of the Placement Agent Agreement, the Company also entered into a definitive securities purchase agreement (the "Direct Offering Purchase Agreement"), dated as of December 17, 2009, with 33 investors set forth on the signature pages thereto (collectively, the "Direct Offering Investors") with respect to the Direct Offering of the Units, whereby, on an aggregate basis, the Direct Offering Investors agreed to purchase 3,747,558 Units for a negotiated purchase price of $2.00 per Unit, amounting to gross proceeds of approximately $7.5 million and net proceeds after commissions and expenses of approximately $6.2 million. Each Unit consists of one share of the Company's common stock, one Series A Warrant exercisable for 0.5 of a share of the Company's common stock and one Series B Warrant exercisable for 0.5 of a share of the Company's common stock. The shares of the Company's common stock and the Warrants were issued separately. The Series A Warrants will be exercisable during the period beginning one hundred eighty (180) days after the date of issue and ending on the fifth (5th) anniversary of the date of issue. The Series B Warrants will be exercisable during the period beginning one hundred eighty (180) days after the date of issue and ending on the eighteen (18) month anniversary of the date of issue. The Investor Warrants have a per share exercise price of $2.45. At closing of the financing, the Series A Warrants were valued at $1.3 million (using the following Black-Scholes pricing model assumptions: risk-free interest rate 2.23%; expected term 5 years and annual volatility 49.28%) and the Series B Warrants were valued at $0.5 million (using the following Black-Scholes pricing model assumptions: risk-free interest rate 0.56%; expected term 18 months and annual volatility 49.28%). Based on the underlying terms of the Investor Warrants and Placement Agent Warrants, the Investor Warrants are classified as liability, as discussed further below in Note 11.

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ISSUANCES OF COMMON STOCK IN CONNECTION WITH AN EQUITY LINE

On April 16, 2010, the Company signed a purchase agreement with Lincoln Park Capital Fund, LLC ("LPC"), together with a registration rights agreement, whereby LPC has agreed to purchase up to $15 million of the Company's common stock over a 25 month period. Under the registration rights agreement, the Company agreed to file a registration statement related to the transaction with the U.S. Securities and Exchange Commission ("SEC") covering the shares that have been issued or may be issued to LPC under the purchase agreement. Such registration statement was declared effective by the SEC on May 7, 2010. The Company has the right over a 25-month period to sell its shares of common stock to LPC in amounts of $100,000 to up to $1,000,000 per sale, depending on certain conditions as set forth in the purchase agreement, up to the aggregate amount of $15 million. The purchase agreement may be terminated by the Company at any time at its discretion without any cost to the Company.

The purchase price of the shares issued to LPC under the purchase agreement is based on the prevailing market prices of the Company's shares at the time of sale without any fixed discount. The Company controls the timing and amount of any sales of shares to LPC. LPC does not have the right or the obligation to purchase any shares of the Company's common stock on any business day that the purchase price of the Company's common stock is below $1.50 per share.

In consideration for entering into the purchase agreement, the Company issued to LPC 145,033 shares of common stock valued at $246,556 (recorded as deferred offering costs on the Company's balance sheet and amortized over the usage of the equity line) as a commitment fee and is required to issue up to an additional 217,549 shares of its common stock pro rata as LPC purchases the $15 million of the Company's common stock over the 25-month period. During the year ended August 31, 2010, the Company sold 2,170,798 shares to LPC at a weighted average price of $2.26 and paid commitment fees to LPC in the form of 71,064 shares (in addition to the 145,033 shares issued as the initial commitment fee), valued at $228,581.

2010 PRIVATE PLACEMENT

On August 9, 2010, we entered into a securities purchase agreement with 23 investors set forth on the signature pages thereto (or, the U.S. Investors) and a separate securities purchase agreement with a certain Canadian investor (or, the Canadian Investor and together with the U.S. Investors, the 2010 Private Placement Investors) set forth on the signature pages thereto (or collectively, the 2010 Private Placement Purchase Agreements), for the private placement, or the 2010 Private Placement, of our common stock and warrants to purchase our common stock, at a purchase price of $3.075 per unit, with each unit comprised of one share of common stock and a warrant to purchase one share of common stock. JMP Securities LLC, or the Placement Agent, served as our placement agent in the 2010 Private Placement.

The closing of this private placement occurred on August 12, 2010. We issued and sold an aggregate of 4,897,614 units, comprised of 4,897,614 shares of common stock and warrants to purchase up to 4,897,614 shares of our common stock for gross proceeds of approximately $15.1 million. Each warrant, exercisable for 5 years from August 12, 2010, has an exercise price of $3.075 per share. At closing of the 2010 Private Placement, the warrants issued to investors were valued at approximately $7.8 million (using the following Black-Scholes pricing model assumptions: risk-free interest rate 1.74%; expected term 5 years and annual volatility 85.14%.) As the placement agent for the 2010 Private Placement, the Placement Agent was issued one warrant to purchase 97,952 shares of our common stock (valued at approximately $0.2 million, based upon the same Black-Scholes inputs as the investor warrants), paid a cash commission of $978,911 and reimbursed for certain of its expenses incurred in connection with the 2010 Private Placement.

In connection with the 2010 Private Placement, on August 12, 2010, we entered into a registration rights agreement, or the 2010 Private Placement Registration Rights Agreement, with the 2010 Private Placement

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Investors, pursuant to which we filed with the SEC a registration statement related to the 2010 Private Placement covering the resale of the common stock issued to the 2010 Private Placement Investors under the 2010 Private Placement Purchase Agreements and the shares of common stock that will be issued to the 2010 Private Placement Investors upon exercise of the warrants, including the warrant issued to the Placement Agent. Such registration statement was declared effective on August 31, 2010.

The following is a summary of common stock outstanding as of August 31, 2010:

Transaction	Date of Issuance	Common Stock Issued
Founders' shares	Sept. 2005	1,398,742
Seed round	Feb. 2006	466,247
PIPE concurrent with reverse merger	May 2006	1,942,695
Shares issued in connection with reverse merger	May 2006	3,100,541
Warrant exercises	Jan. – Nov. 2007	1,513,359
Stock option exercises	Mar. 2007	3,380
Loan finder's fee	Sept. 2007	46,625
Convivia asset purchase	Oct. 2007 – June 2010	160,272
Encode merger DR Cysteamine asset purchase	Dec. 2007	802,946
Shares issued pursuant to consulting agreement	May 2008	2,040
PIPE — initial tranche	May 2008	1,030,405
PIPE — second tranche	May 2008	69,937
PIPE — third tranche	June 2008	3,562,126
Warrant exercises from warrant exchange	June/July 2009	2,031,670
PIPE	August 2009	1,738,226
Warrant exercises	Sept. 2009 – Aug. 2010	196,736
Shares issued in connection with reverse merger	September 2009	940,863
Stock option exercises	October 2009 – June 2010	37,881
Registered direct financing	December 2009	3,747,558
Shares issued to equity line investor (incl. fee shares)	April 2010 – July 2010	2,386,895
2010 private placement	August 2010	4,897,614
Total shares of common stock outstanding		30,076,758

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(11) WARRANTS

The table reflects the number common stock warrants outstanding as of August 31, 2010:

	Number of shares exercisable	Exercise price	Expiration date
Issued in lieu of deferred legal fees	13,987	$ 2.57	2/13/2011
Issued in connection with Encode merger	233,309	$ 2.87	12/13/2015
Issued to placement agents in May / June 2008	465,816	$ 2.36	5/21/2013
Issued to PIPE investors in August 2009	752,551	$ 3.22	8/21/2011
Issued to placement agents in August 2009	129,733	$ 1.50	8/21/2014
TorreyPines warrants assumed in 2009 Merger	8,507	$ 81.48*	12/7/2010-9/26/2015
Issued to registered direct investors in Dec. 2009	1,825,029	$ 2.45	6/22/2011
Issued to registered direct investors in Dec. 2009	1,873,779	$ 2.45	12/23/2014
Issued to placement agent in Dec. 2009	74,951	$ 2.50	12/23/2014
Issued to private placement investors in Aug. 2010	4,897,614	$ 3.075	8/11/2015
Issued to placement agent in Aug. 2010	97,952	$ 3.075	8/11/2015
Total warrants outstanding	10,373,228	$ 2.87*	

* Average exercise price

The warrants issued by the Company in the August 2010 private placement and the December 2009 equity financing contain a conditional obligation that may require the Company to transfer assets to repurchase the warrants upon the occurrence of potential future events. Under ASC Topic 480, *Distinguishing Liabilities from Equity* ("ASC 480"), a financial instrument that may require the issuer to settle the obligation by transferring assets is classified as a liability. Therefore, the Company has classified the warrants from both financings as liabilities and will mark them to fair value at each period end.

A Black-Scholes option-pricing model was used to obtain the fair value of the warrants issued in the December 2009 equity financing using the following assumptions:

	December 2009 equity financing						August 2010 private placement	
	Series A		Series B		Placement Agent		Investors and placement agent	
	At issuance December 23, 2009	At August 31, 2010	At issuance December 23, 2009	At August 31, 2010	At issuance December 23, 2009	At August 31, 2010	At issuance August 12, 2010	At August 31, 2010
Fair value ($ millions)	1.3	3.7	0.5	2.0	0.05	0.1	8.0	9.9
Black-Scholes inputs:								
Stock price	$1.89	$2.98	$1.89	$2.98	$1.89	$2.98	$2.50	$2.98
Exercise price	$2.45	$2.45	$2.45	$2.45	$2.50	$2.50	$3.075	$3.075
Risk free interest rate	2.23%	1.36%	0.56%	0.24%	2.23%	1.36%	1.74%	1.74%
Volatility	49.28%	85.1%	49.28%	85.1%	49.28%	85.1%	85.1%	85.1%
Expected term (years)	5.0	4.25	1.5	0.75	5.0	4.25	5.0	5.0
Dividend	0	0	0	0	0	0	0	0

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For the year ended August 31, 2010, as a result of the marking-to-market of the warrant liability, the Company recorded a loss of $5.89 million, in the line item adjustment to fair value of common stock warrants in its consolidated statement of operations. See Note 5 for further discussion on the marking-to-market of the warrant liability.

(12) COMMITMENTS AND CONTINGENCIES

CONTRACTUAL OBLIGATIONS WITH BIOMARIN

Pursuant to the terms of the asset purchase agreement the Company entered into with BioMarin Pharmaceutical Inc. ("BioMarin") for the purchase of intellectual property related to the Company's receptor-associated protein ("RAP") based technology (including NeuroTrans™), the Company is obligated to make the following milestone payments to BioMarin upon the achievement of the following events:

$50,000 (paid by the Company in June 2006) within 30 days after Raptor receives total aggregate debt or equity financing of at least $2,500,000;

$100,000 (paid by the Company in June 2006) within 30 days after Raptor receives total aggregate debt or equity financing of at least $5,000,000;

$500,000 upon the Company's filing and acceptance of an investigational new drug application for a drug product candidate based on the NeuroTrans™ product candidate;

$2,500,000 upon the Company's successful completion of a Phase 2 human clinical trial for a drug product candidate based on the NeuroTrans™ product candidate;

$5,000,000 upon on the Company's successful completion of a Phase 3 human clinical trial for a drug product candidate based on the NeuroTrans™ product candidate;

$12,000,000 within 90 days of the Company's obtaining marketing approval from the FDA or other similar regulatory agencies for a drug product candidate based on the NeuroTrans™ product candidate;

$5,000,000 within 90 days of the Company's obtaining marketing approval from the FDA or other similar regulatory agencies for a second drug product candidate based on the NeuroTrans™ product candidate;

$5,000,000 within 60 days after the end of the first calendar year in which the Company's aggregated revenues derived from drug product candidates based on the NeuroTrans™ product candidate exceed $100,000,000; and

$20,000,000 within 60 days after the end of the first calendar year in which the Company's aggregated revenues derived from drug product candidates based on the NeuroTrans™ product candidate exceed $500,000,000.

In addition to these milestone payments, the Company is also obligated to pay BioMarin a royalty at a percentage of the Company's aggregated revenues derived from drug product candidates based on the NeuroTrans™ product candidate. On June 9, 2006, the Company made a milestone payment in the amount of $150,000 to BioMarin because the Company raised $5,000,000 in its May 25, 2006 private placement financing. If the Company becomes insolvent or if the Company breaches its asset purchase agreement with BioMarin due to non-payment and the Company does not cure its non-payment within the stated cure period, all of the Company's rights to the RAP technology (including NeuroTrans™) will revert back to BioMarin.

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CONTRACTUAL OBLIGATIONS WITH THOMAS E. DALEY (ASSIGNEE OF THE DISSOLVED CONVIVIA, INC.)

Pursuant to the terms of the asset purchase agreement ("Asset Purchase Agreement"), the Company entered into with Convivia, Inc. and Thomas E. Daley for the purchase of intellectual property related to its 4-MP product candidate program, Mr. Daley will be entitled to receive the following, if at all, in such amounts and only to the extent certain future milestones are accomplished by the Company (or any of its subsidiaries thereof), as set forth below:

23,312 shares of Raptor's restricted, unregistered Common Stock within fifteen (15) days after the Company enters into a manufacturing license or other agreement to produce any product that is predominantly based upon or derived from any assets purchased from Convivia ("Purchased Assets") in quantity ("Product") if such license agreement is executed within one (1) year of execution of the Asset Purchase Agreement or, if thereafter, 11,656 shares of Raptor's restricted, unregistered Common Stock. Should the Company obtain a second such license or agreement for a Product, Mr. Daley will be entitled to receive 11,656 shares of the Company's restricted, unregistered Common Stock within 30 days of execution of such second license or other agreement. In January 2008, Mr. Daley earned a $30,000 cash bonus pursuant to his employment agreement for executing the Patheon formulation agreement for manufacturing Convivia™. On March 31, 2008, the Company issued 23,312 shares of Raptor's Common Stock valued at $56,000 to Mr. Daley pursuant to this milestone reflecting the execution of an agreement to supply the active pharmaceutical ingredient for Convivia™, combined with the execution of a formulation agreement to produce the oral formulation of Convivia™. In July 2010, the Company issued 11,656 shares of its restricted common stock valued at $35,551 and paid a $10,000 cash bonus to Mr. Daley as a result of the execution of the license agreement with Uni Pharma for the development of Convivia™ in Taiwan.

23,312 shares of the Company's restricted, unregistered Common Stock within fifteen (15) days after it receives its first patent allowance on any patents which constitute part of the Purchased Assets in any one of certain predetermined countries (each, a "Major Market").

11,656 shares of the Company's restricted, unregistered Common Stock within fifteen (15) days after the Company receives its second patent allowance on any patents which constitute part of the Purchased Assets different from the patent referenced in the immediately preceding paragraph above in a Major Market.

23,312 shares of the Company's restricted, unregistered Common Stock within fifteen (15) days of completing predetermined benchmarks in a Major Market by the Company or its licensee of the first Phase 2 human clinical trial for a Product ("Successful Completion") if such Successful Completion occurs within one (1) year of execution of the Asset Purchase Agreement or, if thereafter, 11,656 shares of the Company's restricted, unregistered Common Stock within thirty (30) days of such Successful Completion. In October 2008, the Company issued 23,312 shares of Raptor's Common Stock valued at $27,000 and a $30,000 cash bonus (pursuant to Mr. Daley's employment agreement) to Mr. Daley pursuant to the fulfillment of this milestone.

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11,656 shares of the Company's restricted, unregistered Common Stock within fifteen (15) days of a Successful Completion in a Major Market by the Company's or its licensee of the second Phase 2 human clinical trial for a Product (other than the Product for which a distribution is made under the immediately preceding paragraph above).

23,312 shares of the Company's restricted, unregistered Common Stock within fifteen (15) days after the Company or its licensee applies for approval to market and sell a Product in a Major Market for the indications for which approval is sought ("Marketing Approval").

11,656 shares of the Company's restricted, unregistered Common Stock within fifteen (15) days after the Company or its licensee applies for Marketing Approval in a Major Market (other than the Major Market for which a distribution is made under the immediately preceding paragraph above).

46,625 shares of the Company's restricted, unregistered Common Stock within fifteen (15) days after the Company or its licensee obtains the first Marketing Approval for a Product from the applicable regulatory agency in a Major Market.

23,312 shares of the Company's restricted, unregistered Common Stock within fifteen (15) days after the Company or its licensee obtains Marketing Approval for a Product from the applicable regulatory agency in a Major Market (other than the Major Market for which a distribution is made under the immediately preceding paragraph above).

As discussed above, in aggregate, the Company has issued to Mr. Daley, 58,281 shares of Raptor's common stock valued at $118,551 and paid $70,000 in cash bonuses related to Convivia™ milestones along with another $20,000 in cash bonuses related to employment milestones pursuant to Mr. Daley's employment agreement.

CONTRACTUAL OBLIGATIONS WITH FORMER ENCODE STOCKHOLDERS AND UCSD RELATING TO THE ACQUISITION OF THE DR CYSTEAMINE LICENSE

As a result of the merger between the Company's clinical subsidiary and Encode, as discussed in Note 9 above, the Encode Securityholders are eligible to receive up to an additional 559,496 shares of Raptor's common stock, Company Options and Company Warrants to purchase Raptor's common stock in the aggregate based on certain triggering events related to regulatory approval of DR Cysteamine, an Encode product program, if completed within the five year anniversary date of the merger agreement.

Also as a result of the merger, the Company will be obligated to pay an annual maintenance fee to UCSD for the exclusive license to develop DR Cysteamine for certain indications of $15,000 until it begins commercial sales of any products developed pursuant to the License Agreement. In addition to the maintenance fee, the Company will be obligated to pay during the life of the License Agreement: milestone payments ranging from $20,000 to $750,000 for orphan indications and from $80,000 to $1,500,000 for non-orphan indications upon the occurrence of certain events, if ever; royalties on commercial net sales from products developed pursuant to the License Agreement ranging from 1.75% to 5.5%; a percentage of sublicense fees ranging from 25% to 50%; a percentage of sublicense royalties; and a minimum annual royalty commencing the year the Company begins commercially selling any products pursuant to the License Agreement, if ever. Under the License Agreement, the Company is obligated to fulfill predetermined milestones within a specified number of years ranging from 0.75 to 6 years from the effective date of the License Agreement, depending on the indication. In addition, the Company is obligated to, among other things, secure $1 million in funding prior to December 18, 2008 (which the Company has

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fulfilled by raising $10 million in its May/June 2008 private placement) and annually spend at least $200,000 for the development of products (which, as of its fiscal years ended August 31, 2010 and 2009, the Company has fulfilled by spending approximately $6.2 million and $4.1 million, respectively, on such programs) pursuant to the License Agreement. To-date, the Company has accrued $470,000 in milestone payments to UCSD based upon the initiation of clinical trials in cystinosis and in NASH. To the extent that the Company fails to perform any of its obligations under the License Agreement, then UCSD may terminate the license or otherwise cause the license to become non-exclusive.

CONTRACTUAL OBLIGATIONS TO TPTX, INC. EMPLOYEES

Pursuant to the documents related to the 2009 Merger, including amended employment agreements with the TPTX, Inc. employees, who were former executives of TorreyPines prior to such merger, the Company was obligated to pay such former executives their salaries, benefits and other obligations through April 1, 2010, which obligations were settled in mid-April 2010. There were no remaining obligations to the former executives as of August 31, 2010.

OFFICE LEASES

In March 2006, the Company entered into a lease for the Company's executive offices and research laboratory in Novato, California and expanded the lease on April 1, 2007. Base monthly payments were subject to annual rent increase of between 3% to 5%, based on the Consumer Price Index ("CPI") and annual adjustments to base operating expenses. In October 2010, the Company executed a lease addendum to the Novato lease for an additional 3,100 square feet ($5,309 per month) starting in January 2011. Effective April 1, 2010, the Company's monthly base rent including base operating expenses were $10,826 and effective January 1, 2011, the Company's monthly base including base operating expenses will be $16,135 with an adjustment for CPI and operating expenses in April 2012. The Novato lease expires in March 2013. In January 2010, the Company entered into a one year lease for administrative offices in San Mateo, California for $2,655 per month. The Company anticipates continuing the San Mateo lease.

During the years ended August 31, 2010 and 2009 and the cumulative period from September 8, 2005 (inception) to August 31, 2010, the Company paid $150,536, $128,830 and $518,931, respectively, in rent.

The minimum future lease payments under this operating lease assuming a 3% CPI increase per year are as follows:

Period	Amount
September 1, 2010 to August 31, 2011	$ 187,773
September 1, 2011 to August 31, 2012	196,043
September 1, 2012 to August 31, 2013	116,335

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CAPITAL LEASE

In September 2008, the Company leased a photocopier which is subject to a 39-month lease at $469 per month. The future lease payments under the capital lease are as follows:

Period	Amount
Fiscal year ending August 31, 2011	$ 5,625
September 1, 2011 to December 31, 2011	1,875
Total future capital lease payments	7,500
Less interest	(824)
Total current and long-term capital lease liability	$ 6,676

Interest rate on the capital lease is 17% based on the lessor's implicit rate of return.

CONTRACT/CLINICAL RESEARCH AGREEMENTS

During the year ended August 31, 2010, the Company maintained several contracts with consultants, research and clinical organizations and clinical sites to research drug pricing in the E.U., develop research assays, to assist with clinical research and to conduct clinical research for Raptor's cystinosis program.

The future commitments pursuant to the research agreement are as follows:

Period	Amount
Fiscal year ending August 31, 2011	$ 4,310,511
Fiscal year ending August 31, 2012	620,718

STORAGE AND CLINICAL DISTRIBUTION AGREEMENT

During the year ended August 31, 2010, the Company maintained an agreement with a company that stores and distributes clinical materials for Raptor's cystinosis trial. The future commitments pursuant to this agreement are as follows:

Period	Amount
Fiscal year ending August 31, 2011	$ 181,096

FORMULATION / MANUFACTURING AGREEMENTS

In April 2008, the Company executed an agreement with a contract manufacturing organization to formulate and manufacture DR Cysteamine for its cystinosis and Huntington's Disease programs. The costs are invoiced to the Company in installments throughout the formulation and manufacturing process. In July 2008, the Company executed a supply agreement with a contract manufacturer for the active pharmaceutical agreement of DR Cysteamine. In July 2010, the Company executed a manufacturing agreement to provide tezampanel study drug for the Company's thrombosis program. The future commitments pursuant to these contracts are as follows:

Period	Amount
Fiscal year ending August 31, 2011	$ 1,529,573
Fiscal year ending August 31, 2012	269,696

RAPTOR PHARMACEUTICAL CORP.

(A Development Stage Company)

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

(13) RELATED PARTY TRANSACTIONS

Pursuant to the terms of the Share Purchase Agreement, the Company issued to each of Drs. Starr and Zankel (its Chief Executive Officer and its Chief Scientific Officer, respectively) 699,370 shares of the Company's common stock and to Erich Sager (one of the Company's directors) 233,123 shares of its common stock. Mr. Sager purchased his shares pursuant to a promissory note when the Company was privately held in February 2006 in the amount of $100,000 plus accrued interest at 8% per annum. Mr. Sager repaid $50,000 of the note on February 8, 2006, another $50,000 on March 9, 2006 and $373 of accrued interest on April 11, 2006. Drs. Starr and Zankel and Mr. Sager did not own any shares of the Company's common stock at the time when the Share Purchase Agreement was first approved and executed.

In connection with the May / June 2008 private placement, the Company issued to Limetree Capital warrants to purchase 438,890 shares of Raptor's Common Stock and $627,550 in cash commissions. In connection with the August 2009 private placement, the Company issued to Limetree Capital warrants to purchase 129,733 shares of Raptor's Common Stock and $59,360 in cash commissions. Also, commencing on April 1, 2009, we engaged Limetree to support our investor relations efforts in Europe for a retainer of $2,500 per month. Through August 31, 2009, we have paid $12,500 in such fees to Limetree. One of Raptor's Board members serves on the Board of Limetree Capital. In August 2010, the Company entered into a consulting agreement with one if its Board members to provide business development support for a six-month period at a monthly retainer plus living expenses totaling approximately $10,000 per month.In the ordinary course of business, Raptor's officers occasionally utilize their personal credit cards or cash to pay for expenses on behalf of the Company and the Company reimburses the officers within 30 days.

(14) SUBSEQUENT EVENTS

In October 2010, the Company received a tax grant under the U.S. Government's Qualifying Therapeutic Discovery Project for five of its research programs including its cystinosis, Huntington's Disease and NASH (non-alcoholic steatohepatitis) clinical programs and its HepTide™ and WntTide™ preclinical cancer research programs. Raptor was granted an aggregate of $1 million for all five programs of which approximately $827,000 was funded in October 2010 and the balance will be funded in October 2011.

In November 2010, the Company executed a 10-year agreement with Cambrex Profarmaco Milano, for supply of the active pharmaceutical ingredient used in DR Cysteamine, cysteamine bitartrate for Raptor's clinical and commercial material needs. The Company is unable to determine the financial impact of the agreement due to the uncertainty related to timing of commercial manufacturing and future clinical material needs until the Company is able to obtain marketing approval of DR Cysteamine for cystinosis and funding for a clinical trial in NASH or in indications other than cystinosis.

In November 2010, the Company executed a seven-year commercial manufacturing agreement of DR Cysteamine with Patheon Pharmaceutical Inc. with the option for two year extensions if not cancelled 18 months prior to expiration. The Company is unable to determine the financial impact of the agreement due to the uncertainty related to the timing of the marketing approval of DR Cysteamine for cystinosis, if at all.

The following exhibits are filed as part of, or incorporated by reference into this Annual Report on Form 10-K:

Exhibit Index

2.1	Agreement and Plan of Merger and Reorganization, dated as of June 7, 2006, by and among Axonyx Inc., Autobahn Acquisition, Inc. and TorreyPines Therapeutics, Inc. (incorporated by reference to Annex A to Registration Statement No. 333-136018 filed on July 25, 2006).
2.2	Amendment No. 1 to Agreement and Plan of Merger and Reorganization, dated as of August 25, 2006, by and among Axonyx Inc., Autobahn Acquisition, Inc. and TorreyPines Therapeutics, Inc. (incorporated by reference to Annex A to Amendment No. 1 to Registration Statement No. 333-136018 filed on August 25, 2006).
2.3	Agreement and Plan of Merger and Reorganization, dated July 27, 2009, by and among Raptor Pharmaceuticals Corp., TorreyPines Therapeutics, Inc., a Delaware corporation, and ECP Acquisition, Inc., a Delaware corporation (incorporated by reference to Exhibit 2.3 to the Registrant's Current Report on Form 8-K, filed on July 28, 2009).
2.4	Form of Voting Agreement between TorreyPines Therapeutics, Inc. and certain stockholders of Raptor Pharmaceuticals Corp. (incorporated by reference to Exhibit 99.3 to the Registrant's Current Report on Form 8-K, filed on July 28, 2009).
2.5	Form of Voting Agreement between Raptor Pharmaceuticals Corp. and certain stockholders of TorreyPines Therapeutics, Inc. (incorporated by reference to Exhibit 99.2 to the Registrant's Current Report on Form 8-K, filed on July 28, 2009).
3.1	Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K, filed on October 10, 2006).
3.2	Bylaws of the Registrant (incorporated by reference to Exhibit 3.2 to the Registrant's Current Report on Form 8-K, filed on October 10, 2006).
3.3	Certificate of Amendment filed with the Secretary of State of the State of Nevada effecting an 8-for-1 reverse stock of the Registrant's common stock and changing the name of the Registrant from Axonyx Inc. to TorreyPines Therapeutics, Inc. (incorporated by reference to Exhibit 3.3 to the Registrant's Current Report on Form 8-K, filed on October 10, 2006).
3.4	Articles of Conversion filed with the Secretary of State of the State of Nevada changing the state of incorporation of the Registrant (incorporated by reference to Exhibit 3.4 to the Registrant's Current Report on Form 8-K, filed on October 10, 2006).
3.5	Certificate of Conversion filed with the Secretary of State of the State of Delaware (incorporated by reference to Exhibit 3.5 to the Registrant's Current Report on Form 8-K, filed on October 10, 2006).
3.6	Amendment to Bylaws of the Registrant (incorporated by reference to Exhibit 3.6 to the Registrant's Annual Report on Form 10-K, filed on March 29, 2007).
3.7	Charter Amendment for TorreyPines (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K, filed on October 9, 2009).
3.8	Certificate of Merger between Raptor Pharmaceuticals Corp., ECP Acquisition, Inc. and TorreyPines Therapeutics, Inc. (incorporated by reference to Exhibit 3.2 to the Registrant's Current Report on Form 8-K, filed on October 9, 2009).
4.1	Specimen common stock certificate of the Registrant (incorporated by reference to Exhibit 4.7 to the Registrant's Current Report on Form 8-K, filed on October 9, 2009).
4.2	Form of Warrant to Purchase Common Stock issued to previous holders of TPTX, Inc. redeemable convertible preferred stock in connection with the business combination between TorreyPines Therapeutics, Inc. and Axonyx, Inc. (incorporated by reference to Exhibit 4.2 to the Registrant's Annual Report on Form 10-K, filed on March 29, 2007).
4.3	Form of Registration Rights Agreement 1999 (incorporated by reference to Exhibit 4.4 to the Registrant's Annual Report on Form 10-KSB, filed on March 13, 2000).
4.4	Registration Rights Agreement dated as of January 8, 2004 between Axonyx Inc. and certain investors (incorporated by reference to Exhibit 4.2 to the Registrant's Current Report on Form 8-K, filed on January 12, 2004).
4.5	Registration Rights Agreement dated as of May 3, 2004, between Axonyx Inc. and certain investors (incorporated by reference to Exhibit 4.2 to the Registrant's Current Report on Form 8-K, filed on May 5, 2004).
4.6	Form of Warrant issued to Comerica Bank on July 1, 2003 (incorporated by reference to Exhibit 4.14 to the Registrant's Annual Report on Form 10-K, filed on March 29, 2007).
4.7	Form of Warrant issued to Silicon Valley Bank on December 8, 2000 (incorporated by reference to Exhibit 4.15 to the Registrant's Annual Report on Form 10-K, filed on March 29, 2007).

4.8	Form of Warrant issued to Oxford Financial and Silicon Valley Bank on September 27, 2005 (incorporated by reference to Exhibit 4.16 to the Registrant's Annual Report on Form 10-K, filed on March 29, 2007).
4.9	Rights Agreement, dated as of May 13, 2005, between the Registrant and The Nevada Agency and Trust Company, as Rights Agent (incorporated by reference to Exhibit 99.2 to the Registrant's Current Report on Form 8-K, filed on May 16, 2005).
4.10	Amendment to Rights Agreement, dated as of June 7, 2006, between the Registrant and The Nevada Agency and Trust Company, as Rights Agent (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K, filed on June 12, 2006).
4.11	Form of Warrant issued to Comerica Bank on June 11, 2008 (incorporated by reference to Exhibit 4.1 to the Registrant's Report on Form 8-K, filed on June 17, 2008).
4.12	Amendment to Rights Agreement, dated as of October 3, 2006, between the Registrant and The Nevada Agency and Trust Company, as Rights Agent (incorporated by reference to Exhibit 4.19 to the Registrant's Annual Report on Form 10-K, filed on March 29, 2007).
4.13	Rights Agreement Amendment, dated as of July 27, 2009, to the Rights Agreement dated May 13, 2005 between TorreyPines and American Stock Transfer and Trust Company (replacing The Nevada Agency and Trust Company) (incorporated by reference to Exhibit 2.3 to the Registrant's Current Report on Form 8-K, filed on July 28, 2009).
4.14	Amendment to Rights Agreement, dated August 6, 2010, by and between the Registrant and American Stock Transfer & Trust Company, LLC (incorporated by reference to Exhibit 4.2 to the Registrant's Current Report on Form 8-K, filed on August 10, 2010).
4.15 *	Warrant to purchase common stock dated December 14, 2007 issued to Flower Ventures, LLC (incorporated by reference to Exhibit 4.1 to Raptor Pharmaceuticals Corp.'s Quarterly Report on Form 10QSB/A, filed on April 15, 2008).
4.16 *	Warrant Agreement Amendment, dated December 17, 2009, between the Registrant and Flower Ventures, LLC (incorporated by reference to Exhibit 4.15 to Registrant's Quarterly Report on Form 10QSB, filed on April 9, 2010).
4.17 *	Warrant to purchase common stock dated December 14, 2007 issued to ICON Partners, LP (incorporated by reference to Exhibit 4.2 to Raptor Pharmaceuticals Corp.'s Quarterly Report on Form 10QSB/A, filed on April 15, 2008).
4.18 *	Form of Warrant to purchase common stock of Raptor Pharmaceuticals Corp. (incorporated by reference to Exhibit 4.1 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K, filed on May 22, 2008).
4.19 *	Form of Placement Agent Warrant to purchase common stock of Raptor Pharmaceuticals Corp. (incorporated by reference to Exhibit 4.2 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K/A, filed on May 28, 2008).
4.20 *	Form of Warrant to purchase common stock of Raptor Pharmaceuticals Corp. (incorporated by reference to Exhibit 4.1 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K, filed on August 25, 2009).
4.21*	Form of Placement Agent Warrant to purchase common stock of Raptor Pharmaceuticals Corp. (incorporated by reference to Exhibit 4.2 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K, filed on August 25, 2009).
4.22	Form of Senior Debt Indenture of the Registrant (incorporated by reference to Exhibit 4.10 to the Registrant's Registration Statement on Form S-3, filed on October 7, 2009).
4.23	Form of Subordinated Debt Indenture of the Registrant (incorporated by reference to Exhibit 4.11 to the Registrant's Registration Statement on Form S-3, filed on October 7, 2009).
4.24	Form of Investor Warrants (incorporated by reference to Exhibit 4.1 on Registrant's Current Report on Form 8-K filed on December 18, 2009).
4.25	Form of Investor Warrants (incorporated by reference to Exhibit 4.1 on Registrant's Current Report on Form 8-K filed on August 10, 2010).
4.26	Placement Agent Warrant (incorporated by reference to Exhibit 4.2 on Registrant's Current Report on Form 8-K filed on August 13, 2010).
4.27	Reference is made to Exhibits 3.1 through 3.8.
10.1#	TorreyPines Therapeutics, Inc. 2006 Equity Incentive Plan (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K, filed on October 4, 2006).
10.2#	Form of Stock Option Agreement under TorreyPines Therapeutics, Inc. 2006 Equity Incentive Plan (incorporated by reference to Exhibit 10.9 to the Registrant's Current Report on Form 8-K, filed on October 14, 2006).
10.3**	Development and License Agreement between TPTX, Inc. (formerly Neurogenetics, Inc.) and Eli Lilly and the Registrant, effective as of April 21, 2003 (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K, filed on October 10, 2006).

10.4**	Research and License Agreement by and between TPTX, Inc. and Life Science Research Israel Ltd. dated as of May 10, 2004 (incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K, filed on October 10, 2006).
10.5**	License Agreement by and between TPTX, Inc. and University of Iowa Research Foundation dated as of May 10, 2006 (incorporated by reference to Exhibit 10.5 to the Registrant's Current Report on Form 8-K, filed on October 10, 2006).
10.6	Lease Agreement by and between TPTX, Inc. and Slough TPSP LLC dated as of July 18, 2005, which became effective February 10, 2006 (incorporated by reference to Exhibit 10.10 to the Registrant's Current Report on Form 8-K, filed on October 10, 2006).
10.7	Form of Indemnity Agreement (incorporated by reference to Exhibit 10.13 to the Registrant's Current Report on Form 8-K, filed on October 10, 2006).
10.8#	Employment Agreement by and between Evelyn Graham and TorreyPines Therapeutics, Inc. dated December 14, 2006 (incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K, filed on December 20, 2006).
10.9#	Employment Agreement by and between Craig Johnson and TorreyPines Therapeutics, Inc. dated December 14, 2006 (incorporated by reference to Exhibit 10.3 to the Registrant's Current Report on Form 8-K, filed on December 20, 2006).
10.10#	Form of Restricted Stock Unit Award Agreement under TorreyPines Therapeutics, Inc. 2006 Equity Incentive Plan (incorporated by reference to Exhibit 10.17 to the Registrant's Annual Report on Form 10-K, filed on March 29, 2007).
10.11#	Employment Agreement between Raptor Pharmaceuticals Corp. and Dr. Christopher Starr dated May 1, 2006 (incorporated by reference to Exhibit 10.5 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K, filed on May 26, 2006).
10.12#	First Amendment to the Employment Agreement between Raptor Pharmaceuticals Corp. and Dr. Christopher Starr dated January 1, 2009 (incorporated by reference to Exhibit 10.1 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K, filed on January 5, 2009).
10.13#	Employment Agreement between Raptor Pharmaceuticals Corp. and Dr. Todd Zankel dated May 15, 2006 (incorporated by reference to Exhibit 10.6 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K filed on May 26, 2006).
10.14#	First Amendment to the Employment Agreement between Raptor Pharmaceuticals Corp. and Dr. Todd Zankel dated January 1, 2009 (incorporated by reference to Exhibit 10.3 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K, filed on January 5, 2009).
10.15#	Employment Agreement between Raptor Pharmaceuticals Corp. and Ms. Kim Tsuchimoto dated May 1, 2006 (incorporated by reference to Exhibit 10.7 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K filed on May 26, 2006).
10.16#	First Amendment to the Employment Agreement between Raptor Pharmaceuticals Corp. and Ms. Kim Tsuchimoto dated January 1, 2009 (incorporated by reference to Exhibit 10.2 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K, filed on January 5, 2009).
10.17#	Employment Agreement between Raptor Therapeutics Inc. and Thomas E. Daley dated September 7, 2007 (incorporated by reference to Exhibit 10.1 to Raptor Pharmaceuticals Corp.'s Quarterly Report on Form 10-QSB filed on January 14, 2008).
10.18#	First Amendment to the Employment Agreement between Raptor Pharmaceuticals Corp. and Thomas E. Daley dated January 1, 2009 (incorporated by reference to Exhibit 10.4 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K, filed on January 5, 2009).
10.19#	Offer Letter from Raptor Therapeutics Inc. dated April 8, 2009 for Dr. Patrice Rioux (incorporated by reference to Exhibit 10.1 to Raptor Pharmaceuticals Corp.'s Current Report on Form 8-K filed on April 14, 2008).
10.20#	2006 Equity Incentive Plan of Raptor Pharmaceuticals Corp., as amended (incorporated by reference to Exhibit 4.3 to Raptor Pharmaceuticals Corp.'s Registration Statement on Form S-8 filed on February 28, 2007).
10.21#	2008 Plan Amendment to 2006 Equity Incentive Plan of Raptor Pharmaceuticals Corp. (incorporated by reference to Exhibit 10.5 to Raptor Pharmaceuticals Corp.'s Annual Report on Form 10-K/A filed on December 23, 2008).
10.22	Asset Purchase Agreement between Raptor Therapeutics, Inc., Raptor Pharmaceuticals Corp. and Convivia, Inc. dated October 17, 2007 (incorporated by reference to Exhibit 10.3 to Raptor Pharmaceuticals Corp.'s Quarterly Report on Form 10QSB filed on January 14, 2008).
10.23	Merger agreement between Raptor Therapeutics, Inc., Raptor Pharmaceuticals Corp. and Encode Pharmaceuticals, Inc. dated December 14, 2007 (incorporated by reference to Exhibit 10.1 to Raptor Pharmaceuticals Corp.'s Quarterly Report on Form 10QSB/A filed on April 15, 2008).

10.24**	Pharmaceutical development services agreement between Raptor Therapeutics Inc. and Patheon Pharmaceuticals Inc. dated January 7, 2008 (incorporated by reference to Exhibit 10.2 to Raptor Pharmaceuticals Corp.'s Quarterly Report on Form 10QSB/A filed on April 15, 2008).
10.25**	License agreement between Raptor Therapeutics Inc. and Regents of the University of California dated October 31, 2007 (incorporated by reference to Exhibit 10.3 to Raptor Pharmaceuticals Corp.'s Quarterly Report on Form 10QSB/A filed on April 15, 2008).
10.26**	Amendment No. 1 to License agreement between Raptor Therapeutics Inc. and Regents of the University of California dated February 29, 2008 (incorporated by reference to Exhibit 10.4 to Raptor Pharmaceuticals Corp.'s Quarterly Report on Form 10QSB/A filed on April 15, 2008).
10.27	Securities Purchase Agreement, dated as of May 21, 2008, by and among Raptor Pharmaceuticals Corp. and the investors listed on the signature pages thereto (incorporated by reference to Exhibit 10.1 to Raptor Pharmaceuticals Corp.'s Quarterly Report on Form 10QSB filed on July 9, 2008).
10.28	Amendment to Securities Purchase Agreement, dated as of May 21, 2008, by and among Raptor Pharmaceuticals Corp. and the investors listed on the signature pages thereto (incorporated by reference to Exhibit 10.2 to Raptor Pharmaceuticals Corp.'s Quarterly Report on Form 10QSB filed on July 9, 2008).
10.29**	Collaboration and License Agreement, effective June 3, 2009, among Hoffmann-La Roche Ltd,, Hoffmann-La Roche Inc. and the Registrant (incorporated by reference to Exhibit 10.19 on Raptor Pharmaceuticals Corp.'s Annual Report on Form 10-K filed on October 28, 2009)
10.30	First Amendment dated January 7, 2009 to Lease by and between TorreyPines Therapeutics, Inc. and HCP TPSP LLC dated July 18, 2005 (incorporated by reference to Exhibit 10.15 to the Registrant's Annual Report on Form 10-K, filed on March 27, 2009).
10.31**	Amendment dated November 21, 2008 to Development and License Agreement by and between TPTX, Inc. and Eli Lilly and the Registrant, effective as of April 21, 2003 (incorporated by reference to Exhibit 10.16 to the Registrant's Annual Report on Form 10-K, filed on March 27, 2009).
10.32#	Amended and Restated Employment Agreement by and between Evelyn Graham and TorreyPines Therapeutics, Inc. dated September 1, 2008 (incorporated by reference to Exhibit 10.17 to the Registrant's Annual Report on Form 10-K, filed on March 27, 2009).
10.33#	Amendment dated February 3, 2009 to Amended Employment Agreement by and between Evelyn Graham and TorreyPines Therapeutics, Inc. dated September 1, 2008 (incorporated by reference to Exhibit 10.18 to the Registrant's Annual Report on Form 10-K, filed on March 27, 2009).
10.34#	Amended and Restated Employment Agreement by and between Craig Johnson and TorreyPines Therapeutics, Inc. dated November 12, 2008 (incorporated by reference to Exhibit 10.19 to the Registrant's Annual Report on Form 10-K, filed on March 27, 2009).
10.35#	Amendment dated February 3, 2009 to Amended Employment Agreement by and between Craig Johnson and TorreyPines Therapeutics, Inc. dated November 12, 2008 (incorporated by reference to Exhibit 10.20 to the Registrant's Annual Report on Form 10-K, filed on March 27, 2009).
10.36#	Amended and Restated Employment Agreement by and between Paul Schneider and TorreyPines Therapeutics, Inc. dated November 12, 2008 (incorporated by reference to Exhibit 10.21 to the Registrant's Annual Report on Form 10-K, filed on March 27, 2009).
10.37#	Amendment dated February 3, 2009 to Amended Employment Agreement by and between Paul Schneider and TorreyPines Therapeutics, Inc. dated November 12, 2008 (incorporated by reference to Exhibit 10.22 to the Registrant's Annual Report on Form 10-K, filed on March 27, 2009).
10.38**	Supply Agreement, effective July 20, 2009, between Raptor Therapeutics Inc. and Mylan Pharmaceutical Inc. (incorporated by reference to Exhibit 10.20 on Raptor Pharmaceuticals Corp.'s Annual Report on Form 10-K filed on October 28, 2009).
10.39#	Second Amended and Restated Employment by and between Evelyn Graham and TPTX, Inc. dated July 27, 2009 (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K, filed on July 28, 2009).
10.40#	Second Amended and Restated Employment by and between Craig Johnson and TPTX, Inc. dated July 27, 2009 (incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K, filed on July 28, 2009).
10.41#	Second Amended and Restated Employment by and between Paul Schneider and TPTX, Inc. dated July 27, 2009 (incorporated by reference to Exhibit 10.3 to the Registrant's Current Report on Form 8-K, filed on July 28, 2009).
10.42	Securities Purchase Agreement, dated as of August 21, 2009, by and among Raptor Pharmaceuticals Corp. and the investors listed on the signature pages thereto (incorporated by reference to Exhibit 10.19 on Raptor Pharmaceuticals Corp.'s Annual Report on Form 10-K filed on October 28, 2009).

10.43	Raptor Form Indemnity Agreement dated on December 9, 2009 (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on December 15, 2009).
10.44	Placement Agent Agreement by and between the Registrant and Ladenburg Thalmann & Co. Inc. dated December 17, 2009 (incorporated by reference to Exhibit 1.1 on Registrant's Current Report on Form 8-K filed on December 18, 2009).
10.45	Securities Purchase Agreement, dated December 17, 2009, by and between the Registrant and the investors signatories thereto (incorporated by reference to Exhibit 10.1 on Registrant's Current Report on Form 8-K filed on December 18, 2009).
10.46#	Raptor Pharmaceutical Corp. 2010 Stock Incentive Plan (incorporated by reference to Appendix A to the Registrant's Revised Definitive Proxy Statement, filed on February 5, 2010).
10.47	Purchase Agreement, dated April 16, 2010, between the Registrant and Lincoln Park Capital Fund, LLC (incorporated by reference to Exhibit 10.1 on Registrant's Current Report on Form 8-K, filed on April 22, 2010).
10.48	Registration Rights Agreement, dated April 16, 2010, between the Registrant and Lincoln Park Capital Fund, LLC (incorporated by reference to Exhibit 10.2 on Registrant's Current Report on Form 8-K, filed on April 22, 2010).
10.49#	Form of Award Agreement under the Raptor Pharmaceutical Corp. 2010 Stock Incentive Plan (incorporated by reference to Exhibit 4.13 to the Registrant's Registration Statement on Form S-8 (File No. 33-166813), filed on May 14, 2010).
10.50	Securities Purchase Agreement, dated August 9, 2010, by and among the Registrant and the Investors signatories thereto (incorporated by reference to Exhibit 10.1 on Registrant's Current Report on Form 8-K, filed on August 10, 2010).
10.51	Securities Purchase Agreement, dated August 9, 2010, by and among the Registrant and the Investor signatory thereto (incorporated by reference to Exhibit 10.2 of the Registrant's Current Report on Form 8-K filed on August 10, 2010).
10.52	Registration Rights Agreement, dated August 12, 2010, by and among the Registrant and the signatories thereto (incorporated by reference to Exhibit 10.3 of the Registrant's Current Report on Form 8-K, filed on August 13, 2010).
21.1†	Subsidiaries of the Registrant.
23.1†	Consent of Burr Pilger Mayer, Inc. Independent Registered Public Accounting Firm to the Registrant
24.1†	Power of Attorney (included in the signature page hereto).
31.1†	Certification of Christopher M. Starr, Ph.D., Chief Executive Officer and Director
31.2†	Certification of Kim R. Tsuchimoto, Chief Financial Officer, Secretary and Treasurer
32.1†	Certification of Christopher M. Starr, Ph.D., Chief Executive Officer and Director, and of Kim R. Tsuchimoto, Chief Financial Officer, Secretary and Treasurer
*	The Raptor Pharmaceuticals Corp. warrants set forth in Exhibits 4.15 - 4.21 have been converted into warrants of the Registrant and the exercise price of such warrants and number of shares of common stock issuable thereunder have been converted as described in Item 1.01 (under the section titled, "Background") of the Registrant's Current Report on Form 8-K, filed on October 5, 2009.
**	Certain information omitted pursuant to a request for confidential treatment filed separately with and granted by the SEC.
#	Indicates a management contract or compensatory plan or arrangement.
†	Filed herewith.

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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d)**
OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2014

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d)**
OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to

Commission File Number: 000-25571

RAPTOR PHARMACEUTICAL CORP.

(Exact name of registrant as specified in its charter)

Delaware	**86-0883978**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)

7 Hamilton Landing, Suite 100, Novato, CA 94949
(Address of Principal Executive Offices)

(415) 408-6200
(Registrant's telephone number)

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	**Name of Each Exchange on Which Registered**
Common Stock, $0.001 par value	**The NASDAQ Global Market**
Preferred Share Purchase Rights	

Securities registered under Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company.

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act.) Yes ☐ No ☒

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant as of June 30, 2014 (the last business day of the registrant's most recently completed second quarter) was $714.1 million.

The number of shares of the registrant’s common stock outstanding, par value $0.001, on February 27, 2015 was 69,144,463.

The documents incorporated by reference are as follows: Portions of the registrant’s definitive Proxy Statement to be filed with the Securities and Exchange Commission under Regulation 14A within 120 days after the end of registrant’s fiscal year covered by this Annual Report are incorporated by reference into Part III.

RAPTOR PHARMACEUTICAL CORP.

2014 Form 10-K Annual Report

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FORWARD-LOOKING STATEMENTS

Change in Fiscal Year End

On December 4, 2012, the board of directors of Raptor Pharmaceutical Corp., or the "Company," approved a change to the Company's fiscal year end from August 31 to December 31. This Annual Report on Form 10-K includes the financial information for 2014 and 2013 which refers to the periods from January 1 to December 31, 2014 and 2013, respectively. The Company previously filed a report on Form 10-K/T, as amended, for the four-month period from September 1, 2012 to December 31, 2012, or the Transition Period. References in this Annual Report on Form 10-K to fiscal years prior to 2013 refer to the period from September 1 through August 31 of such year.

Forward-Looking Statement

In this Annual Report on Form 10-K, in our other filings with the Securities and Exchange Commission, or the SEC, and in press releases and other public statements by our officers throughout the year, we make or will make statements that plan for or anticipate the future. These "forward-looking statements," within the meaning of the Private Securities Litigation Reform Act of 1995, include statements about our future business plans and strategies, as well as other statements that are not historical in nature. These forward-looking statements are based on our current expectations.

In some cases, these statements can be identified by the use of terminology such as "believes," "expects," "anticipates," "plans," "may," "might," "will," "could," "should," "would," "projects," "anticipates," "predicts," "intends," "continues," "estimates," "potential," "opportunity" or the negative of these terms or other comparable terminology. All such statements, other than statements of historical facts, including statements regarding our financial condition, future results of operations, projected revenues and expenses, business strategies, operating efficiencies or synergies, competitive positions, growth opportunities for existing intellectual properties, technologies, products, plans and objectives of management, markets for our securities and other prospective matters, involve substantial risks and uncertainties and constitute forward-looking statements for the purpose of the safe harbor provided by Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. You should not place undue reliance on these statements, which only reflect information available as of the date that they were made. Our business' actual operations, performance, developments and results might differ materially from any forward-looking statement due to various known and unknown risks, uncertainties, assumptions and contingencies, including those described in the section titled "Risk Factors" in Part I, Item 1A of this Annual Report on Form 10-K as well as other documents we file with the SEC. In light of the significant uncertainties inherent in such forward-looking statements, you should not regard the inclusion of this information as a representation by us or any other person that the results or conditions described in those statements or our objectives and plans will be achieved.

All subsequent forward-looking statements attributable to us or any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to herein. Unless required by U.S. federal securities laws and the rules and regulations of the SEC, we do not undertake any obligation and disclaim any intention to update or release publicly any revisions to these forward-looking statements after the filing of this Annual Report on Form 10-K to reflect later events or circumstances or to reflect the occurrence of unanticipated events or for any other reason.

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PART I

ITEM 1: BUSINESS

You should read the following discussion in conjunction with our consolidated financial statements as of December 31, 2014, and the notes to such consolidated financial statements included elsewhere in this Annual Report on Form 10-K.

Unless otherwise stated or the context requires otherwise, for the period from and after the effective time of the 2009 Merger (as described below under "Corporate Information"), all references in this Annual Report on Form 10-K to the "Company," "we," "our," "us," "Raptor" and similar references refer to the company formerly known as TorreyPines Therapeutics, Inc. and now known as Raptor Pharmaceutical Corp. and its direct and indirect wholly-owned subsidiaries Raptor Pharmaceuticals Inc., Raptor European Products, LLC, RPTP European Holdings C.V., Raptor Pharmaceuticals Europe B.V., Raptor Pharmaceuticals France SAS and Raptor Pharmaceuticals Germany GmbH.

Overview

We are a biopharmaceutical company focused on developing and commercializing transformative treatments for people affected by rare and debilitating diseases.

Our product, PROCYSBI® (cysteamine bitartrate) delayed-release capsules, or PROCYSBI, received marketing approval from the U.S. Food and Drug Administration, or FDA, in April 2013 for the management of nephropathic cystinosis in adults and children six years and older. In Europe, PROCYSBI gastro-resistant hard capsules of cysteamine (as mercaptamine bitartrate), received a marketing authorization in September 2013 from the European Commission, or EC, as an orphan medicinal product for the management of proven nephropathic cystinosis in the European Union, or EU. The EU marketing authorization allows us to commercialize PROCYSBI in the 28 Member States of the EU plus Norway, Liechtenstein and Iceland (which are not EU Member States but are part of the European Economic Area, or EEA). PROCYSBI received seven and ten years of market exclusivity due to its designation as an orphan drug in the United States and the EU, respectively. We achieved first commercial sales of PROCYSBI in the United States in June 2013 and in the EU, specifically in Germany, in April 2014.

As of December 31, 2014, insurers of U.S. commercial patients reimburse Raptor for PROCYSBI therapy at a Wholesale Acquisition Cost, or WAC, price for PROCYSBI of $16,650 per bottle of 250 75-mg capsules and $3,996 per bottle of 60 25-mg capsules. Prices for PROCYSBI therapy vary among patients because doses are individually based on a patient's weight. In September 2013, we executed an agreement to participate in the U.S. State Medicare/Medicaid rebate program, which will be reflected in our net revenues in mandatory rebates on reimbursements for patients receiving state Medicare and Medicaid insurance coverage. As of December 31, 2014, our price to German, Swiss and Austrian pharmacies was €5,850.23 per bottle of 250 75-mg capsules and €468.02 per bottle of 60 25-mg capsules.

Cysteamine Mechanism of Action

Cysteamine, or 2-aminoethanethiol, the active pharmaceutical ingredient in PROCYSBI, is a molecule generated naturally in human cells during the metabolism of cysteine. Cysteamine is used to construct the key enzymatic cofactor involved in energy produced from sugars and lipids. Cysteamine's uniquely reactive properties result in many physiological effects when given in pharmaceutical doses.

- Antioxidation – Cysteamine is known to increase levels of a key cellular antioxidant, glutathione. Glutathione is composed of the amino acids gamma-glutamate, cysteine and glycine. The availability of cysteine is the major rate-limiting factor in glutathione production. Cysteamine may release cysteine in the circulation, or from within the cell. Cysteamine has been shown to activate the NRF2 pathway, which leads to the increased expression of a wide variety of proteins involved in antioxidation which may help to reduce oxidative stress in CNS, hepatic and mitochondrial disorders.
- Heat shock response induction – Heat shock proteins, or HSPs, are chaperones that play an important role in protein-protein interactions such as folding and assist in the establishment of proper protein conformation. Proper protein folding may also prevent unwanted protein aggregation. By helping to stabilize partially unfolded proteins, HSPs aid in transporting proteins across membranes within the cell. HSPs are typically produced by cells in response to stress or injury, or other metabolic imbalance. HSPs are part of a cell's mechanism for protein maintenance. The presence of cysteamine within a cell has been shown to increase transcription of certain HSPs that are key components to the cell's ability to maintain the integrity of proteins.

- Anti-fibrosis – Cysteamine blocks TGF-β signaling and thereby inhibits the production and proliferation of myofibroblasts. It also inhibits formation of three cross-links in collagen protein, each of which exacerbate formation of fibrotic tissue: gamma-glutamyl peptide bonds, formed by transglutaminase; oxidized lysyl-lysine conjugates, formed by lysyl oxidase; and inter-chain disulfide bonds.

Cysteamine also inhibits transcription of a variety of collagens and basement membrane-related proteins:

- Metal chelation –*In vitro* studies have shown that cysteamine chelates metals, including copper, zinc and iron. High doses of cysteamine can lead to copper depletion, implying that chelation effects also occur *in vivo*.
- Induction of DNA repair mechanisms – Cysteamine has been known for over sixty years to mitigate the effects of radiation by upregulating cell cycle checkpoints and repair mechanisms.

MARKETED PRODUCT

PROCYSBI®

PROCYSBI is an approved therapy for the management of nephropathic cystinosis, a rare, life-threatening metabolic lysosomal storage disorder that causes the rapid, toxic accumulation of cystine in all cells, tissues and organs in the body. PROCYSBI capsules contain cysteamine bitartrate in the form of innovative microspheronized beads that are individually coated to create delayed and extended-release properties, allowing patients to maintain consistent therapeutic systemic drug levels over a 12-hour dosing period. The enteric-coated beads are pH sensitive and bypass the stomach for dissolution and absorption in the more alkaline environment of the proximal small intestine. Randomized controlled clinical trials and extended treatment with PROCYSBI therapy demonstrated consistent cystine depletion as monitored by levels of the biomarker (and surrogate marker), white blood cell cystine.

About Nephropathic Cystinosis

There are approximately 500 patients diagnosed with cystinosis living in the United States and an estimated 2,000 worldwide. Nephropathic cystinosis comprises 95% of known cases of cystinosis. In these patients, elevated cystine leads to cellular dysfunction and death; without treatment, the disease is usually fatal by the end of the first decade of life. Cystinosis is progressive, eventually causing irreversible tissue damage and multi-organ failure, including kidney failure, blindness, muscle wasting and premature death. Nephropathic cystinosis is usually diagnosed in infancy after children present with symptoms including markedly increased urination, thirst, dehydration, gastrointestinal distress, failure to thrive, rickets, photophobia and kidney symptoms specific to Fanconi syndrome. Management of cystinosis requires lifelong therapy.

Cystine depletion is the only approved treatment strategy for nephropathic cystinosis. Committed adherence and persistence to cystine depletion therapy is critical to achieve optimal clinical outcomes. Failure to adhere to prescribed dosing of cystine depletion therapy results in disease progression, including kidney failure leading to dialysis and kidney transplantation, muscle wasting and in most cases, premature death. Even brief interruptions in daily therapy can permit toxic accumulation of cystine, exposing tissues to renewed, progressive deterioration.

In addition to the population of patients who have already been identified, we believe that a number of patients with end-stage renal disease have their condition as a result of undiagnosed late-onset nephropathic cystinosis, and would benefit from treatment with PROCYSBI. In October 2013, we executed a collaboration agreement with DaVita Clinical Research to screen blood samples from U.S. patients with end-stage renal disease in an effort to identify patients with unrecognized late-onset nephropathic cystinosis and who could potentially be candidates to receive PROCYSBI therapy.

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CLINICAL DEVELOPMENT

RP103 Clinical Development

Huntington's Disease

Huntington's disease, or HD, is a rare, inherited neurodegenerative disorder caused by an autosomal dominant mutation in a gene called huntingtin. The huntingtin gene encodes a protein that is also called "huntingtin." Expansion of a CAG triplet repeat beyond the normal range within the huntingtin gene results in a mutant form of the protein, which gradually damages cells in the brain. HD causes neuronal degeneration in the cerebral cortex and basal ganglia, which play a key role in movement and behavior control. The cumulative damage to these areas results in the hallmark symptoms of HD: a triad of movement, cognitive and neuropsychiatric symptoms which progress gradually in severity over 15-20 years, eventually causing severe physical and mental disability and premature death. The symptoms of HD usually become evident between the ages 35-44 years, but the onset can also begin from childhood to late life (>75 years). The treatment options for HD patients are very limited, with no approved drugs that modify disease course. Recommended treatment strategies consist of drugs for symptomatic relief of chorea, an involuntary motor system (with tetrabenazine, XENAZINE®, approved by FDA) and mood disorder associated with HD as well as a variety of physical, occupational and dietary therapies.

RP103 as a Treatment for Huntington's Disease

RP103, enteric-coated delayed-release cysteamine bitartrate, is currently being evaluated as a treatment for HD. Centre Hospitalier Universitaire, or CHU, d'Angers, France, is conducting the Phase 2/3 clinical trial of RP103. This 36-month clinical trial comprises an 18-month blinded, randomized, placebo-controlled phase followed by an 18-month open-label phase in which all patients transition to RP103. The primary endpoint of the trial is change from baseline of the Total Motor Score, or TMS, of the Unified Huntington's Disease Rating Scale, or UHDRS at 18 months for RP103 vs. placebo groups. TMS, a validated rating scale, is comprised of approximately 15 different measurements that evaluate gross and small motor function in patients with HD. Chorea is one of two involuntary measurements included in the TMS. The Phase 2/3 trial commenced in October 2010, with full enrollment achieved in June 2012. The study enrolled primarily Stage 1 patients showing early disease symptoms with a UHDRS TMS, Score ≥ 5, Total Functional Capacity, or TFC, > 10 and a CAG repeat > 38. Due to the length of the study and the characteristic continuous progression of the disease, patients were allowed to continue their normal medication regime including taking antidepressants and tetrabenazine.

In February 2014, we announced top line results from the planned 18-month analysis of the study. A total of 96 patients with HD were randomized to treatment with RP103 or placebo. A total of 89 patients completed the initial 18-month phase. In the primary analyses (intention to treat population), the change from baseline to month 18 in mean UHDRS TMS was 6.51 in the placebo group and 4.91 in the RP103 group. The between group difference was not statistically significant (p=0.3545).While the results did not reach statistical significance, an overall positive trend was observed.

Patients were not stratified in the study based on concomitant medication use at baseline. We performed post-hoc statistical analyses to assess whether the TMS results were impacted by the effect of tetrabenazine on chorea. In 66 patients not taking tetrabenazine (32 under placebo and 34 under RP103), the results showed a statistically significant difference in the change in total motor score of 2.84 points of progression in the RP103 treatment arm versus 6.78 for the placebo group (p= 0.03).

There were no new or unusual variations from RP103's clinical safety profile with 48 of 52 patients experiencing at least one adverse event, or AE, during the 18-month interim evaluation versus 38 of 44 under placebo. There were slightly more patients under RP103 than under placebo reporting at least one gastrointestinal AE (61.5% RP103 versus 45.5% placebo), mostly nausea, vomiting, abdominal pain, constipation, headache and breath odor. There were five patients treated with RP103 who experienced serious adverse events, or SAEs, compared with four patients treated with placebo. As of the 18-month time point, seven patients discontinued treatment, six in the RP103 arm and one in placebo. Three patients receiving RP103 discontinued for SAEs including one for lymphopenia, one for repetitive faintness and one for elevated liver enzymes. One SAE in the placebo group, anxiety, resulted in discontinuation.

Under our amended collaboration agreement with CHU d'Angers, we supply RP103 and placebo capsules for the clinical trial and open-label extension study and fund the third-party statistical analysis of clinical trial data in exchange for regulatory and commercial rights to the clinical trial data. Clinical expenses of the study are covered by a grant from the Programme Hospitalier de Recherche Clinique, which is funded by the French government.

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In 2008, we received FDA orphan drug designation for cysteamine formulations, including RP103, for the potential treatment of HD. In July, 2014 we received orphan designation from the European Commission for cysteamine bitartrate for the treatment of HD.

RP103 Mechanism in Huntington's Disease

In HD, mutant Htt aggregate formation and processing leads to neuronal, mitochondrial, cellular stress and dysfunction and death. The metabolism of cysteamine boosts systemic cysteine, which may induce several beneficial stress responses, including the production of glutathione, that in aggregate reduce cellular oxidative stress. A major deficiency of cystathionine c-lyase (CSE), the principal generator of endogenous cysteine from cystathionine, has been shown to mediate neurodegeneration in HD. The ability of CSE and cysteine to reverse oxidative stress and lethality in HD cells suggests that cysteine supplementation and intracellular mobilization through cysteamine therapy might be beneficial in treating HD. Through inhibition of intracellular enzymes, such as transglutaminase, cysteamine inhibits protein aggregation, which are known to form in HD. Cysteamine also increases transcription and production of certain heat shock proteins, which may assist in clearing or repairing misfolded Htt and other proteins in neuronal cells. Cysteamine and its dimer cystamine have been shown in preclinical studies to increase levels of brain derived neurotropic factor, or BDNF. BDNF is induced by cortical neurons and helps support survival, growth and differentiation of new neurons and synapses. Two master genes, huntingtin, or Htt, and huntingtin-associated protein, or Hap1, govern BDNF axonal transport and secretion. Expression of the Bdnf gene is reduced in both Alzheimer's and HD patients, and HD patients are believed to be deficient in BDNF. The Bdnf gene may play a role in the regulation of stress response and in the biology of mood disorders. Finally, cysteamine's metal-chelating properties may assist in removing excess copper, a metal that has shown increased accumulation in brains of people with HD as well as other neurodegenerative disorders.

Non-alcoholic Steatohepatitis in Children

Non-alcoholic steatohepatitis, or NASH, is a severe form of non-alcoholic fatty liver disease, or NAFLD, a progressive liver disease associated with deposition of triglycerides in the hepatocytes, in individuals who do not consume hepatotoxic amounts of alcohol. NAFLD is commonly associated with elements of metabolic syndrome, such as obesity, diabetes mellitus and hypertriglyceridemia. Additional factors include family history of diabetes and high blood lipids in people who are not obese. NAFLD refers to a spectrum of conditions ranging from simple fat accumulation in the liver to steatohepatitis, which can lead to cirrhosis, and increase the risk for hepatocellular carcinoma:

- Non-alcoholic fatty liver disease, or NAFLD – A benign condition with simple fat accumulation within liver cells (hepatic steatosis).
- Non-alcoholic steatohepatitis, or NASH – 10% to 15% of patients with NAFLD progress to NASH, an aggressive form of NAFLD characterized by hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis.
- Cirrhosis – 15% to 25% of patients with NASH progress to cirrhosis, usually over a period of 10 to 20 years. Cirrhosis is characterized by the replacement of healthy liver tissue with fibrosis and scar tissue, leading to loss of liver function. NASH cirrhosis is a key risk factor for development of hepatocellular carcinoma, or HCC.

NAFLD and NASH prevalence are increasing along with the rise of obesity. NASH is now among the most common reasons why patients are referred for liver transplantation.

According to the World Gastroenterology Organization Global Guidelines, the prevalence of NAFLD in children is about 15% in the United States and western countries. Many of these children progress to NASH. NAFLD and NASH are underdiagnosed in children often due to the initial asymptomatic nature of the disease, lack of recognition, screening or appreciation of associated complications by healthcare providers. Children may not be recognized as obese during office visits and age-appropriate norms for body mass index may go unacknowledged. Liver disease is screened by measuring serum alanine aminotransferase, or ALT, and aspartate aminotransferase, or AST, starting at 10 years old in obese children, and in children with a body mass index of 85th to 94th percentile with other risk factors.

Currently there are no approved drug treatment options for NAFLD or NASH. Disease management strategies include recommendations for lifestyle changes in diet, exercise and weight reduction.

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RP103 as a Treatment for NASH in Children

In 2010, a single arm Phase 2a clinical trial was conducted to examine the effects of a prototype of RP103 (twice daily enteric coated cysteamine) as a treatment for NASH in children. Results of this trial with a prototype of RP103 showed that patients exhibited a marked decline in serum transaminase levels during the treatment period of 26 weeks. Seven of 11 juvenile NASH patients entering the study with elevated ALT and AST achieved more than 50% reduction in ALT and six of 11 reduced their ALT levels to normal range. AST levels were also improved, with patients averaging 41% reduction by the end of the 26-week treatment phase. This reduction in serum liver enzymes was largely sustained during the 6-month post-treatment monitoring phase. Other important liver function biomarkers improved significantly, suggesting potential improvements in hepatic histopathology. These markers included reduced levels of cytokeratin 18, or CK-18, a potential serum marker of disease activity in NASH, which decreased by an average of 45%. Adiponectin levels showed a positive increase by an average of 35% during the treatment period. Reduced adiponectin levels are thought to be a marker of the pathogenesis and progression of NASH. Overall, the drug was well tolerated and adverse events were predominantly gastrointestinal and mild in nature.

In June 2012, we announced the dosing of the first patient in a Phase 2b clinical trial – **Cy**steamine Bitartrate Delayed-Release for the Treatment of **N**on-alcoholic Fatty Liver Disease in **Ch**ildren, or CyNCh, which is evaluating the safety and efficacy of RP103 as a potential treatment of NASH in children. The clinical trial is being conducted under a Cooperative Research and Development Agreement, or CRADA, with the National Institute of Diabetes and Digestive and Kidney Diseases, or NIDDK, part of the National Institutes of Health, or NIH. Upon full enrollment in January 2014, 169 patients were enrolled at 10 U.S. centers in the NIDDK-sponsored NAFLD Clinical Research Network.

Raptor and NIDDK share the costs of conducting the CyNCh clinical trial. The primary objective of this randomized, multicenter, double-blind, placebo-controlled Phase 2b clinical trial is to evaluate whether 52 weeks of RP103 treatment reverses liver tissue damage caused by NASH as measured by changes in NAFLD Activity Score, or NAS, a histological rating scale of disease activity (based on scoring lobular inflammation, hepatocyte ballooning and steatosis from a liver biopsy), in conjunction with no worsening of liver tissue fibrosis. Secondary endpoints include blood markers for liver health including ALT and AST, antioxidation biomarkers, imaging, as well as safety and tolerability. Top line clinical trial results for this study are anticipated mid-year 2015.

RP103 Mechanism in NASH

Cysteamine's potent antioxidative properties, including the increased production of glutathione, may reduce oxidative damage that results from excessive accumulation of fats in liver cells. In addition, cysteamine's anti-fibrotic activity, including inhibiting the production of transglutaminase, may play a role in stabilizing or even reducing the liver fibrosis that occurs in severe cases of NASH.

Mitochondrial Disorders including Leigh Syndrome

Leigh syndrome is a severe neurological disorder caused by genetic defects in mitochondrial or nuclear DNA affecting respiratory chain function that typically results in death within the first decade of life. The condition causes increased production of reactive oxygen species that disrupt mitochondrial electron transport and affect cellular function in a variety of tissues. Typically observed during the first year of life, Leigh syndrome is characterized by a failure to thrive, lack of coordination, involuntary and sustained muscle contraction, muscle wasting and multiple organ failure. The incidence of Leigh syndrome in the United States is estimated to be 1 in 40,000 newborns.

RP103 as a Treatment for Mitochondrial Disorders including Leigh Syndrome

In June 2014, we initiated a Phase 2 study in the United States designed to evaluate the safety, tolerability and efficacy of RP103 as a potential treatment for Leigh syndrome and other mitochondrial disorders. RP103 potentially increases mitochondrial glutathione which may act as a scavenging agent of reactive oxygen species and thereby reduce the mitochondrial oxidative stress typically associated with these disorders.

The clinical plan includes an open label, 24 week, Phase 2/3 study in 24 patients (up to a maximum of 32 patients). Patients with Leigh syndrome are expected to comprise two-thirds of the enrolled population in the study. Based on an adaptive design statistical plan, we will conduct interim analyses after 4 patients and again after 12 patients have completed the study to determine final sample size. The primary endpoint of the study will be the change from baseline in the Newcastle Pediatric Mitochondrial Disease Scale, or NPMDS, at 24 weeks. Secondary endpoints will include observations of myopathy, dystonia, seizures, motor development, dyskinesia, quality of life and activities of daily living. Interim results from the clinical trial are expected by the end of 2015.

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Other Clinical-Stage Product Candidates

Convivia™ for ALDH2 Deficiency

We are developing Convivia, our proprietary oral formulation of 4-methylpyrazole, or 4-MP, for the potential treatment of acetaldehyde toxicity resulting from ALDH2 deficiency, an inherited metabolic disorder affecting a material percent of East Asian populations.

In June 2010, we entered into an agreement with Uni Pharma Co., Ltd., or Uni Pharma, pursuant to which we granted Uni Pharma an exclusive license under our intellectual property portfolio relating to Convivia, including method of use and formulation patents. Under this agreement, Uni Pharma is responsible for clinical development, registration and commercialization of Convivia in Taiwan.] We continue to seek partners in other Asian countries to which we may license Convivia in the future for such purposes.

Preclinical Product Candidates

Our preclinical programs include our cysteamine dioxygenase, or ADO, program, to improve treatment of diseases for which cysteamine is therapeutic and our HepTide™ program to treat hepatocellular carcinoma and other cancers susceptible to induced lysosomal storage.

Future Activities

We expect that our near-term efforts will be focused on:

- Increasing market penetration and sales of PROCYSBI and providing comprehensive reimbursement and adherence support to commercial patients in the United States;
- Accelerating the launch of PROCYSBI in additional countries in the EEA;
- Increasing market penetration and sales in Germany, Austria and Switzerland;
- Negotiating pricing and reimbursement in specific European countries and launching PROCYSBI in additional EU countries and markets in 2015;
- Continuing a clinical trial to evaluate PROCYSBI in cystinosis patients that are cysteamine-naïve, as well as other supporting trials in underdeveloped markets;
- Developing select global markets with significant numbers of known cystinosis patients;
- Screening for undiagnosed and unidentified late-onset adult nephropathic cystinosis patients;
- Supporting clinical programs and developing clinical and regulatory strategies for the use of RP103 as a potential treatment of HD;
- Prepare for regulatory interactions to determine the clinical regulatory path forward for RP103 for the potential treatment of NASH in children;
- Supporting clinical programs evaluating RP103 for the potential treatment of mitochondrial disorders;
- Supporting our novel preclinical programs;
- Identifying promising in-licensing product and drug development candidates; and
- Continuing the development of our RP103 clinical pipeline in other indications.

Corporate Information

We are incorporated under the laws of the State of Delaware and our business was founded in May 2006. Our principal executive office is located at 7 Hamilton Landing, Suite 100, Novato, CA 94949. Our phone number is (415) 408-6200.

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Corporate History

In September 2009, our subsidiary merged with and into Raptor Pharmaceuticals Corp., a Delaware corporation, or RPC, pursuant to which the stockholders of RPC received shares of our common stock in exchange for their shares of stock and RPC survived as our wholly-owned subsidiary. This merger is referred to herein as the 2009 Merger. Immediately prior to the 2009 Merger, we changed our corporate name from "TorreyPines Therapeutics, Inc." to "Raptor Pharmaceutical Corp." At the time of the 2009 Merger, RPC had two principal subsidiaries, Raptor Discoveries, a development-stage research and development company, and Raptor Therapeutics, which focused on developing clinical-stage drug product candidates through to commercialization and, in connection with the 2009 Merger, these two subsidiaries became our subsidiaries. In December 2012, the two principal subsidiaries were merged and currently operate under the name Raptor Pharmaceuticals Inc. Due to the amount of our stock issued to the stockholders of RPC in the 2009 Merger, RPC was treated as the "accounting acquirer" in the merger, and its board of directors and officers managed and operated the combined company. In December 2011, we merged RPC with and into us and it ceased to exist as a separate company. TorreyPines Therapeutics was incorporated in July 1997 under the name "Axonyx, Inc." and RPC was incorporated in May 2006 under the name "Highland Clan Creations Corp."

Intellectual Property

IP Protection for RP103 for Cystinosis and Other Indications

We seek to protect our proprietary technology and other intellectual property that we believe is important to our business, including by seeking, maintaining and defending patents. We also rely on trade secrets and know-how to protect our business. We own certain of these intellectual property rights and have obtained licenses under other of our intellectual property rights.

Our intellectual property portfolio is directed to the composition of matter, or COM, the method of use, or MOU, and the composition for use, or CFU, of a formulation/pharmaceutical composition for our product candidates, and other proprietary technologies and processes related to our product development candidates. As of February 18, 2015, our patent portfolio included the following patents and patent applications, which we have exclusively licensed from third parties, along with any patents that may issue from these patents and applications in the future:

- Approximately four issued patents and two pending patent application in the United States, and eight issued patents and 26 pending patent applications in other jurisdictions, such as Europe, Australia, China and Japan directed to the formulation/composition, the MOU, and the CFU, of RP103 for cystinosis, metabolic and neurodegenerative conditions (including NASH) and other indications, to which we have an exclusive, worldwide license from the University of California, San Diego, or UCSD. These patents will expire in 2027 and 2028, and additional patents issuing from these patent applications or others that may be filed, if they issue, will expire after the standard 20-year term, subject to available patent term adjustments.
- Approximately two issued patents in the United States directed to the MOU of transglutaminase inhibitors (a class of molecules which includes cysteamine) to treat HD and other neurodegenerative diseases mediated by transglutaminase, or other diseases associated with CAG repeat expansion, to which we have an exclusive, worldwide license from Yeda Research and Development Company Limited (Israel), Niigata University (Japan) and Niigata TLO Inc. (Japan). These patents will expire in 2019.
- Approximately two patent applications pending in the United States directed to the MOU of cysteamine and related compounds for the treatment of parasitic diseases, including malaria, in combination with the current standard of care, artemisinin, to which we have an exclusive, worldwide license from the McGill UniversityPatents issuing from these patent applications or others that may be filed, if they issue, will expire after the standard 20-year term, projected to expire in 2031, subject to available patent term adjustments.
- Approximately one patent application pending in the United States and ten patent applications pending in other jurisdictions, such as Europe, Australia, China and Japan, directed to the MOU of cysteamine and related compounds for the treatment of Parkinson’s disease, to which we have an exclusive, worldwide license from the Université Laval. Patents issuing from these patent applications or others that may be filed, if they issue, will expire after the standard 20-year term, projected to expire in 2031, subject to available patent term adjustments.
- Approximately one patent application pending in the United States and five patent applications pending in other jurisdictions, such as Australia, Canada and Mexico, directed to the MOU of cysteamine and related compounds for the treatment of tissue fibrosis, to which we have an exclusive, worldwide license from the Seattle Children’s Research Institute. Patents issuing from these patent applications or others that may be filed, if they issue, will expire after the standard 20-year term, projected to expire in 2031, subject to available patent term adjustments.

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- Approximately one patent application in the United States and 14 patent applications pending in other jurisdictions, such as Europe, Australia, China and Japan, directed to the MOU of cysteamine and related compounds to treat MeCP2 associated disorders including Rett Syndrome, to which we have an exclusive license in all countries worldwide where the patent has availability from the Technology Transfer Accelerator of South Eastern France that represents the French medical research organizations where the technology was invented. Patents issuing from these patent applications or others that may be filed, if they issue, will expire after the standard 20-year term, projected to expire in 2031, subject to available patent term adjustments.
- Approximately one patent application pending in the United States and four patent applications pending in other jurisdictions,Australia, Canada, Korea and Mexico, directed to the MOU of cysteamine and related compounds to treat metastatic cancers (including pancreatic, breast, and hepatocellular cancer among others), to which we have an exclusive, worldwide license from the U.S. Food and Drug Administration, or FDA. Patents issuing from these patent applications or others that may be filed, if they issue, will expire after the standard 20-year term, projected to expire in 2031, subject to available patent term adjustments.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the date of filing the non-provisional application. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office in granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier-filed patent.

In addition, extensions of the term of a patent that covers an FDA-approved drug are available in the United States, in order to compensate for the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent, based on the length of time the drug is under regulatory review, subject to certain limitations. Similar extensions are available in Europe and other foreign jurisdictions for patents that cover an approved drug. We expect to apply for available patent term extensions for patents covering our product candidates.

Trademarks

Our trademark portfolio consists of several registered U.S. trademarks covering our company name, the name of our products and services programs (which are additionally registered in additional territories as necessary to protect our rights to the name). Our trademark RAPTOR is registered in the United States, in the EU, in Australia, and internationally generally and is currently pending registration in several other countries.

All third-party trademarks and trade names identified in this Annual Report on Form 10-K are the property of their respective owners.

License Agreement with UCSD

In December 2007, by way of a merger with Encode Pharmaceuticals, Inc., we acquired certain patent rights licensed to Encode by UCSD pursuant to a license agreement dated October 2007, later amended in February 2008, amended and restated in December 2012, and further amended in March 2013 and December 2013. Pursuant to this agreement, we obtained an exclusive, worldwide, sublicenseable license under certain patent rights and know-how controlled by UCSD for the commercial development, use and sale, for human therapeutic purposes, of products covered by such patents or incorporating such know-how, including RP103. This license is exclusive with respect to the licensed patent rights and non-exclusive with respect to the licensed know-how. Under the agreement, UCSD is obligated to diligently prosecute and maintain the licensed patent rights, conditioned upon our continued fulfillment of our obligation to reimburse UCSD for related costs incurred.

Pursuant to the license agreement, we are obligated to pay milestone payments (ranging in size for orphan and non-orphan indications), up to an aggregate total of $6,275,000, upon the occurrence of certain specified development-, regulatory- and commercial-related events during the term of the agreement. To date, we have paid UCSD $2.2 million in total milestone payments. We are also obligated to pay UCSD a royalty on commercial net sales of licensed products, on a country-by-country basis, ranging in the low single-digit to mid single-digit percentages, based on whether the licensed product sold is covered by the licensed patent rights in such country, as well as a percentage of sublicensing fees and sublicensing royalties we receive under the agreement, if any. In 2013, we began paying UCSD royalties based upon our net sales of PROCYSBI and are subject to a minimum annual royalty of $15,000 until 2018, and $75,000 thereafter.

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Unless earlier terminated, our license agreement with UCSD will expire upon the later of (i) on a country-by-country basis, the expiration of the last to expire of the licensed patent rights (in the applicable country), and (ii) ten years from the first commercial sale of any royalty-bearing product. We may terminate the agreement at any time upon a specified period of prior written notice to UCSD. In the event of our breach of an obligation under the agreement, which breach is not cured within a specified number of days after receiving notice of such from UCSD, UCSD may terminate the agreement or choose to convert the license into a non-exclusive license. The agreement will immediately terminate if we file a claim asserting that any of the licensed patent rights are invalid or unenforceable.

Orphan Drug Designation

We have been granted Orphan Drug Designation from the FDA for use of PROCYSBI to manage cystinosis, and the use of RP103 to potentially treat HD, pancreatic cancer and Batten Disease. The Orphan Drug Act of 1983 generally provides incentives, including marketing exclusivity, user fee waivers and tax benefits, to companies that undertake development and marketing of products to treat relatively rare diseases, which are defined as diseases for which there is a patient population of fewer than 200,000 persons in the United States or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. A drug that receives orphan drug designation may receive up to seven years of exclusive marketing in the United States for that indication, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity or where the manufacturer is unable to assure sufficient product quantity. A drug may be entitled to an additional six months of exclusive marketing if it satisfies the requirements for pediatric exclusivity; we have applied for this additional six-month pediatric extension for PROCYSBI. See also “Orphan Designation and Exclusivity” and “Pediatric Studies and Exclusivity” below.

PROCYSBI has also been granted Orphan Drug Designation and awarded 10 years of marketing exclusivity by the EC for treatment of cystinosis, and RP103 has been granted Orphan Drug Designation by the EC for the treatment of HD.

Competition

Cystinosis

Other than PROCYSBI, we are aware of two pharmaceutical products currently approved to treat cystinosis. Cystagon® (immediate-release cysteamine bitartrate capsules), is marketed as a systemic cystine-depleting therapy for cystinosis in the United States by Mylan Pharmaceuticals, and by Orphan Europe in markets outside of the United States. Cystagon was approved by the FDA in 1994 and by EC in 1997. Cystaran® (cysteamine ophthalmic solution) was approved by FDA in 2012 for treatment of corneal crystal accumulation in patients with cystinosis and is marketed by Sigma Tau Pharmaceuticals.

While we believe that PROCYSBI will continue to be well received in the market, Cystagon remains on the market and we expect it will compete with PROCYSBI for the foreseeable future. We are not aware of any pharmaceutical company with an active program to develop an alternative therapy for cystinosis. Academic researchers in the United States and Europe are pursuing potential cures for cystinosis through gene therapy and stem cell therapy, as well as pro-drug and pegylated drug approaches as alternatives to cysteamine bitartrate. We believe that the development timeline to an approved product for these approaches is many years with substantial uncertainty.

Huntington's Disease

We are not aware of any approved available treatments to slow the progression of HD. There is only one approved treatment available for specific symptoms of HD, Xenazine® to treat uncontrollable movements (chorea) that result from the disease. There are several pharmaceutical companies pursuing potential cures and disease modifying treatments for HD, as well as numerous academic and foundation sponsored research efforts. To our knowledge, our product candidate, RP103, is the only compound in clinical development which specifically targets deficient BDNF with the goal of slowing motor deterioration.

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Companies with HD product candidates in development include Auspex, Prana Biotechnology, NeuroSearch, Omeros, Teva/Active Biotech, ISIS/Roche, Eli Lilly & Co. and Pfizer. Several other companies have drug candidates in preclinical development. Additionally, nutritional supplements including creatine and coenzyme Q10 have been investigated as potential treatments for HD. The Huntington Study Group sponsors numerous studies of potential therapies for HD, including coenzyme Q10 and the antibiotic minocycline.

NASH and NAFLD

We are not aware of any currently approved treatment options for NASH or NAFLD. Weight loss, healthy diet, abstinence from alcohol and increased physical activity are typically suggested to slow the progression of NASH and NAFLD. There are numerous therapies being studied for NASH, including obeticholic acid, a farnesoid X receptor (FXR) activator (Intercept Pharmaceuticals), lysyl oxidase-like 2 inhibitor and FXR agonist (Gilead), PPAR alpha and delta inhibitor (Genfit), fatty acid/bile acid (FABC) conjugate (Galmed Pharmaceuticals), CCR2/CCR5 inhibitor (Tobira Therapeutics), caspase inhibitor (Conatus Pharma), 5-lipoxygenase inhibitor (MediciNova) and galectin inhibitor (Galectin), as well as anti-oxidants.

ALDH2 Deficiency

We are not aware of any pharmaceutical products currently approved for ALDH2 deficiency, either in the United States or internationally. There are several non-prescription, nutritional supplements available which purport to mitigate the side effects that result from drinking by people with ALDH2 deficiency. Although we are not aware of any study which has demonstrated the efficacy of such non-pharmaceutical alternatives, these products may compete with our ALDH2 deficiency product candidate if it is approved for marketing.

Government Regulations of the Biotechnology Industry

Human therapeutic products are subject to extensive regulation by governmental authorities in the United States and foreign countries. Governmental authorities govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling, and import and export of pharmaceutical products. The nature and extent to which such regulation will apply to us will vary depending on the nature of any drug product candidates developed. Failure to comply with applicable governmental requirements may subject a company to a variety of administrative or judicial sanctions, such as refusal to approve pending applications, a clinical hold, warning letters, recall or seizure of products, partial or total suspension of production, withdrawal of the product from the market, injunctions, fines, civil penalties or criminal prosecution.

Governmental agency approval is required before any new unapproved drug or dosage form, including a new use of a previously approved drug, can be marketed in each jurisdiction in which the product is marketed. We anticipate that all of our drug product candidates will require regulatory approval by governmental agencies prior to commercialization.

In particular, human therapeutic products are subject to rigorous preclinical and clinical testing and other approval procedures of the FDA and similar regulatory authorities in other countries. Various federal statutes and regulations also govern or influence testing, manufacturing, safety, labeling, storage, record-keeping and marketing related to such products. The process of obtaining these approvals and the subsequent compliance with the appropriate federal statutes and regulations requires substantial time and financial resources.

Before obtaining regulatory approvals for the commercial sale of any of our products under development, we must demonstrate through preclinical studies and clinical trials that the product is safe and efficacious for use in each target indication. The results from preclinical studies and early clinical trials might not be predictive of results that would be obtained in large-scale testing. Our clinical trials might not successfully demonstrate the safety and efficacy of any product candidates or result in marketable products, and failure can occur at any point in the testing process.

In order to clinically test, manufacture and market products for therapeutic use, we will have to comply with mandatory procedures and safety and effectiveness standards established by various regulatory bodies. In the United States, the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act, as amended, or FDCA, and the regulations promulgated thereunder, and other federal and state statutes and regulations govern, among other things, the testing, manufacture, labeling, storage, record keeping, approval, advertising, and promotion of our current and proposed product candidates. Product development and approval within this regulatory framework takes a number of years and involves the expenditure of substantial resources.

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The steps required by the FDA before new drug products may be marketed in the United States include:

- Completion of extensive preclinical laboratory and animal studies performed in accordance with the FDA's Good Laboratory Practice, or GLP, regulations;
- The submission to the FDA of a request for authorization to conduct clinical trials in an investigational new drug application, or IND, which must become effective before clinical trials may commence;
- Approval by an independent institutional review board, or IRB, or ethics committee representing each clinical site before each clinical study may be initiated;
- Completion of adequate and well-controlled human clinical trials to establish and confirm the safety and efficacy of a drug candidate for the proposed indication;
- Completion of process validation, quality product release and stability;
- Submission to the FDA of a new drug application, or NDA, for the drug candidate for marketing approval;
- Potential review of the product application by an FDA advisory committee, where appropriate and if applicable;
- Satisfactory completion of an FDA pre-approval inspection of the manufacturing facilities where the proposed product is produced to assess compliance with the FDA's current Good Manufacturing Practice, or cGMP, requirement and to assure that the facilities, methods and controls are adequate to preserve the drugs' identity, strength and purity; and
- Review and approval of the NDA by the FDA before the product may be sold commercially.

The pre-clinical and clinical testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that approvals for our product candidates will be granted on a timely basis, if at all. Preclinical testing includes laboratory evaluation and characterization of the safety and efficacy of a drug and its chemistry, formulation, stability and toxicity, as well as animal studies to assess the characteristics and potential safety and efficacy of the product. Preclinical testing results are submitted to the FDA as a part of an IND. Some pre-clinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises concerns or questions relating to one or more proposed clinical trials and places a trial on clinical hold, including concerns that human research subjects will be exposed to unreasonable health risks. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, the submission of an IND may not result in FDA authorization to commence a clinical trial. A separate submission to an existing IND must also be made for each successive clinical trial conducted during product development. Further, an independent IRB, covering each site proposing to conduct the clinical trial must review and approve the plan for any clinical trial and informed consent information for subjects before the trial commences at that site and it must monitor the study until completed.

Clinical trials involve the administration of an investigational drug to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Sponsors of clinical trials generally must register and report, at the NIH-maintained website ClinicalTrials.gov, key parameters of certain clinical trials. For purposes of an NDA submission and approval, human clinical trials are typically conducted in the following sequential phases, which may overlap or be combined. Phase 1 represents the initial administration of the drug to a small group of humans, either patients or healthy volunteers, typically to test for safety (adverse effects), dosage tolerance, absorption, distribution, metabolism, excretion and clinical pharmacology, and, if possible, to gain early evidence of effectiveness. Phase 2 involves studies in a small sample of the actual intended patient population to assess the efficacy of the drug for a specific indication, to determine dose tolerance and the optimal dose range and to gather additional information relating to safety and potential adverse effects. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more extensive Phase 3 clinical trials. Once an investigational drug is found to have some efficacy and an acceptable safety profile in the targeted patient population, Phase 3 studies are initiated to further establish clinical safety and efficacy of the therapy in a broader sample of the general patient population, in order to determine the overall risk-benefit ratio of the drug and to provide an adequate basis for any physician labeling. During all clinical studies, we must adhere to GCP or good clinical practices, standards. The results of the research and product development, manufacturing, preclinical studies, clinical studies and related information are submitted in an NDA to the FDA.

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The FDA, the IRB or the clinical study sponsor may suspend or terminate a clinical study at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Additionally, some clinical studies are overseen by an independent group of qualified experts organized by the clinical study sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a study may move forward at designated check points based on access to certain data from the study. We may also suspend or terminate a clinical study based on evolving business objectives and/or competitive climate. The process of completing clinical testing and obtaining FDA approval for a new drug is likely to take a number of years and require the expenditure of substantial resources. If an application is submitted, there can be no assurance that the FDA will review and approve the NDA.

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, detailed investigational new drug product information is submitted to the FDA in the form of an NDA requesting approval to market the product for one or more indications. Under federal law, the submission of most NDAs is subject to a substantial application user fee. Applications for orphan drug products are exempt from the NDA user fees, unless the application includes an indication for other than a rare disease or condition.

An NDA must include all relevant data available from pertinent preclinical and clinical studies, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls and proposed labeling, among other things. Data can come from company-sponsored clinical studies intended to test the safety and effectiveness of a use of a product, or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and effectiveness of the investigational new drug product to the satisfaction of the FDA.

Under federal law, the submission of an NDA is subject to a substantial application user fee, and the manufacturer and/or sponsor under an approved NDA are also subject to annual product and establishment user fees. The FDA has 60 days from its receipt of an NDA to determine whether the application will be accepted for filing based on the agency’s threshold determination that it is sufficiently complete to permit substantive review. The FDA may request additional necessary information rather than accept an NDA for filing. In this event, the NDA must be resubmitted with the additional information and may be subject to payment of additional user fees. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission has been accepted for filing, the FDA begins an in-depth substantive review.

The FDA's goal is to review the application within 10 months after it accepts the application for filing, or, if the application relates to an unmet medical need in a serious or life-threatening indication, six months after the FDA accepts the application for filing. The review process is often significantly extended by FDA requests for additional information or clarification. In addition, an application may be referred to an advisory committee, which is a panel of independent experts, to review, evaluate and provide a recommendation to the FDA as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it typically follows such recommendations and considers them carefully when making approval decisions.

Before obtaining FDA approval for each product, the FDA typically will inspect the facility or facilities where the product is manufactured and will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP requirements. Following approval, each product manufacturing establishment must be registered with the FDA and its quality control and manufacturing procedures must continue to conform and adhere at all times to the FDA's cGMP regulations. The FDA and other government agencies regularly inspect manufacturing facilities for compliance with these requirements. If, as a result of these inspections, the FDA determines that any equipment, facilities, laboratories or processes do not comply with applicable FDA regulations and conditions of product approval, the FDA may seek civil, criminal or administrative sanctions and/or remedies against us, including the suspension of the manufacturing operations. Manufacturers must expend substantial time, money and effort in the area of production and quality control to ensure full technical compliance with these standards.

In some cases, the FDA may condition approval of an NDA for a product candidate on the sponsor’s agreement to conduct additional clinical trials to further assess the drug’s safety and effectiveness after NDA approval. Such post-approval trials are typically referred to as Phase 4 studies. In addition, even after initial FDA approval has been obtained, further studies would be required to gain approval for the use of a product as a treatment for clinical indications other than those for which the product was initially tested and approved. Once an NDA is approved, a product will be subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to drug/device listing, recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. Results of post-marketing programs, including Phase 4 clinical studies or post-market surveillance, might limit or expand the further marketing of the products. Further, if there are any modifications to the drug, including changes in indication, manufacturing process, labeling or a change in manufacturing facility, submission and approval of an NDA supplement might be required. Drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and generally require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP or QSR and impose reporting and documentation requirements upon us and any third-party manufacturers that we may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP or QSR compliance.

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Failure to comply with applicable FDA requirements may result in a number of consequences that could materially and adversely affect us. Failure to adhere to approved trial standards and GCPs in conducting clinical trials could cause the FDA to place a clinical hold on one or more studies which would delay research and data collection necessary for product approval. Noncompliance with GCPs could also have a negative impact on the FDA's evaluation of an NDA. Failure to adhere to GCPs, cGMPs and other applicable requirements could result in FDA enforcement action and in civil and criminal sanctions, including but not limited to fines, seizure of product, refusal of the FDA to approve product approval applications, withdrawal of approved applications, and prosecution. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical studies to assess new safety risks; or imposition of distribution restrictions or other restrictions under a Risk Evaluation and Mitigation Strategies, or REMS, program.

The FDA strictly regulates marketing, labeling, advertising, and promotion of products that are placed on the market pursuant to a number of complex regulations which include, among others, standards for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities, and promotional activities involving the internet. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability. Indeed, the FDA has very broad enforcement authority under the FFDCA, and failure to abide by these regulations can result in penalties, including the issuance of a warning letter directing entities to correct deviations from FDA standards, a requirement that future advertising and promotional materials be pre-cleared by the FDA, and state and federal civil and criminal investigations and prosecutions.

Whether or not FDA approval has been obtained, approval of a product by regulatory authorities in foreign countries must be obtained prior to the commencement of marketing of the product in those countries. The requirements governing the conduct of clinical trials and product approvals vary widely from country to country, and the time required for approval might be longer or shorter than that required for FDA approval. Although there are some procedures for unified filings for some European countries, in general, each country at this time has its own procedures and requirements. There can be no assurance that any foreign approvals would be obtained.

In addition to the regulatory framework for product approvals, we and our collaborative partners must comply with federal, state and local laws and regulations regarding occupational safety, laboratory practices, the use, handling and disposition of radioactive materials, environmental protection and hazardous substance control, and other local, state, federal and foreign regulations. All facilities and manufacturing processes used by third parties to produce our drug candidates for clinical use in the United States must conform with cGMPs. These facilities and practices are subject to periodic regulatory inspections to ensure compliance with cGMP requirements. Their failure to comply with applicable regulations could extend, delay, or cause the termination of clinical trials conducted for our drug candidates or of manufacturing and sale of any of our products approved for sale. We cannot accurately predict the extent of government regulation that might result from future legislation or administrative action.

Expedited Review and Accelerated Approval Programs

A sponsor may seek approval of its product candidate under programs designed to accelerate FDA's review and approval of NDAs. For example, Fast Track Designation may be granted to a drug intended for treatment of a serious or life-threatening disease or condition that has potential to address unmet medical needs for the disease or condition. The key benefits of fast track designation are the eligibility for priority review, rolling review (submission of portions of an application before the complete marketing application is submitted), and accelerated approval, if relevant criteria are met. Based on results of clinical studies submitted in an NDA, upon the request of an applicant, the FDA may grant the NDA priority review designation, which sets the target date for FDA action on the application at six months after the FDA accepts the application for filing. Priority review is granted where there is evidence that the proposed product would be a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition. If criteria are not met for priority review, the application is subject to the standard FDA review period of 10 months after FDA accepts the application for filing. Priority review designation does not change the scientific/medical standard for approval or the quality of evidence necessary to support approval.

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Under the accelerated approval program, the FDA may approve an NDA on the basis of either a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Post-marketing studies or completion of ongoing studies after marketing approval are generally required to verify the drug's clinical benefit in relationship to the surrogate endpoint or ultimate outcome in relationship to the clinical benefit. In addition, the Food and Drug Administration Safety and Innovation Act, or FDASIA, which was enacted and signed into law in 2012, established the new Breakthrough Therapy designation. A sponsor may seek FDA designation of its product candidate as a Breakthrough Therapy if the drug is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

European Union Drug Review and Approval

In the EEA (which is comprised of the 28 Member States of the European Union plus Norway, Iceland and Liechtenstein), medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. There are two types of MA:

The Community MA, which is issued by the European Commission through the Centralized Procedure, based on the opinion of the CHMP of the EMA, is valid throughout the entire territory of the EEA. The Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products, and medicinal products containing a new active substance indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes and auto-immune and viral diseases. The Centralized Procedure is optional for products containing a new active substance not yet authorized in the EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU.

National MAs, which are issued by the competent authorities of the Member States of the EEA and only cover their respective territory, are available for products not falling within the mandatory scope of the Centralized Procedure. Where a product has already been authorized for marketing in a Member State of the EEA, this National MA can be recognized in other Member States through the Mutual Recognition Procedure. If the product has not received a National MA in any Member State at the time of application, it can be approved simultaneously in various Member States through the Decentralized Procedure.

Under the above described procedures, before granting the MA, the EMA or the competent authorities of the Member States of the EEA make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy.

Orphan Drug Designation and Exclusivity

The Orphan Drug Act provides incentives for the development of products intended to treat rare diseases or conditions. Under the Orphan Drug Act, the FDA may grant orphan designation to a drug intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making a drug product available in the United States for this type of disease or condition will be recovered from sales of the product. If a sponsor demonstrates that a drug is intended to treat rare diseases or conditions, the FDA will grant Orphan Drug Designation for that product for the orphan disease indication. Orphan Drug Designation must be requested before submitting an NDA. After the FDA grants Orphan Drug Designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA.

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Orphan Drug Designation provides manufacturers with research grants, tax credits and eligibility for orphan drug exclusivity. If a product that has Orphan Drug Designation subsequently receives the first FDA approval of the active moiety for that disease or condition for which it has such designation, the product is entitled to orphan drug exclusivity, which for seven years prohibits the FDA from approving another product with the same active ingredient for the same indication, except in limited circumstances. If a drug designated as an orphan product receives marketing approval for an indication broader than the orphan indication for which it received the designation, it will not be entitled to orphan drug exclusivity. Orphan exclusivity will not bar approval of another product under certain circumstances, including if a subsequent product with the same active ingredient for the same indication is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand. Further, the FDA may approve more than one product for the same orphan indication or disease as long as the products contain different active ingredients. Moreover, competitors may receive approval of for the same product but for a different indication for which the orphan product has exclusivity. As a result, even if we obtain orphan exclusivity, we may still be subject to competition.

In the EU, the EMA's Committee for Orphan Medicinal Products, or COMP, grants Orphan Drug Designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the European Union Community and for which no satisfactory method of diagnosis, prevention, or treatment has been authorized (or the product would be a significant benefit to those affected). Additionally, designation is granted for products intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the EU would be sufficient to justify the necessary investment in developing the medicinal product. In the EU, Orphan Drug Designation entitles a party to financial incentives such as reduction of fees or fee waivers and 10 years of market exclusivity is granted following medicinal product approval. This period may be reduced to six years if the Orphan Drug Designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity.

Orphan Drug Designation must be requested before submitting an application for marketing approval. Orphan Drug Designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

Pediatric Studies and Exclusivity

NDAs must contain data (or a proposal for post-marketing activity) to assess the safety and effectiveness of an investigational new drug product for the claimed indications in all relevant pediatric populations in order to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults or full or partial waivers if certain criteria are met. The requirements for pediatric data do not apply to any drug for an indication for which orphan designation has been granted.

Pediatric exclusivity is another type of non-patent exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the five-year and three-year non-patent and orphan exclusivity. This six-month exclusivity may be granted if an NDA or Biologic License Application sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical study is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of FDA-requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application relying on the NDA sponsor's data. We have applied for this additional six-month pediatric extension for PROCYSBI.

Hatch-Waxman Amendments and Exclusivity

As an alternative path to FDA approval for modifications to formulations or uses of products previously approved by the FDA, an applicant may submit an NDA under Section 505(b)(2) of the FDCA. Section 505(b)(2) was enacted as part of the Hatch-Waxman Amendments and permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by, or for, the applicant. If the 505(b)(2) applicant can establish that reliance on FDA's previous findings of safety and effectiveness is scientifically appropriate, it may eliminate the need to conduct certain preclinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements, including clinical trials, to support the change from the approved branded reference drug. The FDA may then approve the new product candidate for all, or some, of the label indications for which the branded reference drug has been approved, as well as for any new indication sought by the 505(b)(2) applicant.

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In seeking approval for a drug through an NDA, including a 505(b)(2) NDA, applicants are required to list with the FDA certain patents whose claims cover the applicant's product. Upon approval of an NDA, each of the patents listed in the application for the drug is then published in the Orange Book. Any applicant who files an abbreviated new drug application, or ANDA, seeking approval of a generic equivalent version of a drug listed in the Orange Book or a 505(b)(2) NDA referencing a drug listed in the Orange Book must certify to the FDA that (1) no patent information on the drug product that is the subject of the application has been submitted to the FDA; (2) such patent has expired; (3) the date on which such patent expires; or (4) such patent is invalid or will not be infringed upon by the manufacture, use or sale of the drug product for which the application is submitted. This last certification is known as a paragraph IV certification. A notice of the paragraph IV certification must be provided to each owner of the patent that is the subject of the certification and to the holder of the approved NDA to which the ANDA or 505(b)(2) application refers. The applicant may also elect to submit a "section viii" statement certifying that its proposed label does not contain (or carves out) any language regarding the patented method-of-use rather than certify to a listed method-of-use patent.

If the reference NDA holder and patent owners assert a patent challenge directed to one of the Orange Book listed patents within 45 days of the receipt of the paragraph IV certification notice, the FDA is prohibited from approving the application until the earlier of 30 months from the receipt of the paragraph IV certification expiration of the patent, settlement of the lawsuit or a decision in the infringement case that is favorable to the applicant. The ANDA or 505(b)(2) application also will not be approved until any applicable non-patent exclusivity listed in the Orange Book for the branded reference drug has expired. Specifically, the holder of the NDA for the listed drug may be entitled to a period of non-patent exclusivity, during which the FDA cannot approve an ANDA or 505(b)(2) application that relies on the listed drug. For example, a pharmaceutical manufacturer may obtain five years of non-patent exclusivity upon NDA approval of a new chemical entity, or NCE, which is a drug that contains an active moiety that has not been approved by FDA in any other NDA. An "active moiety" is defined as the molecule or ion responsible for the drug substance's physiological or pharmacologic action. During the five-year exclusivity period, the FDA cannot accept for filing any ANDA seeking approval of a generic version of that drug or any 505(b)(2) NDA for the same active moiety and that relies on the FDA's findings regarding that drug, except that FDA may accept an application for filing after four years if the follow-on applicant makes a paragraph IV certification.

A drug, including one approved under Section 505(b)(2), may obtain a three-year period of exclusivity for a particular condition of approval, or change to a marketed product, such as a new formulation for a previously approved product, if one or more new clinical studies (other than bioavailability or bioequivalence studies) was essential to the approval of the application and was conducted/sponsored by the applicant. Should this occur, the FDA would be precluded from approving any ANDA or 505(b)(2) application for the protected modification until after that three-year exclusivity period has run. However, unlike NCE exclusivity, the FDA can accept an application and begin the review process during the exclusivity period.

Coverage and Reimbursement

The commercial success of PROCYSBI and our drug candidates and our ability to commercialize those products successfully will depend in part on the extent to which governmental payor programs at the federal and state levels, including Medicare and Medicaid, private health insurers and other third-party payors provide adequate coverage and reimbursement. These third-party payors generally develop their own policies as to which drugs they will pay for and the reimbursement levels for the drugs. For example, governmental programs in the United States often require manufacturers to pay certain rebates or otherwise provide discounts to secure coverage of drug products. To control healthcare expenditures generally, in the United States, the EU and other potentially significant markets for PROCYSBI and our drug candidates, government authorities and third party payors are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative products and therapies. The measures taken often have resulted in lower average selling prices. Further, the increased emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the EU places additional pressure on product pricing, reimbursement and usage, which may adversely affect our future product sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, as well as drug coverage and reimbursement policies and pricing in general.

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Some of the additional requirements and restrictions on coverage and reimbursement levels imposed by third-party payors influence the purchase of healthcare services and products. For example, there may be limited coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA-approved drug products for a particular indication. There may also be formulary placements that result in lower reimbursement levels and higher cost-sharing borne by patients. Further, third-party payors are increasingly examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain the FDA approvals. Our products may not be considered medically necessary or cost-effective. Even if a third-party payor determines to provide coverage for a drug product, adequate reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in drug development.

Healthcare legislative proposals to reform healthcare or reduce costs under government insurance programs may also result in lower reimbursement for our drugs and drug candidates or exclusion of our drugs and drug candidates from coverage altogether. The cost containment measures that healthcare payors and providers are instituting and any healthcare reform could significantly reduce our revenues from the sale of PROCYSBI and any of our approved drug candidates. We cannot provide any assurances that we will be able to obtain and maintain third party coverage or adequate reimbursement for PROCYSBI or any of our approved drug candidates in whole or in part.

Healthcare Reform

With respect to legislative reform, in the United States, there have been and continue to be a number of significant legislative initiatives to contain healthcare costs. For example, in March 2010, the Affordable Care Act was passed, which substantially changes the way health care is financed by both governmental and private insurers, and significantly impacts the U.S. pharmaceutical industry. The Affordable Care Act, among other things, subjects biologic products to potential competition by lower-cost biosimilars, addresses a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, increases the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extends the rebate program to individuals enrolled in Medicaid managed care organizations, establishes annual fees and taxes on manufacturers of certain branded prescription drugs, and a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer’s outpatient drugs to be covered under Medicare Part D.

In addition, other legislative changes have been proposed and adopted in the United States since the Health Care Reform Law was enacted. On August 2, 2011, the Budget Control Act of 2011 among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013, due to subsequent legislative amendments to the statute, and will remain in effect through 2024 unless additional Congressional action is taken.

We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

Other Healthcare Laws

We are also subject to healthcare regulation and enforcement by the federal government and the states and foreign governments in which we conduct our business. These laws include, without limitation, state and federal anti-kickback, fraud and abuse, false claims, privacy and security and physician sunshine laws and regulations.

The federal Anti-Kickback Statute prohibits, among other things, any person from knowingly and willfully offering, soliciting, receiving or providing remuneration, directly or indirectly, to induce either the referral of an individual, for an item or service or the purchasing or ordering of a good or service, for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs. The Anti-Kickback Statute is subject to evolving interpretations. In the past, the government has enforced the Anti-Kickback Statute to reach large settlements with healthcare companies based on sham consulting and other financial arrangements with physicians. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act. The majority of states also have anti-kickback laws which establish similar prohibitions and in some cases may apply to items or services reimbursed by any third-party payor, including commercial insurers.

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Additionally, the civil False Claims Act prohibits knowingly presenting or causing the presentation of a false, fictitious or fraudulent claim for payment to the United States government. Actions under the False Claims Act may be brought by the Attorney General or as a qui tam action by a private individual in the name of the government. Violations of the False Claims Act can result in very significant monetary penalties and treble damages. The federal government is using the False Claims Act, and the accompanying threat of significant liability, in its investigation and prosecution of pharmaceutical and biotechnology companies throughout the country, for example, in connection with the promotion of products for unapproved uses and other sales and marketing practices. The government has obtained multi-million and multi-billion dollar settlements under the False Claims Act in addition to individual criminal convictions under applicable criminal statutes. Given the significant size of actual and potential settlements, it is expected that the government will continue to devote substantial resources to investigating healthcare providers' and manufacturers' compliance with applicable fraud and abuse laws.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, also created new federal criminal statutes that prohibit among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payors, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense, and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

In addition, a person who offers or transfers to a Medicare or Medicaid beneficiary any remuneration, including waivers of co-payments and deductible amounts (or any part thereof), that the person knows or should know is likely to influence the beneficiary’s selection of a particular provider, practitioner or supplier of Medicare or Medicaid payable items or services may be liable for civil monetary penalties of up to $10,000 for each wrongful act. Moreover, in certain cases, providers who routinely waive copayments and deductibles for Medicare and Medicaid beneficiaries can also be held liable under the Anti-kickback Statute and civil False Claims Act, which can impose additional penalties associated with the wrongful act. One of the statutory exceptions to the prohibition is non-routine, unadvertised waivers of copayments or deductible amounts based on individualized determinations of financial need or exhaustion of reasonable collection efforts. The Office of Inspector General of the Department of Health and Human Services emphasizes, however, that this exception should only be used occasionally to address special financial needs of a particular patient. Although this prohibition applies only to federal healthcare program beneficiaries, the routine waivers of copayments and deductibles offered to patients covered by commercial payers may implicate applicable state laws related to, among other things, unlawful schemes to defraud, excessive fees for services, tortious interference with patient contracts and statutory or common law fraud. To the extent our patient assistance programs are found to be inconsistent with applicable laws, we may be required to restructure or discontinue such programs, or be subject to other significant penalties.

There has also been a recent trend of increased federal and state regulation of payments made to physicians and other healthcare providers. The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, the Affordable Care Act, among other things, imposes new reporting requirements on drug manufacturers for payments made by them to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit required information may result in civil monetary penalties of up to an aggregate of $150,000 per year (or up to an aggregate of $1 million per year for "knowing failures"), for all payments, transfers of value or ownership or investment interests that are not timely, accurately and completely reported in an annual submission. Drug manufacturers were required to begin collecting data on August 1, 2013 and submit reports to the government by March 31, 2014 and June 30, 2014, and the 90th day of each subsequent calendar year. Certain states also mandate implementation of compliance programs, impose restrictions on drug manufacturer marketing practices and/or require the tracking and reporting of gifts, compensation and other remuneration to physicians.

We may also be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology and Clinical Health Act, or HITECH, and their respective implementing regulations, including the final omnibus rule published on January 25, 2013, imposes specified requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA’s privacy and security standards directly applicable to “business associates,” defined as independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney’s fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways, thus complicating compliance efforts.

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The shifting commercial compliance environment and the need to build and maintain robust and expandable systems to comply with different compliance and/or reporting requirements in multiple jurisdictions increase the possibility that a healthcare company may violate one or more of the requirements. If our operations are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs and imprisonment, any of which could adversely affect our ability to operate our business and our financial results.

Research and Development

We have an active research and development effort. We plan to focus our research and development efforts in the discovery, research, preclinical and clinical development of our drug candidates in order to provide therapies that we believe will be safer, less intrusive and more effective than current approaches in treating a wide variety of disorders. During the years ended December 31, 2014 and 2013, the four-month transition period ended December 31, 2012 and the fiscal year ended August 31, 2012, we incurred approximately $43.5 million, $29.2 million, $9.0 million, and $21.4 million, respectively, in research and development expenses.

Operating Segment and Geographic Information

Operating segments are components of an enterprise for which separate financial information is available and is evaluated regularly by a company in deciding how to allocate its resources and to assess its performance. We have reviewed how we allocate our resources and analyze performance worldwide and have determined that, because employees work on integrated programs in the United States and in Europe, encompassing all stages of product development and commercialization, we operate in one segment.

Compliance with Environmental Laws

We estimate the annual cost of compliance with environmental laws, comprised primarily of hazardous waste removal, will be nominal.

Employees

As of December 31, 2014, we had 123 full time employees (100 and 23 in the United States and EU, respectively). Of the 123 employees, 75 are sales and marketing and general and administrative personnel and 48 are in manufacturing, quality control and assurance and research and development. Based on our current plan, over the next 12-month period we intend to expand our U.S. and EU employee base across most functions in the Company.

Facilities

Our primary offices are located at 7 Hamilton Landing, Suite 100, Novato, CA 94949. Our main phone number is (415) 408-6200 and our facsimile number is (415) 382-8002. Our European headquarters are located at Naritaweg 165, 1043 BW Amsterdam, Netherlands and we have administrative offices in Utrecht, Netherlands.

Website

Our corporate website is located at www.raptorpharma.com. Any information contained in, or that can be accessed through, our website is not incorporated by reference into this Annual Report on Form 10-K.

Available Information

Our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act may be accessed through the SEC's website at www.sec.gov and on our website at www.raptorpharma.com. Such filings are placed on our website as soon as reasonably practicable after they are filed with the SEC. Our code of business conduct and ethics, audit committee charter, corporate governance and nominating committee charter and compensation committee charter are also posted on our website.

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ITEM 1A: RISK FACTORS

Investing in our common stock involves a high degree of risk. Before deciding whether to invest in our common stock, you should consider carefully the risk factors described below, together with the other information contained in this Annual Report on Form 10-K and other documents we file with the SEC, such as our quarterly reports on Form 10-Q, our current reports on Form 8-K and any public announcements we make from time to time. If any of these risks actually occur, it may materially harm our business, financial condition, operating results or cash flow. As a result, the market price of our common stock could decline, and you could lose all or part of your investment. Additional risks and uncertainties that are not yet identified or that we think are immaterial may also materially harm our business, operating results and financial condition and could result in a complete loss of your investment.

Risks Associated with Commercialization and Product Development

Our revenues currently depend entirely on the commercial success of our lead drug, PROCYSBI, for the management of nephropathic cystinosis.

PROCYSBI is our only product currently approved for marketing, and as a result, our revenue and operating results substantially depend on the commercial success of PROCYSBI. We commenced marketing for PROCYSBI in the United States in June 2013 and Europe in April 2014. We did not have prior experience commercializing therapeutics. In the United States, we are permitted to market PROCYSBI only for the management of nephropathic cystinosis in adults and children six years and older. In September 2013, we received marketing authorization from the European Commission, or EC, to commercialize PROCYSBI for the treatment of proven nephropathic cystinosis in the Economic European Area, or EEA. However, we only recently commenced commercial sales of PROCYSBI in select countries in Europe, and have no assurance of securing reimbursement and subsequently launching in additional countries in the EEA. We believe that our results of operations and, in particular, net product sales of PROCYSBI will affect the trading price of our common stock substantially. If PROCYSBI sales do not meet expectations, our stock price may fluctuate, including a potential and possibly significant decrease.

The successful commercialization of PROCYSBI will depend on several factors, including:

- our ability to provide acceptable evidence of the safety and efficacy of PROCYSBI;
- compliance with regulatory requirements, including fulfilling post-approval commitments;
- our ability to obtain approval by regulatory agencies in other countries, including appropriate product labeling;
- the effect of current and future healthcare laws;
- the manufacture and supply of adequate quantities of PROCYSBI in compliance with current good manufacturing practices, or cGMPs, as needed to meet commercial demand;
- adequate coverage and reimbursement for PROCYSBI from commercial health plans and government health programs, which we refer to collectively as third-party payors;
- our ability to obtain acceptable prices in EEA countries and other select territories, including reimbursement at the country-specific price;
- limitations or warnings currently contained in or as may later be required in approved labeling and the breadth of product labeling or product insert requirements;
- our ability to enter into agreements with wholesalers, distributors and pharmacies on commercially reasonable terms; and
- the development and maintenance of intellectual property and other product protection for PROCYSBI.

If we fail to grow sales of PROCYSBI in existing markets or to successfully commercialize PROCYSBI in other countries within a reasonable time period, we may never become profitable and may be unable to sustain our business, our business, and results of operations and financial condition will be materially adversely affected.

Our ability to generate significant product sales from PROCYSBI is dependent upon market acceptance among physicians, patients, patient families, third-party payors and the healthcare community.

PROCYSBI may not attain or maintain market acceptance among physicians, patients, patient families, third-party payors or the healthcare community compared to the current standard of care and our competitors. We believe that the degree of market acceptance and our ability to generate significant product sales of PROCYSBI will depend on a number of factors, including:

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- the relative efficacy, safety, availability and ease of administration of alternative treatments;
- the price of our product, both in absolute terms and relative to alternative treatments;
- the timing of market introduction of our product relative to competitive drugs;
- the nature of publicity related to our products relative to the publicity related to our competitors' products;
- the prevalence and severity of adverse side effects of PROCYSBI;
- continued patient adherence to therapy;
- availability of coverage from third-party payors;
- provision of affordable out-of-pocket costs to patients and/or other programs to ensure patient access to PROCYSBI; and
- the identification of currently diagnosed and undiagnosed patients and the continued growth of the cystinosis market.

Our efforts to educate patients, physicians, parents, the medical community and third-party payors on the benefits of PROCYSBI may require significant resources and may not be successful. If PROCYSBI does not achieve and maintain significant market acceptance among physicians, patients, patient families, third-party payors or the healthcare community, our business, results of operations and financial condition will be materially adversely affected.

The amount of our product sales of PROCYSBI in the EEA is dependent in part upon the pricing and reimbursement guidelines adopted in each of the EEA countries, which may not be at acceptable levels.

We currently sell PROCYSBI in select EEA countries at the German price. One or more EEA countries may not support our anticipated pricing and reimbursement levels for PROCYSBI, particularly in light of the budget crises faced by a number of countries and third-party payors in the EEA, which would negatively affect revenues from PROCYSBI. The pricing and reimbursement process in EEA countries can be lengthy and involved, and we do not have significant experience with this process. Failure to timely complete the pricing and reimbursement process in the EEA countries will delay our ability to further market PROCYSBI and our ability to derive revenues from that region.

PROCYSBI is, and any other future product candidates, if approved, will be, subject to extensive and ongoing regulatory requirements and continued regulatory review, which will result in significant expense, and we may be subject to penalties and litigation if we fail to comply with regulatory requirements or experience problems with our products.

Even after we achieve regulatory approvals, we are subject to ongoing obligations and continued regulatory review with respect to our manufacturing processes, labeling, packaging, distribution, storage, adverse event reporting, dispensation, advertising, promotion and recordkeeping. These requirements include submissions of safety and other post-marketing information and reports, ongoing maintenance of product registration and continued compliance with good manufacturing practices, or GMPs, good clinical practices, or GCPs, good distribution practices, or GDPs, and good laboratory practices, or GLPs. If we, our products or product candidates or the manufacturing facilities for our products or product candidates fail to comply with applicable regulatory requirements, a regulatory agency may:

- impose restrictions on the marketing or manufacturing of a product, suspend or withdraw product approvals, revoke necessary licenses or suspend product reimbursement;
- impose injunctions, suspensions or revocations of necessary approvals or other licenses;
- issue warning letters, show cause notices or untitled letters describing alleged violations, which may be publicly available;
- suspend any ongoing clinical trials;
- delay or refuse to approve pending applications or supplements to approved applications filed by us;
- refuse to permit drugs or precursor chemicals to be imported or exported to or from the United States;
- suspend or impose restrictions on operations, including costly new manufacturing requirements;
- seize or detain products or require us to initiate a product recall; or
- commence criminal investigations and prosecutions.

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Moreover, existing regulatory approvals and any future regulatory approvals that we obtain will be subject to limitations on the approved indicated uses for which the product may be marketed, the conditions of approval, requirements for potentially costly, post-market testing and requirements for surveillance to monitor the safety and efficacy of the product. In the EEA, the advertising and promotion of pharmaceuticals is strictly regulated. The direct-to-consumer promotion of prescription pharmaceuticals is not permitted, and some countries of the EEA require the notification and/or prior authorization of promotional or advertising materials directed at healthcare professionals. The FDA, EMA, EC and other authorities in the EEA countries strictly regulate the promotional claims that may be made about prescription products, and our product labeling, advertising and promotion are subject to continuing regulatory review. Physicians nevertheless may prescribe our product to their patients in a manner that is inconsistent with the approved label or that is off-label. Positive clinical trial results in any of our RP103 programs increase the risk that immediate-release cysteamine bitartrate may be used off-label in those indications in certain geographic areas due to the lower cost of immediate-release cysteamine bitartrate. If we are found to have improperly promoted off-label uses, we may be subject to significant sanctions, civil and criminal fines and injunctions prohibiting us from engaging in specified promotional conduct.

In addition, engaging in improper promotion of our products for off-label uses in the United States can subject us to false claims litigation under federal and state statutes. These false claims statutes in the United States include the federal False Claims Act, which allows any individual to bring a lawsuit against a pharmaceutical company on behalf of the federal government alleging submission of false or fraudulent claims or causing to present such false or fraudulent claims for payment by a federal program such as Medicare or Medicaid. Growth in false claims litigation has increased the risk that a pharmaceutical company will have to defend a false claim action, pay civil money penalties, settlement fines or restitution, agree to comply with burdensome reporting and compliance obligations and be excluded from Medicare, Medicaid and other federal and state healthcare programs.

The regulations, policies or guidance of regulatory agencies may change and new or additional statutes or government regulations may be enacted that could prevent or delay regulatory approval of our product candidates or further restrict or regulate post-approval activities. For example, the Food and Drug Administration Safety and Innovation Act, or FDASIA, requires the FDA to issue new guidance describing its policy regarding internet and social media promotion of regulated medical products, and the FDA may soon specify new restrictions on this type of promotion. In January 2014, the FDA released draft guidance on how drug companies can fulfill their regulatory requirements for post-marketing submission of interactive promotional media, and though the guidance provided insight into how the FDA views a company's responsibility for certain types of social media promotion, there remains a substantial amount of uncertainty. We cannot predict the likelihood, nature or extent of adverse government regulation that may arise from pending or future legislation or administrative action, either in the United States or abroad. If we are unable to achieve and maintain regulatory compliance, we may not be permitted to market our drugs, which would adversely affect our ability to generate revenue and achieve or maintain profitability.

If we are unable to expand the use of RP103 and receive regulatory approval for any other indication or for other product candidates, we may delay or terminate some of our product development activities, which would adversely affect the long term value of RP103 or other product candidates and our growth prospects.

The research, testing, manufacturing, labeling, approval, sale, marketing and distribution of drug products, among other things, are subject to extensive regulation by the FDA and other regulatory authorities in the United States and by similar foreign regulatory governmental entities. We are not permitted to market any of our drug product candidates unless we obtain and maintain appropriate pre-market approvals from regulatory agencies in each of the markets in which we intend to market our products. Once approved, we may only market our products for the specific uses that are reflected in the product's approved labeling. A product's approved labeling may contain limitations or warnings or may be for different patient populations or for fewer or more limited indications than what we requested in our pre-market approval application, which could result in reimbursement complications, limit access for intended use or limit the commercial profile of the drug. In the United States, we are permitted to market the active pharmaceutical ingredient of RP103 in the formulation of a final drug product and in the doses approved under the brand name PROCYSBI only for the management of nephropathic cystinosis in adults and children six years and older under the brand name PROCYSBI. We are permitted to market PROCYSBI in the EEA as an orphan medicinal product for the treatment of proven nephropathic cystinosis. We do not have approval of RP103 in any other market nor for any other disease indication. There can be no assurance that we will obtain regulatory approval for any other uses for PROCYSBI or any of our other product candidates or that, even if we obtained additional approvals, we would be able to commercialize the product candidates successfully.

A new drug application, or NDA, submitted to the FDA, or a marketing authorization application, or MAA, submitted to the European Medicine Agency, or the EMA, must be supported by extensive clinical and preclinical data, as well as extensive information regarding chemistry, manufacturing and controls. This information must demonstrate the safety and efficacy of the applicable product candidate for the management of each individual indication to the satisfaction of the applicable regulatory authority. Obtaining approval of an NDA, MAA or any other filing for marketing authorization in a foreign country is an extensive, expensive and uncertain process. The time required to obtain approval by the FDA and comparable foreign authorities is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. The FDA, EC or other regulatory authorities may delay, limit or deny approval of RP103 or our future drug product candidates for many reasons, including:

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- the results of clinical trials may not meet the level of statistical or clinical significance required by regulatory authorities for approval;
- regulatory authorities may disagree with the number, design, size, conduct or implementation of our clinical trials; they may change the requirements for approval even after having reviewed and commented on the design for our clinical trials;
- regulatory authorities may not find the data from preclinical studies and clinical trials sufficient to demonstrate that product candidates have adequate clinical and other benefits or adequate safety profiles, even if they achieve their specified endpoints in clinical trials; or they may disagree with our interpretation of data from preclinical studies or clinical trials and require that we conduct additional trials;
- regulatory authorities may not accept data generated at our clinical trial sites;
- regulatory authorities may have difficulties scheduling an advisory committee meeting (or equivalent, if required) in a timely manner, or the advisory committee may recommend against approval of our application or may recommend that the regulatory agency require, as a condition of approval, additional preclinical studies or clinical trials; approval may also be contingent on a Risk Evaluation and Mitigation Strategy, which limits the labeling, distribution or promotion of a drug product;
- regulatory authorities may require additional preclinical or clinical studies or other data prior to granting approval, and we may not be able to generate the required data on a timely basis, if at all;
- regulatory authorities may identify deficiencies in the manufacturing processes or in the facilities of our third-party suppliers and/or contract manufacturers or may require us to manufacture additional validation batches or change our process, specifications or third-party suppliers or contract manufacturers; and
- we may not be able to validate our manufacturing process to the satisfaction of the regulatory authorities, or they may not agree with our plan for potential retrospective validation.

If we fail to gain regulatory approval for RP103 for other indications or our other future drug product candidates, we will have to delay or terminate some or all of our research product development programs, and our business, results of operations and financial condition will be materially adversely affected.

We do not have internal manufacturing capabilities. Throughout most of 2015, we expect to continue to rely on a single source supplier for our active pharmaceutical ingredient, or API, and a single third-party manufacturer for the conversion to finished drug product. We also rely on third parties for the distribution and pharmaceutical services of PROCYSBI in the United States and the EEA. If we are unable to rely on these third parties, our revenue will be delayed or diminished and our business, results of operations and financial condition will be materially adversely affected.

We do not own or operate manufacturing facilities and currently lack the in-house capability to manufacture PROCYSBI or RP103. As a result, we currently contract with external contract manufacturing organizations, or CMOs, for commercial and clinical quantities of PROCYSBI and RP103 for the indications under development. We rely on a single source supplier for our cysteamine API. While we have procured additional manufacturing support with a second supplier for clinical supply of our finished drug product, for the majority of 2015, we will continue to rely on a single third-party manufacturer for supply of finished products until the second supplier can be validated and provide finished product. Our ability to obtain sufficient quantities of PROCYSBI and RP103 is constrained by limited supplies of raw materials and the limited capacity and output of these third parties. Furthermore, any reduction, delay or interruption in our supply of API from the single source supplier or of our supply of finished goods from our CMO, together with any additional required efforts to identify and qualify alternative sources of API supply, could result in significant additional operating costs, interruptions in product supply, delays in sales of PROCYSBI and delays in developing RP103 for additional indications. In addition, supply arrangements from alternative sources not currently under contract may not be available on acceptable economic terms, if at all.

The manufacture of pharmaceutical products requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of pharmaceutical products often encounter difficulties in production, particularly in scaling up initial production to commercial requirements. Difficulties may arise related to internal processes, production costs and yields, quality control, including stability of the product and quality control testing, sourcing scarcities, resource constraints, equipment problems, shortages of qualified personnel, labor disputes, severe weather events, unstable political environments or financial difficulties at foreign facilities, as well as compliance with strictly enforced federal, state and foreign regulations. Manufacturers may breach their agreements with us or may terminate or decline to renew their agreements with us, whether due to our breach of the relevant agreements or based on their own business priorities. In addition, due to our small patient population, the manufacture of our drug may be given lower prioritization on the production line if manufacturing prioritization is decided by scale.

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Manufacturers and suppliers are subject to regulatory requirements covering, among other things, manufacturing, process controls, testing, quality control and record keeping and are subject to ongoing inspections by regulatory agencies. We have no direct control over the ability of our contract manufacturing parties to maintain adequate quality control, quality assurance and qualified personnel, and while final outputs are reviewed by our own internal quality control, we depend on our third-party supplier and manufacturers for compliance with the FDA's current cGMP requirements and other FDA requirements, the Drug Enforcement Administration's regulations and other rules and regulations prescribed by applicable non-U.S. regulatory authorities. If our contract manufacturing partners cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or other regulatory authorities, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities, and we may experience long delays and interruptions to our manufacturing supply and increased costs.

Pursuant to ongoing obligations from our NDA for PROCYSBI, we are required to collect and submit data to the FDA regularly regarding our currently observed clinical and commercial product profile and overall product safety assessment. While our current inventory falls within the specifications used during our clinical trials that support our NDA in the U.S. and marketing authorization application, or MAA, in Europe, we are currently evaluating our product specifications limit in light of new analytic data characterizing impurities and related substances and intend to submit requests to regulators in the U.S. and Europe for approval of revised PROCYSBI and RP103 specifications. We expect that there will continue to be intermittent delays in manufacturing or release of drug product as these issues are identified and addressed, and future release of drug product may depend on agreement of those and future specifications updates. If regulators reject our proposal to modify the specifications or require additional data to support the updated specifications, our ability to release drug product may be limited. Although we have stock of PROCYSBI on hand and believe we have enough PROCYSBI inventory to meet our near-term commercial needs in both the United States and the EEA, if there are material delays in the regulators' review and potential approval, we may experience an inventory shortfall, which would have a material adverse effect on sales of PROCYSBI.

If we or our third-party suppliers and manufacturers fail to comply with applicable regulatory requirements, we could experience significant delays or interruptions to our manufacturing supply that may result in the delay or suspension of our pre-clinical or clinical trials. In addition, a regulatory agency could issue warning letters or untitled letters, seek an injunction, impose civil or criminal penalties or monetary fines, suspend or withdraw regulatory approval, suspend any ongoing clinical trials, refuse to approve pending applications or supplements to applications, suspend or impose restrictions on operations, including costly new manufacturing requirements, seize or detain products or request that we initiate a product recall.

We also rely on a third-party logistics provider and specialty pharmacy to distribute PROCYSBI to patients in the United States and to pharmacies in the EEA and to collect from insurance companies and government agencies in the United States and from pharmacies in the EEA. Our ability to collect from a particular logistics provider is not only subject to such provider's credit worthiness but is also dependent, in part, on its ability to arrange for full reimbursement from third-party payors. The outsourcing of our distribution function is complex, and we may experience difficulties that could reduce, delay or stop shipments of PROCYSBI. If we encounter such distribution problems, and we are unable to quickly enter into a similar agreement with another specialty distributor on substantially similar terms, if at all, the distribution of PROCYSBI could become disrupted, resulting in reduced revenues, healthcare provider dissatisfaction and/or patient dissatisfaction, which may materially adversely affect our business, results of operations and financial condition.

If any of these events were to occur, our reputation would be harmed, revenues from sales of our products would be delayed or diminished and our business, results of operations and financial condition would be materially adversely affected.

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If serious adverse side effects become associated with PROCYSBI, our business, results of operations and financial condition will be materially adversely affected.

The prescribing information for PROCYSBI includes several warnings relating to observed adverse reactions of cysteamine bitartrate usage. The FDA may require products approved under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, or FDCA, to bear the same or similar warning statements as the reference product used in the approval. We expect to update adverse reactions listed in the prescribing information based on continued commercial use and additional clinical trials. If additional adverse reactions emerge, or if there is a pattern of severe or persistent previously observed side effects in the relevant patient populations, the FDA, the EMA or other regulatory agencies could modify or revoke our marketing approval, require us to modify our label or require us to suspend production, require a product recall, or we may choose to withdraw PROCYSBI from the market. Regulatory authorities could also require us to change the way the product is administered or modify the product in some other way, or they could require us to conduct additional clinical trials or costly post-marketing testing and surveillance to monitor the safety or efficacy of the product. If this were to occur, we may be unable to maintain marketing approval in our approved indications and/or obtain marketing approval in other indications. In addition, patients or their representatives may bring claims against us alleging serious adverse side effects or harm suffered as a result of use of PROCYSBI. Any such side effects or related claims could have a material adverse effect on our business, results of operations and financial condition. See also the risk factor titled "*We may be subject to product liability claims*."

If we fail to demonstrate safety or efficacy in our preclinical studies or clinical trials or to keep to the terms of a product development program, our future business prospects for these drug product candidates will be materially adversely affected.

Clinical trials are very expensive, time consuming and difficult to design and implement. The outcome of clinical trials is uncertain, and results of earlier studies and trials may not be predictive of future trial results. Delays in the commencement or completion of clinical testing for RP103 or pre-clinical or clinical testing for any of our other product candidates could significantly affect our product development costs and business plan.

Preclinical studies involve testing in appropriate multiple non-human disease models to demonstrate efficacy and safety. Regulatory agencies evaluate these data carefully as part of their determination whether to authorize clinical testing in humans. If certain preclinical data reveal potential safety issues or if the results are inconsistent with an expectation of the drug product candidate's efficacy in humans, the regulatory agencies may require additional testing before allowing human clinical trials. This additional testing will increase program expenses and extend timelines. There are many potential preclinical models to test for different disease states, and we could fail to choose the best preclinical model to determine proof of concept, safety and efficacy of our drug product candidates. We may decide to suspend further testing on our drug product candidates or technologies if, in the judgment of our management and advisors, the preclinical test results do not support further development.

Following successful preclinical testing, drug product candidates must be tested in a clinical development program to provide data on safety and efficacy in humans prior to becoming eligible for product approval and licensure by regulatory agencies. Success in preclinical testing and early clinical trials does not ensure that later clinical trials will be successful. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through preclinical studies and initial clinical trials. Clinical trials may also be delayed or repeated as a result of ambiguous or negative interim results or unforeseen complications in testing. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials. The clinical trial process may fail to demonstrate with statistical significance that our drug product candidates are safe for humans and effective for indicated uses. This failure may cause us to abandon a drug product candidate and may delay development of other drug product candidates. Any delay in, or termination of, our preclinical testing or clinical trials will delay the filing of relevant marketing applications with regulatory agencies and, ultimately, our ability to commercialize our drug product candidates and generate revenues from related products.

The rate of completion of any clinical trials will be dependent upon, among other factors, the rate of patient enrollment. Patient enrollment is a function of many factors, including the size of the patient population, the nature of the trial, the nature of the disease or medical condition being studied, the availability of alternative therapies and drugs, the proximity of patients to clinical sites and the eligibility criteria for the study. Delays in planned patient enrollment may result in increased costs and delays. In addition, because many of our clinical trials involve small patient populations, the results of these early clinical trials may not be indicative of future results.

Under the Prescription Drug User Fee Act, the FDA seeks to respond to NDAs within ten months of the filing date, but this timeframe is often extended. For example, a sponsor may seek FDA designation of a drug candidate as a "fast track product." Fast track products are those products intended for the treatment of a serious or life-threatening disease or condition and which demonstrate the potential to address unmet medical needs for such disease or condition. If fast track designation is obtained, the FDA may initiate review of sections of an NDA before the application is complete. This "rolling review" is available if the applicant provides and the FDA approves a schedule for the remaining information. In addition, FDASIA established a new category of drugs referred to as "breakthrough therapies," which are defined as drugs intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. In the future, we may request breakthrough designation or fast track designation from the FDA for our other drug product candidates, but we there can be no assurance that we will obtain such designations. Moreover, even if we obtain breakthrough designation or fast track designation from the FDA, the designations do not guarantee that the FDA will approve our NDA, that the development program or review timeline will ultimately be shorter than if we had not obtained the designations or that the FDA will not request additional information, including additional clinical studies, during its review.

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We do not know whether our investigational new drug, or IND, applications for future products or the protocols for any future clinical trials will be accepted by the FDA. We do not know if our clinical trials will begin or be completed on schedule or at all. Even if completed, we do not know if these trials will produce clinically meaningful results sufficient to support an application for marketing approval. The commencement and completion of our planned clinical trials could be substantially delayed or prevented by several factors, including:

- a limited number of, and competition for, suitable patients with particular types of disease for enrollment in clinical trials;
- delays or failures in obtaining regulatory clearance to commence a clinical trial;
- delays or failures in obtaining sufficient clinical materials;
- inability to design appropriate clinical trial protocols;
- delays or failures in reaching agreement on acceptable clinical trial agreement terms or clinical trial protocols with prospective sites;
- inability of our clinical research organizations, or CROs, or other third-party contractors to comply with all contractual requirements or to perform their services in a timely or acceptable manner;
- inability by us, our CROs or their employees to conduct the clinical trial in accordance with all applicable FDA, Drug Enforcement Administration or other regulatory requirements or our clinical protocols;
- lack of efficacy during, or other unfavorable results from, clinical trials or pre-clinical studies;
- discovery of serious or unexpected toxicities or side effects experienced by study participants or other unforeseen safety issues;
- failure of patients to complete the clinical trial, or inability or unwillingness of patients or medical investigators to follow our clinical trial protocols;
- inability to monitor patients adequately during or after treatment;
- regulatory action by the FDA or other regulatory authorities; and
- lack of adequate funding to continue the clinical trial, including the incurrence of any unforeseen costs.

In addition, changes in applicable regulatory requirements and guidance may occur, and we may need to amend clinical trial protocols to reflect these changes. Amendments may require us to resubmit our clinical trial protocols to Institutional Review Boards for reexamination, which may affect the costs, timing or successful completion of a clinical trial.

Sales of our products outside of the United States are also subject to foreign regulatory requirements governing clinical trials, manufacturing and marketing approvals. Even if the FDA and EC grant marketing approval for a product candidate, comparable regulatory authorities of foreign countries must also approve the manufacturing and marketing of our product candidates in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and greater than, those in the United States, including additional preclinical studies or clinical trials or manufacturing and control requirements. In many countries outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In many cases, the price that we propose to charge for our products is also subject to approval by individual countries before we can launch our product candidates in those countries. Obtaining foreign regulatory approvals, complying with foreign regulatory requirements and gaining approved pricing and reimbursement could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries. Further, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries. Regulatory approval in one country does not ensure approval in any other country, while a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory approval process in others.

Any delay in our preclinical or clinical programs or the failure to demonstrate safety or efficacy in our clinical trials would have a material adverse effect on our business, results of operations and financial condition.

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If we fail to maintain orphan drug or other regulatory exclusivity for PROCYSBI or to obtain and maintain exclusivity for our orphan drug product candidates, our competitors may sell products to treat the same conditions, possibly at lower prices, and our revenues will be significantly reduced.

PROCYSBI has received marketing approval from the FDA for the management of nephropathic cystinosis in adults and children six years and older and seven years of market exclusivity as an orphan drug in the United States. PROCYSBI has also received approval as an orphan medicinal product for the management of proven nephropathic cystinosis and 10 years of market exclusivity in the EEA. As part of our business strategy, we intend to develop RP103, and potentially other drugs, for additional therapeutic indications that may be eligible for FDA and EMA orphan drug designation.

Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug intended to treat a rare disease or condition, defined as a patient population of less than 200,000 in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. The company that first obtains FDA approval for a designated orphan drug for a given rare disease receives marketing exclusivity for use of that drug for the stated condition for a period of seven years, plus an additional six months if designated for a pediatric indication.

In the EU, the EMA's Committee for Orphan Medicinal Products grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the EU and for which no satisfactory method of diagnosis, prevention or treatment has been authorized (or if the product would be a significant benefit to those affected). In addition, designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition as well as when it is unlikely that sales of the drug in the EU would be sufficient to justify the necessary investment in developing the medicinal product without incentives. An EU orphan drug designation entitles a party to financial incentives such as reduced fees or fee waivers, and 10 years of market exclusivity is granted following medicinal product approval. This period may be reduced to six years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. An applicant must request orphan drug designation before submitting an application for marketing approval.

Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

Even though we have been granted orphan drug designation in the United States and in the EU prior to the approval of RP103 for the potential treatment of HD, and even if we obtain orphan drug designation for our future drug product candidates, we may not fulfill the criteria for exclusivity, or we may not be the first to obtain marketing approval for any orphan indication. Further, even if we obtain orphan drug exclusivity for a particular product, that exclusivity may not effectively protect the product from competition because different drugs can be approved for the same condition. Even after an orphan drug is approved, the FDA can subsequently approve a drug for the same condition if the FDA concludes that the later drug is safer, more effective or makes a major contribution to patient care. Orphan drug exclusive marketing rights may also be lost if the FDA later determines that the request for designation was materially defective, if a subsequent product is deemed clinically superior or if the manufacturer is unable to deliver sufficient quantities of the drug.

Because the extent and scope of patent protection for some of our drug products may be particularly limited, orphan drug designation is especially important for our eligible products and we plan to rely on the orphan exclusivity period to maintain a competitive position. However, if we do not obtain and/or maintain orphan drug exclusivity for RP103, or if our drug products do not have strong patent protection, our competitors may sell the same drug to treat the same condition, possibly at lower prices, and our revenues will be reduced. Also, without strong patent protection, competitors may sell a generic version of our products upon the expiration of orphan exclusivity if our patent position is not upheld.

If our competitors succeed in developing products and technologies that are more effective than our own, or if scientific developments change our understanding of the potential scope and utility of our drug product candidates, then our technologies and future drug product candidates may be rendered less competitive.

We face significant competition from industry participants that are pursuing technologies similar to those that we are pursuing and are developing pharmaceutical products that are competitive with PROCYSBI or our drug product candidates. Many of the pharmaceutical companies in areas competitive with us have greater capital resources, larger overall research and development staff and facilities and a longer history in drug discovery, development, regulatory approval, manufacturing and marketing than we do. With these additional resources and experience, our competitors may be able to respond to rapid and significant technological changes in the biotechnology and pharmaceutical industries faster than we can.

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We expect that the technologies associated with biotechnology research and development will continue to develop rapidly. Our future success will depend in large part on our ability to maintain a competitive position with respect to these technologies. Rapid technological development, as well as new scientific developments, may result in our compounds, drug products, drug product candidates or processes becoming obsolete before we can recover any or all of the expenses incurred to develop them. For example, changes in our understanding of the appropriate population of patients who should be treated with a targeted therapy like those we are developing may limit the drug's market potential if it is subsequently demonstrated that only certain subsets of patients should be treated with the targeted therapy.

Because the target patient populations for PROCYSBI and some of our drug product candidates are small, we must achieve significant market share and obtain relatively high per-patient prices for our products to achieve meaningful gross margins.

PROCYSBI and our clinical development of RP103 target diseases with small patient populations, including cystinosis and Huntington's Disease, or HD, respectively. To successfully commercialize a drug product for these indications, we must identify patients and a targeted prescriber base for the drug product. Due to small patient populations, we believe that we would need to have significant market penetration to achieve meaningful revenues. In addition, the per-patient prices at which we sell PROCYSBI and RP103 for these indications will need to be relatively high in order for us to generate an appropriate return for the investment in these product development programs and to achieve meaningful gross margins. Patients who discontinue therapy or do not fill prescriptions are not easily replaced by new patients because of the limited patient population. There can be no assurance that we will successfully obtain or maintain sufficient market share or per-patient prices. Because the potential target populations are very small, even if we obtain significant market share for PROCYSBI and RP103, we may never achieve profitability despite obtaining such significant market share.

Our development strategy for RP103 depends upon the FDA's prior findings of safety and effectiveness of cysteamine bitartrate based on data not developed by us but upon which the FDA may rely in reviewing any future NDA.

The Hatch-Waxman Amendments added to the FDCA Section 505(b)(2), which permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference. Under this statutory provision, the FDA may rely, for purposes of approving an NDA, on safety and effectiveness data not developed by the filer of the NDA. We also plan to submit an NDA for RP103 for approval of other indications under Section 505(b)(2), and if we are able to submit those NDAs, they will rely, in part, on the FDA's previous findings of safety and effectiveness for cysteamine bitartrate. Even though we may be able to take advantage of Section 505(b)(2) to support potential U.S. approval for these additional product candidates, the FDA may require us to perform additional studies or measurements to support approval. In addition, the FDA's interpretation and use of Section 505(b)(2) has been controversial and has previously been challenged in court, though without a definitive ruling on the propriety of the FDA's approach. Future challenges, including a direct challenge to the approval of our products and product candidates, may be possible and, if successful, could limit or eliminate our ability to rely on the Section 505(b)(2) pathway for the approval of RP103 and our other product candidates. Such a result could require us to conduct additional testing and costly clinical trials, which could substantially delay or prevent the approval and launch of any future product candidates and would materially adversely affect our business, results of operation and financial condition.

If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs in the United States, we could be subject to additional reimbursement requirements, penalties, sanctions and fines, which could have a material adverse effect on our business, results of operations and financial condition.

We participate in the Medicaid Drug Rebate Program, as administered by the Centers for Medicare & Medicaid Services, or CMS, and other federal and state government pricing programs in the United States, and we may participate in additional government pricing programs in the future. These programs generally require us to pay rebates or otherwise provide discounts to government payors in connection with drugs, including PROCYSBI, that are dispensed to beneficiaries of these programs. In some cases, such as with the Medicaid Drug Rebate Program, the rebates are based on pricing and rebate calculations that we report on a monthly and quarterly basis to the government agencies that administer the programs. Pricing and rebate calculations are complex, vary among products and programs, and are often subject to interpretation by governmental or regulatory agencies and the courts. The terms, scope and complexity of these government pricing programs change frequently. Responding to current and future changes may increase our costs and the complexity of compliance will be time consuming.

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In addition, the Office of Inspector General has recently increased its focus on the methodologies used by manufacturers to calculate average manufacturer price, or AMP, and best price, or BP, to assess manufacturer compliance with reporting requirements under the Medicaid Drug Rebate Program. We are liable for errors associated with our submission of pricing data and for any overcharging of government payors. For example, failure to submit monthly/quarterly AMP and BP data on a timely basis could result in a civil monetary penalty of $10,000 per day for each day the submission is late beyond the due date. Failure to make necessary disclosures and/or to identify overpayments could result in allegations against us under the Federal False Claims Act and other laws and regulations.

Any required refunds to the U.S. government or responding to a government investigation or enforcement action would be expensive and time consuming and could have a material adverse effect on our business, results of operations and financial condition. In the event that the CMS were to terminate our rebate agreement, no federal payments would be available under Medicaid or Medicare for our covered outpatient drugs.

Pressure from third-party payor coverage, reimbursement and pricing policies may impair our customers' ability to be reimbursed for PROCYSBI and our other future product candidates at adequate prices or on adequate terms, which may in turn materially adversely affect our business, results of operations and financial condition.

Market acceptance and sales of PROCYSBI and any product candidates that we may develop will depend in large part on third-party payor coverage and reimbursement policies and may be affected by future healthcare reform measures in the United States, the EEA countries and other key international markets. The continuing efforts of governmental and other third-party payors to contain, reduce or shift the costs of healthcare through various means, including an increased emphasis on managed care and attempts to limit or regulate the price of medicinal products and services, particularly for new and innovative products and therapies, may result in downward pressure on pricing, reimbursement and utilization, which may adversely affect our product sales and results of operations. Moreover, because private health insurers and other third-party payors often follow the coverage and reimbursement policies of government payors, including the Medicare and Medicaid programs, cost-containment measures under these programs play a particularly significant role in the reimbursement landscape. The government programs relevant to our products include, without limitation, the following:

- the Medicaid Drug Rebate Program, under which manufacturers must report pricing information and pay rebates in order for their drug products to be covered under state Medicaid programs;
- the Public Health Service's 340B Drug Pricing Program, under which manufacturers must offer discounts to certain healthcare organizations that care for underserved populations;
- the Department of Veterans Affairs' Federal Supply Schedule pricing program, under which manufacturers agree to offer drugs to certain governmental providers at reduced rates;
- the TRICARE Retail Pharmacy Program, under which manufacturers must agree to honor certain discounted prices, specifically Federal Ceiling Prices under the Veterans Health Care Act, as a condition for placement in the Department of Defense uniform formulary; and
- the Medicare Part D program, under which manufacturers contract with plan sponsors to offer certain outpatient drugs to Medicare beneficiaries.

In addition, in the United States, third-party payors often develop cost containment measures using policies that specifically target specialty products and high-cost drugs. For example, formulary placements may be less favorable for brand and higher-costing drugs, which may result in, among other things, greater out-of-pocket costs to patients. PROCYSBI often is subject to such measures, and similar future policies addressing such cost-containment measures may also affect PROCYSBI.

Further, third-party payors also are increasingly considering new metrics as the basis for reimbursement rates, such as average sales price, AMP or actual acquisition cost, and for cost-benefit analyses with comparable drugs. Although the changes to reimbursement methodologies are generally intended to limit payment increases, it is difficult to project the impact of these and other alternative reimbursement methodologies on the willingness of payors to reimburse PROCYSBI and any product candidates that we may develop. To date, PROCYSBI generally has been covered and reimbursed in the United States and the select countries we have entered in Europe, but we do not know whether third-party payors will continue to cover and reimburse PROCYSBI in these markets or at the level PROCYSBI is currently covered, will reimburse PROCYSBI in other EEA countries or will reimburse RP103 and our future products until we enter into payor negotiations. If coverage and reimbursement are not available or are available only at limited levels, our business, results of operations and financial condition will be materially adversely affected.

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Legislative changes may increase the difficulty and cost for us to commercialize PROCYSBI or any other product candidate that we develop and affect the prices we may obtain.

In the United States, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that restrict or regulate post-approval activities. The changes may affect our ability to sell PROCYSBI or any other product candidate for which we obtain marketing approval at adequate prices.

In 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, which we refer to together as the "Affordable Care Act," was adopted. This law intends to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. The Affordable Care Act, among other things:

- increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program;
- revised the definition of AMP for reporting purposes, which could further increase the amount of rebates paid by manufacturers under the Medicaid Drug Rebate Program;
- extended the Medicaid Drug Rebate Program to beneficiaries enrolled in Medicaid managed care organizations;
- addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected and for oral solid line extensions and reformulated drugs, which, depending on how the provision is interpreted and implemented, could increase our Medicaid rebate rate substantially;
- imposed a significant annual fee on companies that manufacture or import branded prescription drug products and established an annual non-deductible fee on entities that sell branded prescription drugs or biologics to specified government programs in the United States, beginning in 2011;
- expanded the 340B drug discount program (excluding orphan drugs), including the creation of new penalties for non-compliance; and
- included a 50% point-of-sale discount off negotiated prices on applicable brand-name drugs for Medicare Part D participants in the coverage gap, or "donut hole," as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D.

Other legislative and regulatory changes have also been proposed and adopted in the United States since the enactment of the Affordable Care Act. On August 2, 2011, the Budget Control Act of 2011 created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These automatic reductions included aggregate reductions of Medicare payments to providers of 2%. These reductions went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2024 unless additional Congressional action is taken.

In addition, legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. Increased scrutiny by the U.S. Congress of the FDA's approval process may subject us to more stringent product labeling and post-marketing testing and other requirements, and delays in feedback from the FDA may affect our ability to update or adjust our label in a timely manner in the interest of patient adherence and tolerability. We cannot predict whether other legislative changes will be adopted or how such changes would affect the pharmaceutical industry generally and the commercialization of PROCYSBI specifically.

Legislative changes regarding manufacturers' rebate obligations for new formulations of oral solid dosage form drugs under the Medicaid Drug Rebate Program, if applied to PROCYSBI, would have a material adverse effect on our business, results of operations and financial condition.

The Affordable Care Act created a new formula to determine the rebate amount owed by manufacturers of "line extension" drugs that would likely lead to higher rebates owed by such manufacturers under the Medicaid Drug Rebate Program. The Affordable Care Act defined a line extension drug to mean a new formulation of a drug, "such as an extended release formulation." In April 2010, CMS stated that it would issue additional guidance to manufacturers and other stakeholders concerning line extensions of existing drugs. In 2012, in implementing the new law, CMS proposed a broad definition of a line extension drug to include any single source or innovator multiple source drug that is an oral solid dosage form approved by the FDA as a change to the initial brand name listed drug; a new formulation of a previously approved oral solid dosage form drug; a new combination of two or more oral solid dosage form drugs; or a new indication for an already marketed oral solid dosage form drug. In the proposed rule, orphan drugs were included as part of the definition of a line extension drug. Although CMS has not yet issued a final rule, CMS expects to finalize the rule in 2015. In the event that CMS finalizes the rule as currently proposed, PROCYSBI would likely be subject to the new rebate calculations under the Medicaid Drug Rebate Program, and, as a result, PROCYSBI sales to Medicaid beneficiaries would be reimbursed at cost and any profits from those sales would be eliminated. Approximately 20% of our current PROCYSBI sales are to Medicaid beneficiaries. Accordingly, the implementation of the proposed rules may have a material adverse effect on our business, results of operations and financial condition.

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We are subject, directly and indirectly, to federal and state healthcare fraud and abuse laws, false claims laws, physician payment transparency laws, corrupt practices and bribery laws and health information privacy and security laws. Failure to comply with these laws may subject us to substantial penalties.

We do not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid or other third-party payors. However, federal and state healthcare laws and regulations pertaining to fraud and abuse, physician payment transparency and privacy and security laws and regulations apply to us and our arrangements with healthcare providers, customers and other entities, including our marketing practices, educational programs and pricing policies. These laws include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in exchange for or to induce either the referral of an individual for, or the purchase, order or recommendation of, any good or service for which payment may be made under federal healthcare programs, such as the Medicare and Medicaid programs. A person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation; in addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act;
- federal false claims laws which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid or other federal third-party payors that are false or fraudulent;
- the federal Civil Monetary Penalties law, which prohibits, among other things, offering or transferring remuneration to a federal healthcare beneficiary that a person knows or should know is likely to influence the beneficiary's decision to order or receive items or services reimbursable by the government from a particular provider or supplier;
- federal criminal laws that prohibit executing a scheme to defraud any federal healthcare benefit program or making false statements relating to healthcare matters. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it to have committed a violation;
- the federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, which governs the conduct of certain electronic healthcare transactions and protects the security and privacy of protected health information;
- the federal Physician Payment Sunshine Act, which requires manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually to CMS information related to payments or other "transfers of value" made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, and requires applicable manufacturers and group purchasing organizations to report annually to CMS ownership and investment interests held by the physicians described above and their immediate family members and payments or other "transfers of value" to such physician owners (manufacturers are required to submit reports to CMS by the 90th day of each calendar year);
- in the EEA, in various member states including France, the United Kingdom, the Netherlands, Italy and Spain, rules adopted by the legislator or self-regulatory industry bodies requiring the notification and/or publication of certain transfers of value from pharmaceutical companies to healthcare professionals (for example, France has recently adopted legislation (Law No. 2011-2012, or the "French Sunshine Act," and Decree no. 2013-414 which implements it) requiring pharmaceutical companies to disclose and publish agreements with or transfers of value to healthcare professionals);

- the U.S. Foreign Corrupt Practices Act, or the FCPA, which prohibits corporations and individuals from paying, offering to pay or authorizing the payment of anything of value to any foreign government official, government staff member, political party or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in an official capacity; the UK Bribery Act, which prohibits both domestic and international bribery, as well as bribery across both public and private sectors; and bribery provisions contained in the German Criminal Code, which, pursuant to draft legislation being prepared by the German government, may make the corruption and corruptibility of physicians in private practice and other healthcare professionals a criminal offense; and
- analogous state and foreign law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payor, including commercial insurers; state laws that require pharmaceutical companies to comply with the industry's voluntary compliance guidelines and the applicable compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

The risk of our being found in violation of these laws is increased by the fact that many of them have not been fully interpreted by the regulatory authorities or the courts, and their provisions are open to a variety of interpretations. In addition, as we expand our development and commercialization activities outside of the United States, we will need to establish and expand business relationships with various third parties, such as independent contractors, distributors, vendors, advocacy groups and physicians, and we will interact more frequently with foreign officials, including regulatory authorities and physicians employed by state-run healthcare institutions who may be deemed to be foreign officials under the FCPA, the UK Bribery Act or similar laws of other countries that may govern our activities. Any interactions with any such parties or individuals where compensation is provided that are found to be in violation of such laws could result in significant civil and criminal penalties.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available under such laws, it is possible that some of our business activities, including our relationships with physicians and other healthcare providers, some of whom recommend, purchase and/or prescribe our products, could be subject to challenge under one or more of such laws. We are also exposed to the risk that our employees, independent contractors, principal investigators, consultants, vendors, distributors and CROs may engage in fraudulent or other illegal activity. While we have policies and procedures in place prohibiting such activity, misconduct by these parties could include, among other infractions or violations, intentional, reckless and/or negligent conduct or unauthorized activity that violates FDA regulations, including those laws that require the reporting of true, complete and accurate information to the FDA, manufacturing standards, federal and state healthcare fraud and abuse laws and regulations, laws that require the true, complete and accurate reporting of financial information or data or other commercial or regulatory laws or requirements. It is not always possible to identify and deter misconduct by our employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If our operations are found to violate any of the laws described above or any other laws and regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs and imprisonment, any of which could adversely affect our ability to market PROCYSBI, RP103 and other future drug candidates and materially adversely affect our business, results of operations and financial condition. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. See also the risk factor titled "*If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs in the United States, we could be subject to additional reimbursement requirements, penalties, sanctions and fines which could have a material adverse effect on our business, results of operations and financial condition*."

Our reliance on third parties may result in delays in completing, or a failure to complete, preclinical testing, clinical trials or regulatory marketing submissions.

In the course of product development, we engage and collaborate with a variety of external organizations to perform services essential to drug product development. The organizations which perform services may include, but are not limited to: governmental agencies and university laboratories; other biotechnology and pharmaceutical companies; CMOs; CROs; distribution and supply (logistics) service organizations; contract testing organizations; consultants or consulting organizations with specialized knowledge based expertise; and intellectual property law firms.

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As a result of our engagement of these types of organizations to help us with our product development programs, many important aspects of our business are and will be out of our direct control. Nevertheless, we are responsible for ensuring that each of our product development programs complies with applicable regulatory requirements, and our reliance on these organizations does not relieve us of our regulatory responsibilities. If any such organizations we engage in the future fail to perform their obligations under our agreements with them or fail to perform in a satisfactory manner in compliance with applicable regulatory requirements, we may face delays in completing our development and commercialization processes for any of our drug product candidates and could be required to repeat testing or clinical trials, which would delay the regulatory approval process. Furthermore, any loss or delay in obtaining contracts with such entities may also delay the completion of our clinical trials, regulatory filings and the potential market approval of our drug product candidates.

Specifically, we have and will continue to rely on third parties, such as CROs and/or co-operative groups, to assist us in overseeing and monitoring clinical trials as well as to process the clinical results. Any failure of such third parties to perform or to meet the applicable standards will result in delays in or failures to complete trials. A failure by such third parties to observe the terms of a product development program for any particular product candidate or to complete the clinical trials for a product candidate in the anticipated time frame could materially adversely affect our business, results of operations and financial condition.

In addition, our dependence on collaborative arrangements with third parties subjects us to a number of risks that could harm our ability to develop and commercialize products:

- collaborative arrangements might not be available on terms which are reasonably favorable to us, or at all;
- disagreements with partners may result in delays in the development and marketing of products, termination of collaboration agreements or time consuming and expensive legal action;
- agreement terms may be difficult or costly to enforce;
- partners may not allocate sufficient funds or resources to the development, promotion or marketing of our product candidates, or may not perform their obligations as expected;
- partners may choose to develop, independently or with other companies, alternative products or treatments, including products or treatments which compete with ours;
- agreements with partners may expire or be terminated without renewal, or partners may breach agreements with us;
- business combinations or significant changes in a partner's business strategy or financial resources might adversely affect that partner's willingness or ability to fulfill its obligations to us; and
- the terms and conditions of the relevant agreements may no longer be suitable.

We cannot guarantee that we will be able to negotiate acceptable future collaboration agreements or that those currently in existence will make it possible for us to fulfill our objectives.

We depend on the support of key scientific and medical collaborators.

We must establish and maintain relationships with key opinion leaders, leading scientists and research institutions. We believe that such relationships are critical to establishing products as a standard of care for their approved indications. Although we have various medical and scientific advisors and research collaborations, there is no assurance that our advisors and our research collaborators will continue to work with us or that we will be able to attract additional advisors or collaborators. If we are not able to maintain existing or establish new clinical and scientific relationships to assist in our commercialization and research and development, we may not be able to establish our products as the standard of care or successfully develop our drug product candidates.

If we fail to maintain an effective system of internal controls, we may not be able to accurately report our financial results and prevent fraud.

The Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, requires, among other things, that we maintain effective internal control over financial reporting and disclosure controls and procedures. In particular, we must perform system and process evaluation and testing of our internal control over financial reporting to allow management to report on the effectiveness of our internal control over financial reporting, as required by Section 404 of the Sarbanes-Oxley Act. A report of our management is included under Item 9A. "Controls and Procedures" of this Annual Report on Form 10-K, and our auditors have provided an attestation report on our internal control over financial reporting in this annual report. During its evaluation of the effectiveness of internal control over financial reporting as of December 31, 2014, management identified a material weakness related to our inventory costing and overhead allocations for our commercial product PROCYSBI and determined that our review of our inventory costing and overhead allocations were not performed at a sufficiently detailed level to detect errors in our inventory and related accounts. With the oversight of management and our Audit Committee, we have initiated actions to address the root causes of the material weakness identified in 2014. There can be no assurance that such actions will be sufficient to remedy the material weakness identified or that additional material weaknesses or other control or significant deficiencies will not be identified in the future. If we continue to experience a material weakness in our internal controls or fail to maintain or implement required new or improved controls, such circumstances could cause us to fail to meet our periodic reporting obligations or result in material misstatements in our financial statements, or adversely affect the results of periodic management evaluations and annual auditor attestation reports. Each of the foregoing results could cause stockholders to lose confidence in our reported financial information and lead to a decline in our stock price. See Item 9A. "Controls and Procedures" for more information.

We may be subject to product liability claims.

The nature of our business exposes us to potential liability risks inherent in the testing (including through human trials), manufacturing and marketing of drugs. PROCYSBI and our drug product candidates could potentially harm people, and we may be subject to costly and damaging product liability claims regardless of actual harm. Many of the participants in our clinical trials and cystinosis patients who use PROCYSBI are already critically ill or suffering from chronic debilitating diseases. The waivers we obtain from participants in clinical trials may not be enforceable and may not protect us from liability or the costs of product liability litigation.

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We may not be able to avoid significant liability if any product liability claim is brought against us. Although we currently carry product liability insurance, it may not be sufficient to cover any claims. We may be unable to maintain product liability insurance in the future at satisfactory rates or in adequate amounts.

Regardless of the merits or eventual outcome, product liability claims may result in decreased demand for our product candidates, injury to our reputation, withdrawal of clinical trial participants and inability to continue clinical trials, costs to defend the related litigation, diversion of management's time, substantial monetary awards to trial participants, or patients, regulatory investigations, product recalls or withdrawals, labeling, marketing or promotional restrictions and loss of revenue, any of which may materially adversely affect our business, results or operations and financial condition.

Our success depends on our ability to manage our projected growth.

Our business strategy, including continued commercial sales of PROCYSBI in the United States and certain countries in the EEA, expansion of our commercial operations into other markets, the continuation of our clinical-stage programs and the in-license and acquisition of additional clinical-stage product candidates, will require us to retain existing and add required new qualified and experienced personnel in multiple functional areas over the next several years.

Our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. We may not be able to manage the expansion of our operations effectively, which may result in weaknesses in our infrastructure, operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could require significant capital expenditures and may divert financial resources from other projects, including additional product candidates.

In addition, in connection with the commercial launch of PROCYSBI in the EEA, we have expanded our operations in Europe where we expect to continue to add personnel. We may encounter difficulties successfully managing remotely a substantially larger and internationally diverse organization and may encounter delays in commercialization if we are not successful in integrating our international operations. Challenges related to managing international operations may arise from staffing and managing foreign operations, reduced or varied protection for intellectual property rights in some countries, potential strain on our financial and managerial controls and reporting systems and procedures, diverse individual country regulatory and statutory laws, the costs of maintaining EEA presence, in-country legal entities and related tax structures, fluctuations in currency exchanges and political and economic instability, including wars, terrorism and political unrest, boycotts, curtailment of trade and other business restrictions.

If our management is unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate revenue could be reduced, and we may not be able to implement our business strategy.

Credit risks from customers outside the United States may materially adversely affect our business, results of operations and financial condition.

Sales of our products to government supported customers outside of the United States are likely to be subject to significant payment delays due to government funding and reimbursement practices, which will result in an increase in the length of time that we may have accounts receivable outstanding. In addition, many governments in Europe are facing significant liquidity crises. If government reimbursement for sales of PROCYSBI or any future products in EEA countries is delayed or becomes unavailable, we may not be able to collect on amounts payable to us in reasonable time frames from such customers, which would cause our capital requirements to increase and would materially adversely affect our business, results of operations and financial condition.

Macroeconomic conditions could materially adversely affect our business, results of operations and financial condition.

Various macroeconomic factors, such as changes in inflation, interest rates, foreign currency exchange rates and overall business and economic conditions and uncertainties, including those resulting from conditions in the global financial markets, could adversely affect our business, results of operations and financial condition. For example, if inflation or other factors were to significantly increase our business costs, it may not be feasible to increase the price of PROCYSBI or any future products due to reimbursement procedures and other pricing pressures.

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In the recent past, the global financial crisis caused financing to be unavailable in many cases or caused the cost of financing to significantly increase. Any similar disruption in the financial markets may increase uncertainty in the debt and equity markets, which may adversely affect our ability to access financing on favorable terms in the future. In addition, our suppliers, manufacturers and other third parties important to our business also may be negatively affected by such potential market dislocations and disruptions, and their businesses may be disrupted, which could materially adversely affect our business, results of operations and financial condition.

Our product sales in the United States could be reduced by imports from countries where our products are available at lower prices.

Our recognized product sales in the United States may be reduced if PROCYSBI is imported into the United States from lower-priced markets, whether legally or illegally. In the United States, prices for pharmaceuticals are generally higher than in the bordering nations of Canada and Mexico. There have been proposals to legalize the import of pharmaceuticals from outside the United States. If such legislation were enacted, our revenues could be reduced, and our business, results of operations and financial condition could be materially adversely affected.

Our international sales and operating expenses are subject to fluctuations in currency exchange rates.

A portion of our business is conducted in currencies other than our reporting currency, the U.S. dollar. We recognize foreign currency gains or losses arising from our operations in the period in which we incur those gains or losses. As a result, currency fluctuations between the U.S. dollar and the currencies in which we do business cause foreign currency translation gains and losses. Because of the number of currencies that may be involved as we enter new markets, the variability of currency exposures and the potential volatility of currency exchange rates, we may suffer significant foreign currency translation and transaction losses due to the effect of exchange rate fluctuations. We have not entered into derivative instruments to offset the impact of foreign exchange fluctuations. Given the volatility of exchange rates, there is no assurance that we will be able to effectively manage currency transaction and/or conversion risks.

We may engage in strategic transactions that could affect our liquidity, increase our expenses and present significant challenges in focus and energy to our management.

From time to time, we may consider strategic transactions, such as acquisitions of companies, asset purchases and out-licensing or in-licensing of intellectual property, products or technologies. Additional potential transactions that we may consider include a variety of business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and investments. These transactions may entail numerous operational and financial risks, including exposure to unknown liabilities; disruption of our business and diversion of our management's time and attention in order to develop acquired products or technologies or to conduct business in new markets; use of existing cash reserves, dilutive issuances of equity securities to replenish cash requirements or to directly pay for transactions, or incurrence of substantial debt to pay for acquisitions; higher-than-expected acquisition and integration costs; increases in near- and long-term expenditures; unexpected difficulties or shortcomings in the development or commercialization of acquired assets, products, or businesses; write-downs of assets or goodwill or impairment charges; increased amortization expenses; difficulty and cost in combining the operations and personnel of any future acquired businesses with our operations and personnel; impairment of relationships with key suppliers or customers of any acquired businesses due to changes in management and ownership; and inability to retain key employees of any acquired businesses.

Accordingly, although we cannot assure you that we will undertake or successfully complete any transactions of the nature described above, any transactions that we do complete may be subject to the foregoing or other risks and could have a material adverse effect on our business, results of operations and financial condition.

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Our business involves the use of hazardous materials, and we and our third-party manufacturers and suppliers must comply with environmental laws and regulations, which can be expensive and restrict how we do business.

Our research and development activities and those of our third-party manufacturers and suppliers involve the controlled storage, use and disposal of hazardous materials, including components of our product and product candidates and other hazardous compounds. We and our manufacturers and suppliers are subject to laws and regulations governing the use, manufacture, storage, handling and disposal of these hazardous materials. In some cases, these hazardous materials and various wastes resulting from their use are stored at our and our manufacturers' facilities pending their use and disposal. We cannot eliminate the risk of contamination, which could cause an interruption of our commercialization efforts, research and development efforts and business operations, environmental damage resulting in costly clean-up and liabilities under applicable laws and regulations governing the use, storage, handling and disposal of these materials and specified waste products. Although we believe that the safety procedures utilized by our third-party manufacturers for handling and disposing of these materials generally comply with the standards prescribed by these laws and regulations, we cannot guarantee that this is the case or eliminate the risk of accidental contamination or injury from these materials. In such an event, we may be held liable for any resulting damages and such liability could exceed our resources and state or federal or other applicable authorities may curtail our use of certain materials and/or interrupt our business operations. We do not currently carry biological or hazardous waste insurance coverage. Furthermore, environmental laws and regulations are complex, change frequently and have tended to become more stringent. We cannot predict the impact of such changes and cannot be certain of our future compliance.

Significant disruptions of information technology systems or breaches of data security could materially adversely affect our business, results of operations and financial condition.

We are increasingly dependent on information technology systems and infrastructure to operate our business. In the ordinary course of our business, we collect, store and transmit large amounts of confidential information, including intellectual property, proprietary business information and personal information. It is critical that we do so in a secure manner to maintain the confidentiality and integrity of such confidential information. We have also outsourced elements of our information technology infrastructure, and as a result a number of third-party vendors may or could have access to our confidential information. The size and complexity of our information technology systems, and those of third-party vendors with whom we contract, make such systems potentially vulnerable to breakdown, malicious intrusion, security breaches and other cyber-attacks. In addition, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information, trade secrets or other intellectual property. The costs to us to eliminate or alleviate network security problems, bugs, viruses, worms, malicious software programs and security vulnerabilities could be significant, and while we have implemented security measures to protect our data security and information technology systems, our efforts to address these problems may not be successful, and these problems could result in unexpected interruptions, delays, cessation of service and other harm to our business. Despite the extensive measures we may take to secure data and our information technology systems, a determined hacker or other bad actor may still breach these security measures and our information technology systems. Moreover, if a computer security breach affects our systems or results in the unauthorized release of personally identifiable information, our reputation could be materially damaged. In addition, such a breach may require notification to governmental agencies, the media or individuals pursuant to various federal and state privacy and security laws, if applicable, including the Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Clinical Health Act of 2009, and its implementing rules and regulations, as well as regulations promulgated by the Federal Trade Commission and state breach notification laws. We would also be exposed to a risk of loss or litigation and potential liability, which could materially adversely affect our business, results of operations and financial condition.

Business disruptions from the occurrence of a catastrophic disaster could cause damage to our facilities and equipment or that of our third-party manufacturers or suppliers.

Our executive offices and laboratory facility are located in the San Francisco Bay Area near known earthquake fault zones and are vulnerable to significant damage from earthquakes. We and our contract manufacturers and source suppliers of raw materials and critical services are also vulnerable to damage from other types of disasters, including fires, storms and other extreme weather conditions, floods, water shortages, power losses, telecommunications failures, outbreaks of disease and similar events. If such a disaster were to occur, our ability to continue our operations, including commercial sales and product development programs, could be seriously, or potentially completely, impaired. The insurance we maintain may not be adequate to cover our losses resulting from disasters or other business interruptions, and we may not be able to maintain insurance in the future at satisfactory rates or in adequate amounts.

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Risks Related to Intellectual Property and Competition

If we are unable to protect adequately our proprietary technology, we may not be able to compete as effectively, and our business, results of operations and financial condition will be materially adversely affected.

Our success depends significantly on our ability to protect our proprietary technology from unauthorized use by third parties. We will be able to obtain such protection only to the extent our products are covered by valid and enforceable patents or trade secrets. Any non-confidential disclosure to or misappropriation by third parties of our confidential or proprietary information could enable competitors to quickly duplicate or surpass our technological achievements and erode our competitive position in the market. Where we elect to pursue patent protection on our proprietary technology, we file, prosecute and maintain patent applications covering certain aspects of our technology. Patent protection may not be available, however, for some of the drug product candidates we are developing. In addition, if we are required to spend significant time and money obtaining, maintaining and enforcing our patent rights, designing around patents held by others or obtaining licenses to third-party patents or other proprietary rights that cover aspects of our product candidates, our business, results of operations and financial condition will be materially adversely affected.

The patent application process, also known as patent prosecution, is expensive and time consuming. It is possible that we or our current licensors, or any future licensors or licensees, may not be able to prepare, file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner or identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection on them. If our current licensors, or any future licensors or licensees, are not fully cooperative or disagree with us regarding any aspect of the prosecution, maintenance or enforcement of the patent rights covering our product candidates where they have decision-making rights on such matters, our preferred approach may not be followed and the scope, strength, duration or other aspects of such patent rights could be compromised.

In addition, our patents and applications or those of our licensors may not be prosecuted and enforced in a manner consistent with the best interests of our business. Defects in form in the preparation or filing of our patents or patent applications or those of our licensors may adversely affect proper priority claims, inventorship, claim scope or patent term adjustments. As a result, the patent rights we depend upon to protect our technology may be held invalid or unenforceable or may be limited in scope. Moreover, we cannot assure you that all of the patent applications that we own or license will issue as patents or that, if issued, the claims of such patents will have a scope that will be advantageous to us.

The rights granted to us under the issued patents, as well as those that may be granted on pending patent applications that we own or license, may not be of sufficient scope or strength to provide us with any meaningful protection or commercial advantage. In such case, competitors may be able to design around our patents or develop products that provide outcomes comparable to ours without infringing on our intellectual property rights. In addition, we may in the future be subject to claims by our former employees or consultants asserting an ownership right in our patents or patent applications as a result of the work they performed on our behalf. Although we generally require all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to assign or grant similar rights to us under their inventions arising while working for us, we cannot be certain that we have executed such agreements with all who may have contributed to our inventions and intellectual property, nor can we be certain that our agreements with such parties will not be breached.

If any of our patents or those of our licensors are challenged, invalidated or legally circumvented by third parties, and if we do not own other enforceable patents protecting our products, competitors could market products and use processes that are substantially similar to, or superior to, ours, and our business will suffer. Any of these outcomes could impair our ability to succeed against competition from third parties and materially adversely affect our business, results of operations and financial condition.

Our patents, even if issued, may not afford us the degree of protection we require to maintain a competitive advantage.

We own or license issued U.S. and foreign patents and pending U.S. and foreign patent applications related to certain of our drug product candidates and our other technologies. Evaluating the strength of patents covering our products candidates and other technologies in the biopharmaceutical field involves complex legal and scientific questions and can be highly uncertain. While we also rely on orphan drug exclusivity for PROCYSBI for commercial protection, the degree of patent protection we require may be unavailable or severely limited in some cases and may not adequately protect our products or permit us to gain or keep any competitive advantage. For example, the patent applications that we own or license may fail to result in issued patents in the United States or in other countries. Even if patents do issue on such patent applications, third parties may challenge the validity, enforceability or scope thereof, which may result in such patents being narrowed, invalidated or held unenforceable. For example, U.S. patents can be challenged by any person before the new USPTO Patent Trial and Appeals Board at any time within the one-year period following that person’s receipt of an allegation of infringement of the patents. Patents granted by the European Patent Office may be similarly opposed by any person within nine months from the publication of the grant. Similar proceedings are available in other jurisdictions, and in the United States, Europe and other jurisdictions, third parties can raise questions of validity with a patent office even before a patent has granted.

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Even if they are unchallenged, our patents and patent applications, if granted, may not adequately protect our product candidates or technology or prevent others from designing around our patent claims. For example, a third party may develop a competitive product that provides therapeutic benefits similar to one or more of our product candidates but that has a different composition that falls outside the scope of our patent protection. If the breadth or strength of protection provided by the patents and patent applications we own or license covering our product candidates is successfully challenged, then our ability to commercialize such product candidates could be adversely affected, and we may face unexpected competition that may materially adversely affect our business, results of operations and financial condition.

In addition, competitors may interfere with our success in obtaining and maintaining patent protection for our product candidates and technologies in a variety of ways. Competitors may claim that they invented the claimed invention prior to us or our licensors or may file patent applications before we or our licensors do. Competitors may also claim that we are infringing on their patents and that we therefore cannot develop or commercialize our product candidates or practice our technology. Competitors may also challenge our patents, if issued, by showing the patent examiner that the invention claimed was not original, was not novel or was obvious. In litigation, a competitor could claim that our patents, if granted, are not valid for a number of reasons. If a court agrees, we would lose some or all of our rights to the challenged patents.

Furthermore, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after it is filed. Various extensions may be available; however, the life of a patent, and the protection it affords, is limited. Without adequate and continuing patent protection for our product candidates and technologies, we may be open to competition from generic versions of such products and competitive versions of our technologies.

If we do not obtain, or if we lose, adequate patent protection for our product candidates, and if we do not have other regulatory exclusivity for such product candidates as described under the risk factor titled "*If we fail to maintain orphan drug or other regulatory exclusivity for PROCYSBI or to obtain and maintain exclusivity for our orphan drug product candidates, our competitors may sell products to treat the same conditions, possibly at lower prices, and our revenues will be significantly reduced*," others may develop and commercialize products that are the same as, or similar to, our product candidates, which would adversely affect our business, results of operations and financial condition.

We may in the future become involved in lawsuits to defend against third-party allegations of infringement or to protect or enforce our intellectual property, which could be expensive, time consuming and unsuccessful and have a material adverse effect on our business, results of operations and financial condition.

The drug product and biopharmaceutical industry has been characterized by frequent and extensive intellectual property litigation. Our competitors or other third-party patent holders may assert that our products are covered by their patents. Although we believe we have adequate defenses available if faced with any allegations that we infringe third-party patents, we cannot be certain that we do not infringe on those patents or that we will not infringe on patents granted in the future. Furthermore, because patent applications can take many years to issue and may be confidential for 18 months or more after filing, and because pending patent claims can be revised before issuance, there may be applications now pending which may later result in issued patents that may be infringed by the manufacture, use or sale of our products. If a patent holder believes our drug product infringes on its patent, the patent holder may sue us even if we have received patent protection for our technology. Moreover, we may face patent infringement claims from non-practicing entities that have no relevant product revenue and against whom our own patent portfolio may thus have no deterrent effect. If our products are found to infringe, we could be prevented from manufacturing or marketing those products.

In addition, competitors may infringe our patents or misappropriate or otherwise violate our intellectual property rights. To stop any such infringement or unauthorized use, litigation may be necessary. If we or one of our licensors or licensees were to initiate legal proceedings against a third party to enforce a patent, the defendant could counterclaim that our patent is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements for patent issuance, including lack of novelty, obviousness or non-enablement. Patents may be unenforceable if someone connected with prosecution of the patent withheld relevant information from the USPTO or made a misleading statement during prosecution. The outcomes of proceedings involving assertions of invalidity and unenforceability are unpredictable. Furthermore, prior art that would render our patents invalid may exist. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability of our patents covering one of our product candidates or technologies, we would lose at least part, and perhaps all, of the patent protection on such product candidates or technologies. Such a loss of patent protection would materially adversely affect our business, results of operations and financial condition, particularly if we do not have other regulatory protection. Moreover, our competitors could counterclaim in any suit to enforce our patents that we infringe their intellectual property.

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Third parties may initiate legal proceedings against us to challenge the validity or scope of our intellectual property rights or may allege an ownership right in our patents resulting from their past employment or consultancy with us. Many of our current and potential competitors have the ability to dedicate substantially greater resources to defend their intellectual property rights than we can. Accordingly, despite our efforts, we may not be able to prevent third parties from claiming an ownership interest in or infringing upon or misappropriating our intellectual property. Competing products may also be sold in other countries in which our patent coverage might not exist or be as strong. If we lose a foreign patent lawsuit alleging our infringement of a competitor's patents, we could be prevented from marketing our product candidates in one or more foreign countries.

Litigation related to infringement or misappropriation of intellectual property rights, with or without merit, is unpredictable, is generally expensive and time consuming and can divert management's attention from our core business. If we do not prevail in any litigation in which we are alleged to have infringed or misappropriated intellectual property rights, a court could require us to pay substantial damages, treble damages and attorneys' fees and could prohibit us from using technologies essential to our product candidates, any of which would have a material adverse effect on our business, results of operations and financial condition. If patents asserted against us are upheld as valid and enforceable and we are found to infringe them, we could be prevented from selling our product candidates or technologies unless we can obtain licenses to use the technology or ideas covered by such patents. We do not know whether any necessary licenses would be available to us on satisfactory terms, if at all. If we cannot obtain such licenses, we could be forced to design around the infringed patents at additional cost or to abandon the infringing product candidate or technology altogether. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the market price of our common stock. As a result, our ability to grow our business and compete in the market may be harmed.

We may also support and collaborate in research conducted by government organizations, hospitals, universities or other educational institutions. These research partners may be unwilling to grant us any exclusive rights to technology or product candidates derived from these collaborations. If we do not obtain required licenses or rights, we could encounter delays in our product development efforts while we attempt to design around other patents or even be prohibited from developing, manufacturing or selling drug product candidates requiring these licenses. There is also a risk that disputes may arise as to the rights to technology or drug product candidates developed in collaboration with other parties. Any such disputes may cause our competitive position to be adversely affected and may materially adversely affect our business, results of operations and financial condition.

Obtaining and maintaining patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. In addition, periodic maintenance fees on issued patents often must be paid to the USPTO and foreign patent agencies over the lifetime of the patent. While an unintentional lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we fail to maintain the patents and patent applications covering our product candidates or technologies, we may not be able to prevent a competitor from marketing products that are the same as or similar to our products, which would have a material adverse effect on our business, results of operations and financial condition, particularly if we do not have other regulatory protection for our products.

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We may not be able to effectively enforce our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on our product candidates and technologies in all countries throughout the world would be prohibitively expensive. The requirements for patentability may differ in certain countries, particularly in developing countries. Moreover, our ability to protect and enforce our intellectual property rights may be adversely affected by unforeseen changes in foreign intellectual property laws. In addition, laws of some countries outside of the United States do not afford intellectual property protection to the same extent as the laws of the United States. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property rights. This could make it difficult for us to stop the infringement of our patents or the misappropriation of our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States. In addition, competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection, if our ability to enforce our patents to stop infringing activities is inadequate. These products may compete with our products, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing. See also the risk factor titled "*Our success depends on our ability to manage our projected growth.*"

Proceedings to enforce our patent rights in foreign jurisdictions, whether or not successful, could result in substantial costs and divert our efforts and resources from other aspects of our business. Furthermore, while we intend to protect our intellectual property rights in major markets for our products, there can be no assurance that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our products. In addition, our efforts to protect our intellectual property rights in such countries may be inadequate.

Changes to the patent law in the United States and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biopharmaceutical companies, our success is heavily dependent on our having valid and enforceable intellectual property rights, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involve both technological and legal complexity and is therefore costly, time consuming and inherently uncertain. Recent patent reform legislation in the United States and other countries, including the Leahy-Smith America Invents Act, or Leahy-Smith Act, signed into law on September 16, 2011, could increase those uncertainties and costs. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications are prosecuted, redefine prior art and provide more efficient and cost-effective avenues for competitors to challenge the validity of patents. In addition, the Leahy-Smith Act has transformed the U.S. patent system into a "first to file" system. The first-to-file provisions, however, only became effective on March 16, 2013. Accordingly, it is not yet clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could make it more difficult to obtain patent protection for our inventions and increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could materially adversely affect our business, financial condition and results of operations.

The U.S. Supreme Court has ruled on several patent cases in recent years, narrowing the scope of patent protection available in certain circumstances and weakening the rights of patent owners in certain situations. In addition, there have been recent proposals for additional changes to the patent laws of the United States and other countries that, if adopted, could affect our ability to obtain patent protection for our proprietary technology or our ability to enforce our proprietary technology. Depending on future actions by the U.S. Congress, the U.S. courts, the USPTO and the relevant law-making bodies in other countries, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

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If we are limited in our ability to utilize acquired or licensed technologies, or if we lose our rights to critical in-licensed technology, we may be unable to successfully develop, out-license, market and sell our products, which could prevent or delay new product introductions.

We have acquired and licensed certain proprietary technologies and plan to further license and acquire various patents and proprietary technologies owned by other parties. The agreements in place are critical to our product development programs. For example, most of our patent portfolio pertaining to PROCYSBI and RP103 for cystinosis and other therapeutic indications has been licensed from academic institutions. Our license agreements with these institutions include termination clauses that permit the licensor to terminate our license under certain circumstances, including if we materially breach our obligations under the applicable agreement. If one or more of our licenses is terminated, we would have no further right to use or exploit the patents, know-how and other intellectual property rights licensed to us under the agreement, which could adversely affect our ability to market PROCYSBI or continue our development programs of RP103 in other clinical indications.

Our business strategy depends on the successful development of licensed and acquired technologies into commercial products. Therefore, any limitations on our ability to utilize these technologies may impair our ability to develop, out-license or market and sell our product candidates, could delay new product introductions and could adversely affect our reputation, any of which could have a material adverse effect on our business, results of operations and financial condition.

If we are unable to protect the confidentiality of our trade secrets, our competitive position may be harmed, and our business, results of operations and financial condition will be materially adversely affected.

In addition to patent protection, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. Our trade secrets may not be adequately protected, however. We have taken steps to protect our trade secrets and proprietary information, including entering into confidentiality agreements and intellectual property assignment agreements with our employees, consultants, advisors and corporate and educational institution partners. Nevertheless, such agreements may not be enforceable or may not provide meaningful protection for our trade secrets or other proprietary information in the event of unauthorized use or disclosure, whether willful or unintentional, or other breaches of the agreements, and we may not be able to prevent such unauthorized disclosure. Monitoring unauthorized disclosure is difficult, and we do not know whether the steps we have taken to prevent such disclosure are, or will be, adequate. In addition, we may not be able to obtain adequate remedies for any such breaches. Enforcing a claim that someone illegally obtained and is using our trade secrets, like patent litigation, is expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the United States may be less willing to protect trade secrets. Our competitors may independently develop equivalent knowledge, methods and know-how. Competitors could purchase our products and attempt to replicate some or all of the competitive advantages we derive from our development efforts, willfully infringe or misappropriate our intellectual property rights, design around our protected technology or develop their own competitive technologies that fall outside of our intellectual property rights. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us.

We may be subject to damages resulting from claims that we or our employees have wrongfully used or disclosed alleged trade secrets of our competitors or are in breach of non-competition or non-solicitation agreements with our competitors.

We could in the future be subject to claims that we or our employees have inadvertently or otherwise used or disclosed alleged trade secrets or other proprietary information of former employers or competitors. Although we try to ensure that our employees and consultants do not use the intellectual property, proprietary information, know-how or trade secrets of others in their work for us, we may in the future be subject to claims that we caused an employee to breach the terms of his or her non-competition or non-solicitation agreement or that we or these individuals have, inadvertently or otherwise, used or disclosed the alleged trade secrets or other proprietary information of a former employer or competitor in breach of their obligations to that employer or competitor. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and could be a distraction to management. If our defenses to these claims fail, in addition to requiring us to pay monetary damages, a court could prohibit us from using technologies or features that are essential to our products, if such technologies or features are found to incorporate or be derived from the trade secrets or other proprietary information of the former employers. An inability to incorporate such technologies or features would have a material adverse effect on our business, and may prevent us from successfully commercializing our products. In addition, we may lose the right to practice valuable intellectual property rights or personnel as a result of such claims. Moreover, any such litigation or the threat thereof may adversely affect our ability to hire employees or contract with independent sales representatives. A loss of key personnel or their work product could hamper or prevent our ability to commercialize our products. Any of these events, or a combination thereof, could have a material adverse effect on our business, results of operations and financial condition.

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Risks Related to Our Financial Position and Capital Requirements

Our commercial operations and clinical development programs will require substantial future funding which will affect our operational and financial condition.

Our commercial sales programs for PROCYSBI and any future approved products and our product development programs will require substantial additional capital, arising from costs incurred to:

- conduct research, preclinical testing and human studies and clinical trials; develop and submit regulatory submissions for marketing approvals;
- develop and submit regulatory submissions for marketing approvals;
- establish or contract for pilot scale and commercial scale manufacturing processes and facilities;
- obtain adequate reimbursement for our products;
- market and distribute PROCYSBI and any future approved products; and
- establish, develop and maintain quality control, manufacturing, regulatory, medical, distribution, marketing, sales, finance and administrative capabilities to support these programs.

We base our outlook regarding the need for funds on many uncertain variables. Such uncertainties include the success of our commercial sales of PROCYSBI in the United States, the EEA and any additional markets; the success of our efforts to commercialize any future approved products; the scope and results of our research initiatives, preclinical testing and human clinical trials; regulatory approvals; the timing of events outside our direct control, such as competing technological and market developments, negotiations with third-party payors and potential strategic partners; and other factors. In addition, certain product programs may require collaborative agreements with corporate partners with greater financial and organizational resources than we have. Such agreements may require substantial time to complete and may not be available in the time frame desired or with acceptable financial terms, if at all. Any of these factors may significantly change the timing and amount of our cash requirements as they determine such one-time events as the receipt or payment of milestone-based and other payments.

If we fail to raise additional financing when needed, we may have to delay or terminate some or all of our research and development programs, scale back our operations and/or reduce our commercial finance and administrative expenses to sustainable levels, which would have a material adverse effect on our business, results of operating and financial condition.

While we believe that, based upon our projected PROCYSBI sales and planned operations, our cash and cash equivalents as of December 31, 2014 of approximately $150 million will be sufficient to meet our projected operational requirements and obligations through 2016, we will need to sell equity or debt securities to raise additional funds to support, among other things, our development and commercialization programs. The sale of additional equity securities or convertible debt securities will result in additional dilution to our stockholders, and newly issued securities may have rights, preferences and privileges senior to those of holders of our common stock. Additional financing may not be available on a timely basis, in amounts or on terms satisfactory to us, or at all. We may be unable to raise additional capital due to a variety of factors, including our financial condition, the status of our research and development programs, the status of regulatory reviews for marketing approvals, the status of our commercialization activities, sales of PROCYSBI in existing and additional markets and the general condition of the financial markets. If we fail to raise additional financing when needed, we may have to delay, partner, or terminate some or all of our research and development programs, scale back our operations and/or reduce our commercial expenses. If such actions are required, our business, results of operations and financial condition will be adversely affected, and the market value of our common stock may significantly decline.

Our loan agreement with HC Royalty and outstanding convertible senior notes contain a number of restrictive covenants and other provisions, which, if violated, could result in the acceleration of the payment terms of our outstanding indebtedness, which in turn could have a material adverse effect on our business, results of operations and financial condition.

In December 2012, we entered into a loan agreement with HealthCare Royalty Partners II, L.P., or HC Royalty, as lender, which we refer to as the HC Royalty Loan Agreement. Under the HC Royalty Loan Agreement, we agreed to borrow $50.0 million in two $25.0 million tranches. We drew down the first tranche in the amount of $25.0 million in December 2012 and the second tranche of $25.0 million in May 2013 when we achieved the milestone of U.S. approval of PROCYSBI. In July 2014, we entered into an amendment and restatement of the original HC Royalty Loan Agreement and borrowed from HC Royalty a third, $10.0 million tranche under the loan facility. Also in July 2014, we issued $60.0 million aggregate principal amount of 8.0% convertible senior notes due 2019 to HC Royalty and other purchasers.

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The HC Royalty Loan Agreement includes a number of affirmative and negative covenants, including requirements to use commercially reasonable efforts to exploit PROCYSBI and RP103 in specific markets and to comply with applicable laws, and additional restrictions on mergers, sales of assets, the incurrence of liens, the incurrence of additional indebtedness and transactions with our affiliates, among other requirements. The convertible senior notes also include a number of affirmative and negative covenants, including our obligation to offer to repurchase the notes upon a change of control of our company, limitations on the incurrence of additional indebtedness, registration rights for the holders of the notes and other requirements.

The performance of our obligations under the HC Royalty Loan Agreement is secured by our grant of a security interest to HC Royalty in substantially all of our assets and the assets of our domestic subsidiaries and a pledge of stock of certain of our domestic subsidiaries. Our failure to comply with the terms of the HC Royalty Loan Agreement, the convertible senior notes and related documents could result in an event of default. A change of control of our company, an uncured material adverse effect on our company and certain other specified events could also constitute an event of default under the agreements. In the event of an event of default that is not cured or waived, the payment of all of our indebtedness to HC Royalty and interest thereon and the repayment of the convertible senior notes could accelerate. Under the terms of the security agreement, an event of default could also enable the lender to take possession of, foreclose on, sell, assign or grant a license to use our pledged collateral and to assign and transfer the pledged stock of certain of our subsidiaries. An event of default, a material adverse effect or a change of control would also trigger a prepayment penalty under the HC Royalty Loan Agreement, which would require us to pay a substantially higher amount due than the current balance of our loan.

Any of the events described above, or a combination thereof, could have a material adverse effect on our financial condition and results of operations.

Our cash flows and capital resources may be insufficient to make required payments on our indebtedness.

The required payments of principal and interest on our indebtedness under the HC Royalty Loan Agreement and convertible senior notes may require a substantial portion, or all, of our available cash to be dedicated to the service of these debt obligations. Both the HC Royalty Loan Agreement and the convertible senior notes bear interest at an annual fixed rate of 8.0%. The HC Royalty Loan Agreement also bears a synthetic royalty based on our net revenues from PROCYSBI and other future-approved products in a calendar year. This royalty and the interest under the HC Royalty Loan Agreement and the convertible senior notes are payable quarterly. Principal payments under the HC Royalty Loan Agreement will become due beginning in June 2015. The convertible senior notes will mature on August 1, 2019, unless earlier converted, redeemed or repurchased.

There can be no assurance that our business will generate sufficient cash flow or that we will have capital resources in an amount sufficient to enable us to pay our indebtedness to HC Royalty or the holders of the convertible senior notes. Our debt obligations may also limit our flexibility to plan for or react to changes in our business and industry and place us at a competitive disadvantage compared to competitors with superior financial resources including less debt. If our cash flows and capital resources are insufficient to fund these debt service obligations, we may be forced to reduce or delay product development, sales and marketing and capital and other expenditures. We may also be forced to restructure our indebtedness or raise additional capital through the issuance of equity or debt instruments, and there can be no assurance that we will be able to refinance any of our indebtedness or raise additional capital on a timely basis, in sufficient amounts, on satisfactory terms or at all. The terms of the HC Royalty Loan Agreement and convertible senior notes may also limit our ability to pursue any of these financing alternatives, and these alternatives nonetheless may not enable us to meet our scheduled debt service obligations.

Failure to meet our debt service obligations may result in an event of default under the HC Royalty Loan Agreement, which would permit the lender to accelerate the payment of all of our indebtedness to HC Royalty and interest thereon. An event of default could also enable the lender to take possession of, foreclose on, sell, assign or grant a license to use our pledged collateral and to assign and transfer the pledged stock of certain of our subsidiaries. An event of default, a material adverse effect or a change of control would also trigger a prepayment penalty under the HC Royalty Loan Agreement, which would require us to pay a substantially higher amount than the current balance of our loan.

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Failure to meet our debt service obligations may also result in an event of default under the convertible senior notes, which would permit the holders to accelerate the payment of the outstanding principal amount of the notes and interest thereon and require us to pay a repayment premium and higher interest. A change of control would also trigger an obligation to repurchase the convertible senior notes.

Any of the events described above, or a combination thereof, could have a material adverse effect on our business, financial condition and results of operations.

Our ability to use our net operating losses to offset future taxable income may be subject to certain limitations.

In general, under Section 382 of the Internal Revenue Code of 1986, as amended, a corporation that undergoes an "ownership change" is subject to limitations on its ability to utilize its pre-change net operating loss carryforwards to offset future taxable income. Our existing net operating loss carryforwards may be subject to limitations arising from previous ownership changes, and if we undergo an ownership change in the future, our ability to utilize our net operating loss carryforwards could be further limited by Section 382. Future changes in our stock ownership, some of which are outside of our control, could result in an ownership change. Furthermore, we may be unable to use a substantial part of our net operating loss carryforwards if we do not attain profitability in an amount sufficient to utilize such losses.

Risks Related to Our Common Stock

Our stock price has been volatile and may continue to be volatile in the future, and our stockholders may not be able to resell shares of our common stock at or above the prices that they paid. The trading volume in our common stock may be relatively small.

Our common stock is quoted on the NASDAQ Global Market. The trading price of our common stock has been and may continue to be volatile. During the 52-week period ended February 20, 2015, our average daily trading volume was approximately 813,664 shares and the closing sales price per share of our common stock on the NASDAQ Global Market ranged from $7.51 to $17.41. Our operating performance, both financial and in the development of approved products, significantly affects the market price of our common stock. A number of factors may affect the market price of our common stock, including:

- the success of our testing and clinical trials and those of others with products similar or related to our products;
- announcements regarding regulatory approvals or approved label indications and patient populations or changes or delays in the regulatory review process;
- unexpected difficulties in commercialization or lower than expected sales;
- lower than expected pricing and reimbursement levels, or no reimbursement at all, for our products in various markets;
- actions taken by regulatory agencies with respect to our clinical trials, manufacturing supply chain or sales and marketing activities;
- changes in our relationships with manufacturers, suppliers or collaborators, or our inability to supply enough product to meet demand;
- announcements of new products or innovations by us or our competitors and announcements concerning our competitors or our industry in general;
- our ability to obtain additional funding;
- changes or developments in applicable laws or regulations;
- any intellectual property infringement actions in which we may become involved;
- sales and profitability;
- announcements of significant acquisitions, strategic partnerships, joint ventures, or capital commitments by us, our strategic collaboration partners or our competitors;
- our ability to manage our projected growth;
- actual or anticipated fluctuations in our results of operations;
- changes in financial estimates or recommendations by securities analysts or their ceasing to publish research or reports about our business;
- the trading volume of our common stock;
- general economic and market conditions and overall fluctuations in the U.S. equity markets;

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- the appeal and current level of investor interest in the biotechnology/biopharmaceutical capital market sector and in companies in general with business, research strategies and product development pipelines which are similar to us; and
- the loss of any of our key scientific or management personnel.

For planning purposes, we estimate the timing of the accomplishment of various scientific, clinical, regulatory, market launch and commercialization goals, which we sometimes refer to as milestones. These milestones include the completion of reimbursement and pricing negotiations and commercial launches in additional territories, commencement or completion of scientific studies and clinical trials and the submission of regulatory filings. We also prepare estimates of future financial results for planning and budget purposes. From time to time, we may publicly announce the estimated timing of some of these milestones and provide guidance regarding financial results and other metrics. All of these projections will be based on a variety of assumptions. The actual timing of these milestones and actual financial results can vary dramatically compared to our estimates for a number of reasons, including those set forth above, in many cases for reasons beyond our control. If we do not meet the milestones, financial guidance or other expectations as publicly announced or as projected by various security analysts who follow our company, our stockholders or potential stockholders may lose confidence in our ability to meet overall objectives and our financial planning capabilities, and as a result, the market price of our common stock may decline.

In addition, the NASDAQ Global Market has, from time to time, experienced extreme price and trading volume fluctuations. The market prices of securities of pharmaceutical, biotechnology and other life sciences companies in a comparable stage to ours historically have been particularly volatile, and trading volume in such securities and our common stock has often been relatively small. Moreover, the stock markets in general have experienced substantial volatility that has often been unrelated or disproportionate to the operating performance of individual companies. During certain periods, the favor of certain industry segments, such as the biotechnology segment, may also be volatile. These changes may affect in particular the market price of our common stock and the stock prices of companies such as ours that do not have conventional measures of financial and business health such as sales, earnings, profitability and related measures. These broad market fluctuations, during which our industry and companies at our stage may experience a stronger degree of market sensitivity, will adversely affect the market price of our common stock. In the past, following periods of volatility in the market resulting in substantial declines in the market price of a company's securities, stockholders have often instituted class action securities litigation against those companies. Such litigation can result in substantial costs and diversion of management attention and resources, which could significantly harm our and reputation and materially adversely affect our business, financial condition and results of operations.

Future sales or issuances of our common stock or other securities in the public market, including shares issuable upon conversion of our convertible senior notes, or the perception of such future sales or issuances, could lead to a decline in the market price of our common stock.

Any issuance of shares of our common stock or other securities, including for the purposes of raising capital to fund our operations, acquisitions and the expansion of our business, will have a dilutive effect on our existing stockholders. In addition, any issuance or the perceived market risk associated with any possible issuance could cause the market price of our common stock to decline. Subsequent sales of our common stock in the open market, exercises of our currently outstanding stock options, conversion of our convertible senior notes and the subsequent sale of the shares acquired thereunder or any other issuance by us of shares of our common stock or other securities could also have an adverse effect on the market price of our common stock. If the market price of our common stock declines, it will be more difficult for us to raise additional capital, or we may be unable to raise additional capital at all.

In addition, we have in the past and may in the future grant rights to some of our stockholders that require us to register the resale of shares or our common stock on behalf of these stockholders and/or to facilitate offerings of shares of our common stock held by these stockholders, including in connection with potential future acquisitions of additional products, product candidates or companies. If holders of such registration rights sell a large number of shares of our common stock, the sale could cause the market price of our common stock to decline. We have also filed registration statements to register the sale of our shares of our common stock reserved for issuance under our equity incentive plans and our employee stock purchase plan and intend to file additional registration statements to register any shares added to the reserves under these plans.

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In July 2014, we issued $60.0 million aggregate principal amount of 8.0% convertible senior notes due 2019. The convertible senior notes are convertible at the option of the holder at an initial conversion rate of approximately 57.14 shares of common stock per $1,000 principal amount of convertible senior notes, which is equivalent to an initial conversion price of $17.50, and is subject to adjustment upon certain events and conditions. In addition, we may redeem for cash or require holders to convert the convertible senior notes into shares of common stock if the price of the common stock is at or above 175% of the applicable conversion price over a period of 30 consecutive trading days. The note purchase agreement governing the convertible senior notes provides the holders with registration rights for the shares issued upon conversion of their convertible senior notes subject to certain conditions, and we have filed a registration statement to register the resale of the shares of common stock issuable upon conversion of the convertible senior notes. We may be required to pay increased interest on the convertible senior notes if we do not comply with the registration rights provisions of the note purchase agreement. A substantial number of shares of our common stock are reserved for issuance upon conversion of the convertible senior notes. The issuance of shares of our common stock upon conversion of the convertible senior notes would dilute the ownership interest of our common stockholders and may materially adversely affect the market price of our common stock and impair our ability to raise capital through the sale of additional equity securities.

In connection with other collaborations, joint ventures, license agreements or future financings that we may enter into in the future, we may issue additional shares of common stock or other equity securities, and the value of the securities issued may be substantial and create additional dilution to our common stockholders.

Because we do not intend to pay any cash dividends on our common stock, investors will benefit from an investment in our common stock only if it appreciates in value. Investors seeking dividend income should not purchase shares of our common stock.

We have not declared or paid any cash dividends on our common stock since our inception. We anticipate that we will retain our earnings to support our operations and to finance the growth and development of our business and do not expect to pay cash dividends in the foreseeable future. Our loan agreement with HC Royalty prohibits us from paying cash dividends. As a result, the success of an investment in our common stock will depend upon any future appreciation in the market price of our common stock. There can be no guarantee that the market price our common stock will appreciate or that it will not depreciate. Investors seeking dividend income should not invest in our common stock.

Anti-takeover provisions under Delaware law, in our stockholder rights plan and in our certificate of incorporation and bylaws, as amended, may prevent or complicate attempts by stockholders to change the board of directors or current management and could make a third-party acquisition of us difficult.

Our certificate of incorporation and bylaws, as amended, contain provisions that could significantly reduce the value of our shares to a potential acquirer or delay or prevent changes in control or changes in our management without the consent of our board of directors. The provisions in our charter documents include the following:

- the right of our board of directors to elect a director to fill a vacancy created by the expansion of the board of directors or the resignation, death or removal of a director, which prevents stockholders from being able to fill vacancies on our board of directors;
- the required approval of at least 66 ⅔% of the shares entitled to vote to remove a director without cause;
- the ability of our board of directors to authorize the issuance of shares of preferred stock and to determine the price and other terms of those shares, including preferences, dividend rights and voting rights, which may be superior to those of the common stock, without stockholder approval, which could be used to significantly dilute the ownership of a hostile acquiror;
- the ability of our board of directors to alter our bylaws without obtaining stockholder approval;
- the required approval of at least 66 ⅔% of the shares entitled to vote at an election of directors to adopt, amend or repeal our bylaws;
- a prohibition on stockholder action by written consent, which forces stockholder action to be taken at an annual or special meeting of our stockholders;
- the requirement that a special meeting of stockholders may be called only by the chairman of the board of directors, the chief executive officer or the board of directors, which may delay the ability of our stockholders to force consideration of a proposal or to take action, including the removal of directors; and
- advance notice procedures that stockholders must comply with in order to nominate candidates to our board of directors or to propose matters to be acted upon at a stockholders' meeting, which may discourage or deter a potential acquiror from conducting a solicitation of proxies to elect the acquiror's own slate of directors or otherwise attempting to obtain control of us.

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We are also subject to the anti-takeover provisions contained in Section 203 of the Delaware General Corporation Law. Under Section 203, a corporation may not, in general, engage in a business combination with any holder of 15% or more of its capital stock unless the holder has held the stock for three years or, among other exceptions, the board of directors has approved the transaction.

We are also party to a stockholder rights plan, also referred to as a "poison pill," which is intended to deter a hostile takeover of us by making such proposed acquisition more expensive for and less desirable to the potential acquirer.

Our board of directors may use the provisions described above to prevent changes in the management and control of our company. These provisions could limit the price that investors might be willing to pay in the future for shares of our common stock. These provisions would apply even if we were to receive an offer that some stockholders may consider beneficial. Also, under applicable Delaware law, our board of directors may adopt additional anti-takeover measures in the future.

Provisions of the note purchase agreement governing our convertible senior notes may discourage a takeover, which could cause the market price of our common stock to decline.

The repurchase rights and related repurchase premium provided in our convertible senior notes triggered by the occurrence of a change of control may discourage, delay or prevent a third party from acquiring us, even if doing so would benefit our stockholders. In turn, this could cause the market price of our common stock to decline.

ITEM 1B: UNRESOLVED STAFF COMMENTS

None.

ITEM 2: PROPERTIES

We lease 52,319 square feet of office and laboratory space as our headquarters in Novato, California. This space is situated in two adjacent facilities.

In addition, we lease small office spaces in Paris, France and Frankfurt, Germany; and in Utrecht, Netherlands as our European sales, marketing and administrative headquarters. We believe that our current facilities are sufficient to meet our present requirements.

ITEM 3: LEGAL PROCEEDINGS

From time to time we are involved in litigation arising out of claims in the normal course of business. We are not aware of any material pending legal proceedings against us, nor are we involved as a plaintiff in any material pending legal proceedings.

ITEM 4: MINE SAFETY DISCLOSURES

Not applicable.

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PART II

ITEM 5: MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

Our common stock trades on the NASDAQ Global Market under the symbol "RPTP." As of February 20, 2015, there were 69,144,463 shares of our common stock outstanding. There is no public trading market for our warrants. The closing price for our common stock on February 20, 2015 was $9.89 per share.

The following table sets forth the range of high and low sales prices of our common stock for the quarterly periods indicated, as reported by NASDAQ.

	High	Low
Fiscal Year Ended December 31, 2014:		
First Quarter (January 1 – March 31, 2014)	$ 17.72	$ 9.38
Second Quarter (April 1 – June 30, 2014)	12.19	7.12
Third Quarter (July 1 – September 30, 2014)	12.20	8.00
Fourth Quarter (October 1 – December 31, 2014)	11.10	7.85
Fiscal Year Ended December 31, 2013:		
First Quarter (January 1 – March 31, 2013)	6.28	4.71
Second Quarter (April 1 – June 30, 2013)	10.47	5.40
Third Quarter (July 1 – September 30, 2013)	15.00	9.26
Fourth Quarter (October 1 – December 31, 2013)	15.29	11.09

Holders of Record

As of February 20, 2015, there were approximately 118 holders of record of our common stock. In addition, as of February 20, 2015 there were warrants held by six holders of record to acquire up to, in the aggregate, 334,764 shares of our common stock.

Dividends

We have not declared or paid any cash dividends on our common stock since our inception. We anticipate that we will retain our earnings to support our operations and to finance the growth and development of our business and do not expect to pay cash dividends in the foreseeable future. In addition, our loan agreement with HC Royalty prohibits us from paying cash dividends.

Securities Authorized for Issuance under Equity Compensation Plans

Information regarding securities authorized for issuance under equity compensation plans is incorporated by reference into the information in Part III, Item 12 of this Annual Report on Form 10-K.

Recent Sales of Unregistered Securities

We did not issue any unregistered equity securities during the year ended December 31, 2014.

Purchase of Equity Securities and Affiliated Purchasers

We did not repurchase any shares of our common stock during the three months ended December 31, 2014.

Performance Graph

The following is not deemed "filed" with the Securities and Exchange Commission and is not to be incorporated by reference into any filing we make under the Securities Act of 1933, as amended, whether made before or after the date hereof and irrespective of any general incorporation by reference language in such filing.

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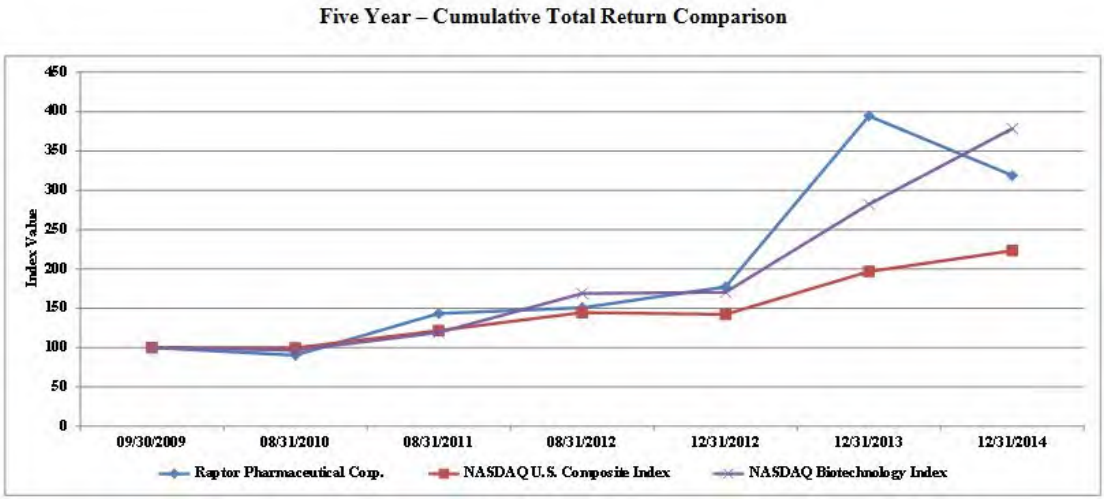
The following graph shows the value of an investment of $100 on September 30, 2009 (the date of our 2009 Merger) in our common stock, the NASDAQ Composite Index (U.S.), and the NASDAQ Biotechnology Index. All values assume reinvestment of the pretax value of dividends paid by companies included in these indices and are calculated as of August 31, 2010, 2011, 2012, for the four months ended December 31, 2012 and as of the years ended December 31, 2013 and 2014. The comparisons shown in the graph are based upon historical data and we caution that the stock price performance shown in the graph is not indicative of, nor intended to forecast, the potential future performance of our stock.



	September 30, 2009	August 31, 2010	August 31, 2011	August 31, 2012	Four Months Ended December 31, 2012	December 31, 2013	December 31, 2014
Raptor Pharmaceutical Corp.	100.00	90.30	143.33	150.61	177.27	394.55	318.79
NASDAQ U.S. Composite Index	100.00	99.60	121.53	144.50	142.27	196.78	223.14
NASDAQ Biotechnology Index	100.00	96.73	119.13	168.82	170.41	282.22	378.45

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ITEM 6: SELECTED FINANCIAL DATA

The following table shows selected historical consolidated financial and operating information for, and as of the end of, each of the periods indicated and should be read in conjunction with the information in the sections titled, "Management's Discussion and Analysis of Financial Condition and Results of Operation" and "Business" and our consolidated financial statements and the corresponding notes to those consolidated financial statements included elsewhere in this Annual Report on Form 10-K. The following tables set forth our consolidated statements of operations and comprehensive loss data for the years ended December 31, 2014 and 2013, the four months ended December 31, 2012 and the fiscal years ended August 31, 2012, 2011 and 2010, and select consolidated balance sheet data as of December 31, 2014 2013 and 2012 and as of August 31, 2012, 2011 and 2010.

	For the Year Ended December 31,		For the Four Months Ended December	For the Year Ended August 31,		
(In millions, except per share data)[1]	**2014**	**2013**	**31, 2012**	**2012**	**2011**	**2010**
Statements of operations and comprehensive loss:						
Revenues	$ 69.5	$ 16.9	$ -	$ -	$ -	$ -
Cost of sales	9.4	1.7	-	-	-	-
Gross profit	60.1	15.2	-	-	-	-
Operating expenses:						
Research and development	43.5	29.2	8.9	21.4	14.8	9.3
Selling, general and administrative	56.7	37.9	9.0	14.7	6.2	3.7
Total operating expenses	100.1	67.1	17.9	36.1	21.0	13.0
Loss from operations	(40.1)	(51.9)	(17.9)	(36.1)	(21.0)	(13.0)
Interest income	0.1	0.1	0.2	0.3	0.1	-
Interest expense	(14.0)	(6.8)	(0.1)	-	-	-
Foreign currency transaction gain	0.3	-	0.1	0.2	-	-
(Loss) gain on short-term investments	-	(0.1)	(0.1)	0.2	-	-
Adjustment to fair value of common stock warrants	(1.1)	(10.7)	(1.5)	(3.2)	(16.3)	(5.9)
Other income	2.3	-	-	-	-	-
Net loss before provision for income taxes	(52.5)	(69.4)	(19.3)	(38.6)	(37.2)	(18.9)
Provision for income taxes	(0.1)	-	-	-	-	-
Net Loss	$ (52.5)	$ (69.4)	$ (19.3)	$ (38.6)	$ (37.2)	$ (18.9)
Other comprehensive gain (loss):						
Foreign currency translation gain (loss)	0.3	(0.3)	(0.1)	(0.1)	-	-
Comprehensive Loss	$ (52.2)	$ (69.7)	$ (19.4)	$ (38.7)	$ (37.2)	$ (18.9)
Net loss per share:						
Basic and diluted	$ (0.83)	$ (1.20)	$ (0.37)	$ (0.80)	$ (1.15)	$ (0.85)
Weighted-average shares outstanding	63.2	57.9	51.7	48.1	32.3	22.2

(In millions)	**December 31,**			**August 31,**		
Balance Sheet:	**2014**	**2013**	**2012**	**2012**	**2011**	**2010**
Cash, cash equivalents and short-term investments	$ 149.6	$ 83.1	$ 58.4	$ 38.9	$ 15.2	$ 17.0
Working capital (deficit)	142.5	66.2	37.0	(20.6)	(11.0)	(0.3)
Total assets	189.1	108.7	68.1	48.3	22.6	24.4
Common stock warrant liability	0.7	7.1	16.4	17.3	23.6	15.8
Note payable	60.0	50.0	25.0	-	-	-
Convertible notes	60.0	-	-	-	-	-
Total liabilities	140.1	80.2	48.2	21.6	26.7	17.6
Accumulated deficit	(257.9)	(205.4)	(135.9)	(116.6)	(78.0)	(40.8)
Total stockholders' equity (deficit)	48.9	28.6	19.9	26.7	(4.1)	6.8

(1) Certain totals may not foot due to rounding

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ITEM 7: MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

Overview

You should read the following discussion in conjunction with our consolidated financial statements as of December 31, 2014, and the notes to such consolidated financial statements included elsewhere in this Annual Report on Form 10-K. The "Management's Discussion and Analysis of Financial Condition and Results of Operations" section contains forward-looking statements. Please see "Forward-Looking Statements" for a discussion of the uncertainties, risks and assumptions associated with these statements. Our actual results and the timing of certain events could differ materially from those anticipated in these forward-looking statements as a result of certain factors, including those discussed below and elsewhere in this Annual Report on Form 10-K, particularly under the heading "Risk Factors," and in other documents we file with the SEC.

Change in Fiscal Year End

On December 4, 2012, our board of directors approved a change in our fiscal year end from August 31 to December 31. The change became effective at the end of the four months ended December 31, 2012. All references to "fiscal years" or "years" prior to this change refer to the twelve-month fiscal period covering September 1 through August 31, and each year after December 31, 2012, the fiscal year covers January 1 through December 31.

Plan of Operation and Overview

We are a biopharmaceutical company focused on developing and commercializing life-altering therapeutics that treat debilitating and often fatal diseases.

Our product, PROCYSBI® (cysteamine bitartrate) delayed-release capsules, or PROCYSBI, received marketing approval from the U.S. Food and Drug Administration, or FDA, in April 2013 for the management of nephropathic cystinosis in adults and children six years and older. In Europe, PROCYSBI gastro-resistant hard capsules of cysteamine (as mercaptamine bitartrate), received a marketing authorization in September 2013 from the European Commission, or EC, as an orphan medicinal product for the management of proven nephropathic cystinosis in the European Union, or EU. The EU marketing authorization allows us to commercialize PROCYSBI in the 28 Member States of the EU plus Norway, Liechtenstein and Iceland (which are not EU Member States but are part of the European Economic Area, or EEA). PROCYSBI received seven and ten years of market exclusivity due to its designation as an orphan drug in the United States and the EU, respectively. We achieved first commercial sales of PROCYSBI in the United States in June 2013 and in the EU, specifically in Germany, in April 2014.

Clinical Development Programs

Our three active clinical development programs utilize RP103, which contains the same active pharmaceutical ingredient as PROCYSBI, cysteamine bitartrate. RP103 is our proprietary extended and delayed-release formulation capsule containing enteric coated microbeads of cysteamine bitartrate. Cysteamine bitartrate was approved in the United States in 1994 and the EU in 1997 as an orally available immediate-release powder in a capsule for the management of cystinosis. We have an exclusive worldwide license from the University of California, San Diego (“UCSD”), to delayed-release cysteamine bitartrate, which is the basis for our proprietary formulation of cysteamine. We currently have product candidates in clinical development designed to potentially treat Huntington's disease (“HD”), non-alcoholic steatohepatitis (“NASH”), and Leigh syndrome and other mitochondrial disorders.

Our other clinical-stage product candidate is Convivia®, our proprietary oral formulation of 4-methylpyrazole, for the potential management of acetaldehyde toxicity due to alcohol consumption by individuals with aldehyde dehydrogenase, or ALDH2, deficiency, an inherited metabolic disorder.

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Preclinical Product Candidates

Our preclinical programs, for which we may seek development partners in the future, include our cysteamine dioxygenase, or ADO, program and our HepTide® program, for the potential treatment of hepatocellular carcinoma and other cancers susceptible to induced lysosomal storage.

Future Activities

Over the next fiscal year, our efforts will be focused on increasing sales of PROCYSBI in the U.S. and Europe; launching PROCYSBI in other countries in the EU; filing a New Drug Submission, or NDS, for cysteamine bitartrate delayed-release capsules with Health Canada in 2015; conducting a clinical trial to evaluate PROCYSBI in cystinosis patients that are cysteamine-naïve, as well as other supporting trials in underdeveloped markets; developing select global markets with significant numbers of known cystinosis patients; screening for undiagnosed and unidentified adult nephropathic cystinosis patients; supporting regulatory pathways and/or clinical trials of RP103 for the potential treatment of HD, pediatric NASH, Leigh syndrome and mitochondrial disorders; enhancing and expanding our product manufacturing capabilities; preparing for potential clinical studies of RP103 in new therapeutic indications; supporting our novel preclinical programs; and identifying promising products and drug development candidates for in-licensing.

We plan to seek additional business development partners in Asia for our Convivia product candidate. We may also develop new preclinical, clinical and or commercial opportunities, including proprietary molecules discovered in-house and in-licensed and acquired technologies.

Application of Critical Accounting Policies

Our consolidated financial statements and accompanying notes are prepared in accordance with generally accepted accounting principles used in the United States. Preparing financial statements requires management to make estimates and assumptions that affect the reported amounts of assets, liabilities, revenue and expenses. These estimates and assumptions are affected by management's application of accounting policies. We believe that understanding the basis and nature of the estimates and assumptions involved with the following aspects of our consolidated financial statements is critical to an understanding of our consolidated financial position and results of operations.

Many of the following critical accounting policies require us to make significant judgments and estimates in the preparation of our consolidated financial statements.

Revenue Recognition and Accounts Receivable

We recognize revenue in accordance with the Financial Accounting Standards Board, or FASB, Accounting Standards Codification, or ASC 605, *Revenue Recognition*, when the following criteria have been met: persuasive evidence of an arrangement exists; delivery has occurred and risk of loss has passed; the seller's price to the buyer is fixed or determinable and collectability is reasonably assured. We determine that persuasive evidence of an arrangement exists based on written contracts that define the terms of the arrangements. Pursuant to the contract terms, we determine when title to products and associated risk of loss has passed onto the customer. We assess whether the fee is fixed or determinable based on the payment terms associated with the transaction and whether the sales price is subject to refund or adjustment. We assess collectability based primarily on the customer's payment history and creditworthiness.

PROCYSBI is currently available for U.S. distribution from our U.S. specialty pharmacy partner, the Accredo Health Group, Inc. (“Accredo”) which is currently our only U.S. customer and ships directly to patients. Our commercial launch in the E.U. commenced in April 2014, with the Almac Group, Ltd. as our distributor. PROCYSBI is not available in U.S. retail pharmacies. Prior to the third quarter of 2014, revenue was recognized in the United States once the product had been shipped by the specialty pharmacy to patients because we had not yet been able to reasonably estimate the third-party payor mix and resulting rebates due to the lack of sufficient historical data. Beginning July 2014, we were able to reasonably estimate and determine sales allowances; therefore we began recognizing PROCYSBI revenue at the point of sale to the specialty pharmacy, which resulted in the one-time non-recurring recognition of an additional $4.4 million in net revenues during the quarter ended September 30, 2014. Revenue is currently recognized in the EU once confirmed orders from the pharmacies have been shipped and invoiced for payment by our distributor on our behalf.

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We record revenue net of expected discounts, distributor fees, and rebates, including government rebates such as Medicare and Medicaid in the United States. Allowances are recorded as a reduction of revenue at the time product sales are recognized. Allowances for government rebates and discounts are established based on the actual payor and payor mix information, which is known in the United States at the time of shipment to the distributor and in Germany at the time of shipment to the pharmacy, and the government-mandated discount rates applicable to government-funded programs. The allowances are adjusted to reflect known changes in the factors that may impact such allowances in the quarter the changes are known.

Trade accounts receivable are recorded net of product sales allowances for prompt-payment discounts and chargebacks. Estimates for chargebacks and prompt-payment discounts are based on contractual terms and our expectations regarding the utilization rates.

Inventories and Cost of Sales

Inventories are stated at the lower of cost or market price, with cost determined on a first-in, first-out basis. Inventories are reviewed periodically to identify slow-moving inventory based on sales activity, both projected and historical, as well as product shelf-life. Prior to the approval of PROCYSBI by the FDA on April 30, 2013 and in Europe, prior to EC approval on September 6, 2013, we recorded the purchase of raw materials and the manufacturing costs relating to PROCYSBI as research and development expense. Subsequent to FDA and EC approval, we began capitalizing these costs and manufacturing overhead as commercial inventory. Upon launching PROCYSBI in mid-June 2013 in the United States and April 2014 in the EU, we began recognizing cost of sales. Cost of sales includes the cost of inventory sold or reserved; manufacturing, manufacturing overhead and supply chain costs; product shipping and handling costs; and amortization of licensing approval milestone payments and licensing royalties payable to UCSD.

We capitalize inventory produced in preparation for product launches and expanded access programs when positive results have been obtained for the clinical trials that we believe are necessary to support regulatory approval and we have determined it is probable that these capitalized costs will provide some future economic benefit in excess of capitalized costs. For these inventories, we also consider the expected approval date in assessing realizability. To the extent that inventory is expected to expire prior to being sold, we will write down the value of inventory. If actual results differ from those estimates, additional inventory write-offs may be required.

Note Payable

Note payable consists of loan agreements with HC Royalty as lender, totaling $60 million. In July 2014, we modified our original December 2012 loan agreement with HC Royalty as lender, under which we borrowed $50 million in two $25 million tranches received in December 2012 and May 2013, to provide for an additional $10 million in term loan funding. The interest rate was revised to an annual fixed rate of 8.0%, compared to the original interest rate of 10.75%. The loan also contains a synthetic royalty component based on net product revenues, including PROCYSBI, in a calendar year, and such royalty is payable quarterly. The variable royalty rate under the amended and restated loan agreement has been revised to 8.0% on the first $50 million of revenue and 2.0% on revenue in excess of $50 million. The first loan principal payment of $3 million per quarter is due in June 2015. All term loans under the amended and restated loan agreement mature on March 31, 2020. The loan and our obligation to make payments thereunder shall terminate immediately when all payments received by HC Royalty equal $120 million.

Prior to July 1 2014, the loan bore interest at an annual fixed rate of 10.75% of outstanding principal and included a synthetic royalty component based on net product sales, including PROCYSBI, in a calendar year. With respect to the first $25 million tranche, for each calendar year, the loan bore a royalty rate of 6.25% of the first $25 million of product net revenues, 3.0% of product net revenues for such calendar year in excess of $25 million and up to $50 million, and 1.0% of product net revenues for such calendar year in excess of $50 million, payable quarterly. With respect to the second $25 million tranche, for each calendar year, the loan bore a royalty rate of 6.0% of the first $25 million of product net revenues for such calendar year, 3.0% of product net revenues for such calendar year in excess of $25 million and up to $50 million, and 1.0% of product net revenues for such calendar year in excess of $50 million, payable quarterly.

The fixed and royalty interest are recognized as interest expense as incurred. The revenue related royalty interest may lead to significant fluctuations in interest expense from period to period.

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Convertible Notes

In July 2014, we sold $60 million aggregate principal amount of 8.0% convertible senior notes due 2019 to HC Royalty and other purchasers. These convertible notes require quarterly interest distributions at a fixed coupon rate equal of 8.0% until maturity or conversion, which will be no later than August 1, 2019. The convertible senior notes are convertible at the option of the holder at a conversion rate of 57.14 common shares per $1,000 principal amount of convertible senior notes at issuance (equivalent to a conversion price of $17.50 per common share), subject to adjustment in certain events. In addition, the convertible senior notes will automatically convert into shares of common stock if the price of the common stock is at or above 175% of the applicable conversion price over a 30 consecutive day period. Upon conversion of these convertible senior notes by a holder, the holder will receive shares of our common stock. The fixed interest payments are recognized as interest expense as incurred.

Impairment of Goodwill and Intangible Assets

Goodwill represents the excess of the purchase price over the fair value of tangible and identified intangible net assets of businesses acquired. Goodwill is not amortized, but is evaluated for impairment on an annual basis or more often when impairment indicators are present. We have one reporting unit. Therefore, our consolidated net assets, including existing goodwill and other intangible assets, are considered to be the carrying value of the reporting unit. If the carrying value of the reporting unit is in excess of its fair value, an impairment may exist, and we must perform the second step of the analysis, in which the implied fair value of the goodwill is compared to its carrying value to determine the impairment charge, if any. If the estimated fair value of the reporting unit exceeds the carrying value of the reporting unit, goodwill is not impaired and no further analysis is required. We performed our goodwill impairment test as of December 31, 2014 and noted no impairment.

We make judgments about the recoverability of purchased intangible assets with finite lives whenever events or changes in circumstances indicate that impairment may exist. Recoverability of purchased intangible assets with finite lives is measured by comparing the carrying amount of the asset to the future undiscounted cash flows the asset is expected to generate. Impairment, if any, is measured as the amount by which the carrying value exceeds the fair value of the impaired asset.

Assumptions and estimates about future values and remaining useful lives of our purchased intangible assets are complex and subjective. They can be affected by a variety of factors, including external factors such as industry and economic trends and internal factors such as changes in our business strategy and our internal forecasts.

Common Stock Warrant Liabilities

The common stock warrants we issued in connection with certain fiscal year 2010 equity financings contain conditional obligations that may require us to transfer cash to settle the warrants upon the occurrence of certain fundamental transactions. Therefore, we have classified the warrants as liabilities. We re-measure the liability at the end of every reporting period with the change in value reported in our consolidated statements of operations. At the exercise date, the fair values of these warrants are re-measured and reclassified to equity.

We use the Black-Scholes option pricing model as our method of valuation for warrants that are subject to warrant liability accounting. The determination of the fair value as of the reporting date is affected by our stock price as well as assumptions regarding a number of highly complex and subjective variables. These variables include, but are not limited to, expected stock price volatility over the term of the security and risk-free interest rate. In addition, the Black-Scholes option pricing model requires the input of an expected life for the securities for which we have estimated based upon the stage of our development. The fair value of the warrant liability is revalued each balance sheet date utilizing Black-Scholes valuation model computations with the decrease or increase in fair value being reported in the statement of operations as other income or expense, respectively. The primary factors affecting the fair value of the warrant liability are our stock price and volatility. In addition, the Black-Scholes option pricing model requires the input of highly subjective assumptions, and other reasonable assumptions could provide differing results.

We reported a net loss of $52.5 million for the year ended December 31, 2014. If our December 31, 2014 closing stock price had been 10% lower, our net loss would have been approximately $0.1 million lower. If our December 31, 2014 closing stock price had been 10% higher, our net loss would have been approximately $0.1 million higher.

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If our December 31, 2014 volatility assumption had been 10% lower, our net loss would have been approximately the same. If our December 31, 2014 volatility assumption had been 10% higher, our net loss would have been approximately the same.

We reported a net loss of $69.4 million for the year ended December 31, 2013. If our December 31, 2013 closing stock price had been 10% lower, our net loss would have been approximately $0.9 million lower. If our December 31, 2013 closing stock price had been 10% higher, our net loss would have been approximately $0.9 million higher

If our December 31, 2013 volatility assumption had been 10% lower, our net loss would have been approximately $0.1 million lower. If our December 31, 2013 volatility assumption had been 10% higher, our net loss would have been approximately $0.1 million higher.

Stock-Based Compensation

Determining the fair value of share-based awards at the grant date requires judgment, including estimating future stock price volatility and employee stock option exercise behavior.

We based our Black-Scholes inputs on the following factors: the expected life of six years was based upon our assessment of the ten-year term of the stock options issued, along with the fact that we have been a commercial company since June 2013 and as a result, more option holders have been exercising stock options; the risk-free interest rate was based on current constant maturity treasury bill rates for six years; the volatility was based on a combination of the actual annualized volatility of our common stock price as quoted on NASDAQ since the closing of our 2009 Merger on September 30, 2009 and of annualized volatility of peer companies; the forfeiture rate was based on our assessment of our historical employee turnover; and the dividend rate was based on our current decision to not pay dividends on our stock at our current corporate stage of development. If actual results differ significantly from these estimates, stock-based compensation expense and results of operations could be materially impacted. Prior to 2014, we utilized an expected life of five years. See *Note 11* of our consolidated financial statements for a further discussion of our accounting for stock-based compensation.

Income Taxes

Income taxes are recorded under the liability method, under which deferred tax assets and liabilities are determined based on the difference between the financial statement and tax bases of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to affect taxable income. Valuation allowances are established when necessary to reduce deferred tax assets to the amount expected to be realized. Based on the weight of available evidence, including cumulative losses since inception and expected future losses, we have determined that it is more likely than not that the deferred tax asset amount will not be realized and therefore a full valuation allowance has been provided on our net deferred tax assets. We intend to maintain the valuation allowance until sufficient positive evidence exists to support the reversal of the valuation allowance. Any decision to reverse part or all of the valuation allowance would be based on our estimate of future profitability.

We identify uncertain tax positions and record or disclose any resulting potential tax liability based upon whether the position is more likely than not sustainable upon examination. We consider proposed assessments by tax authorities, changes in facts and circumstances, issuance of new regulations or new case law and negotiations between tax authorities of different countries concerning our transfer prices or intellectual property transfers. As of December 31, 2014, we had identified no uncertain tax positions.

We file U.S. Federal, California, various other state and other income tax returns and various foreign country income tax returns. We are currently not subject to any income tax examinations. Due to our net operating losses, all tax years generally remain open in each jurisdiction.

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Results of Operations

For the Years Ended December 31, 2014 and 2013

	For the Year Ended December 31,	
(In millions)	**2014**	**2013**
Revenues	$ 69.5	$ 16.9
Cost of sales	9.4	1.7
Gross profit	60.1	15.2
Operating expenses:		
Research and development	43.5	29.2
Selling, general, and administrative	56.7	37.9
Total operating expenses	100.1	67.1
Loss from Operations	(40.1)	(51.9)
Interest expense	(14.0)	(6.8)
Adjustment to the fair value of common stock warrants	(1.1)	(10.7)
Other	2.6	0.1
Net Loss	$ (52.5)	$ (69.4)

Revenue

We recognized $17.3 million and $10.2 million in PROCYSBI net product sales for the fourth quarters of 2014 and 2013, respectively. Net product sales for the years ended December 31, 2014 and 2013 totaled $69.5 million and $16.9 million, respectively. The increase in revenue was driven by continued market penetration in both the United States and Europe. PROCYSBI became commercially available in the U.S. in June 2013 and in Europe in April 2014.

Cost of Sales

Prior to the approval of PROCYSBI by the FDA on April 30, 2013 and in Europe, prior to EMA approval on September 6, 2013, we recorded manufacturing costs relating to PROCYSBI as research and development expense. Subsequent to approval, we began capitalizing these costs as commercial inventory. As a result, our cost of sales for 2013 and 2014 will reflect a lower average per unit cost of goods than will be recorded in the future. Cost of sales primarily includes: raw materials and manufacturing costs for our commercial product PROCYSBI, amortization of licensing milestone payments, royalty fees due to UCSD on our net product sales, other indirect costs such as distribution, labeling, shipping and supplies, and provision for inventory expiration. Costs capitalized as inventory are expensed as cost of sales as product is sold.

During the year ended December 31, 2014, we recorded cost of sales of $9.4 million, primarily due to a $3.2 million provision for inventory expiration, royalties, and allocated manufacturing costs. During the year ended December 31, 2013, we recorded cost of sales of $1.7 million, including a $0.4 million reserve representing commercial inventory that was capitalized subsequent to FDA approval but written off due to an unanticipated minor change in the finished product presentation.

Research and Development

Research and development expenses include medical, clinical, regulatory, quality, pharmacovigilance and research salaries and benefits; expenses associated with the manufacturing and testing of PROCYSBI inventory for our commercial launch in the United States and in Europe which were expensed prior to drug approvals; preclinical studies; clinical trials; regulatory and clinical consultants; research supplies and materials; amortization of intangible assets and allocated human resources and facilities expenses.

For the years ended December 31, 2014 and 2013, our research and development expenses were $43.5 million and $29.2 million, respectively. The increase in research and development expenses relates primarily to increased clinical product manufacture of RP103 for the potential treatment of HD, NASH, cystinosis extension, and other supporting study expenses and related employee compensation, partially offset by a reduction in Phase 3 cystinosis clinical trial expenses.

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The following table shows major program expenses recorded as research and development expenses.

Major Program Expenses Recorded as Research and Development

(In millions)	For the Year Ended December 31, 2014	2013
RP103:		
Cystinosis (pre-commercial and extension)	$ 12.9	$ 14.8
HD (clinical)	2.0	0.8
NASH (clinical)	1.9	2.0
Preclinical programs	2.0	1.1
Other programs	2.2	0.8
R&D personnel and other costs not allocated to programs	22.5	9.7
Total Research and Development Expenses	$ 43.5	$ 29.2

Selling, General and Administrative Expenses

Selling, general and administrative expenses primarily include commercial expenses related to marketing and sales efforts in the United States and EU, including marketing and pricing studies, advertising, sales force commissions and other expenses, and market access support activities; commercial launch expenses for PROCYSBI, including patient support activities such as reimbursement assistance and establishing a customer relationship management system for our PROCYSBI sales team; intellectual property, legal and audit fees, finance, executive and commercial operations salaries and benefits; and other administrative and facilities costs.

For the years ended December 31, 2014 and 2013, our selling, general and administrative expenses were $56.7 million and $37.9 million, respectively. The increase in selling, general and administrative expenses is primarily due to increased expenses related to commercial launch and ongoing operations and marketing activities for PROCYSBI, employee compensation, stock-compensation for employees and directors, accounting fees, legal fees and investor relations costs.

For the year ended December 31, 2013, our program expenses in selling, general and administrative expenses consisted primarily of pre-commercial and commercial launch expenses for PROCYSBI. The following table shows major program expenses recorded as selling, general and administrative expenses.

Major Program Expenses Recorded as Selling, General and Administrative Expenses

(In millions)	For the Year Ended December 31, 2014	2013
RP103:		
Cystinosis (pre-commercial and extension)	$ 6.7	$ 9.8
HD (clinical)	1.0	0.5
NASH (clinical)	0.1	0.1
Other programs	0.5	0.2
Total Selling, General, and Administrative Expenses	$ 8.3	$ 10.6

Interest Expense

Interest expense for the years ended December 31, 2014 and 2013 was $14.0 million and $6.8 million, respectively. The increase in interest expense was due primarily to an increase in royalty fees pursuant to the HC Royalty loan agreement based on net sales for the period. Also contributing to the increase was the issuance of $60 million of convertible notes in July 2014 and an amendment to the $50.0 million loan agreement that we entered into with HealthCare Royalty Partners II, L.P., or HC Royalty, in December 2012, which was amended in July 2014 to provide for an additional $10 million in term loan funding.

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Adjustment to the Fair Value of Common Stock Warrants

Adjustment to the fair value of common stock warrants were losses of $1.1 million and $10.7 million for the years ended December 31, 2014 and 2013, respectively. The decrease in fair value adjustment was due primarily to the decrease in the number of warrants outstanding.

Other Income

In 2014, we received a cash payment in the amount of $2.3 million from a stockholder in disgorgement of alleged short-swing profits under Section 16(b) of the Securities Exchange Act of 1934. This amount is recorded as *Other Income* on our consolidated financial statements.

Current Status of Major Programs

Please refer to the Item 1 of this Annual Report on Form 10-K for a detailed discussion of each of our major programs. We currently have product candidates in clinical development as potential treatments for HD, pediatric NASH, Leigh syndrome and other mitochondrial disorders and ALDH2. Our preclinical programs are based upon bioengineered novel drug candidates that are designed to target cancer and other diseases. We continue efforts to out-license Convivia in additional territories.

Any of our major programs could be partnered for further development and/or could be accelerated, slowed or ceased due to scientific results or challenges in obtaining funding. We anticipate that we will need additional funding in order to pursue our plans beyond the next 24 months. In addition, the timing and costs of development of our programs beyond the next 24 months is highly uncertain and difficult to estimate. See Part I, Item 1A of this Annual Report on Form 10-K titled "Risk Factors" for further discussion about the risks and uncertainties pertaining to drug development.

For the Four Months Ended December 31, 2012 and the Fiscal Year Ended August 31, 2012

(In millions)	For the Four Months Ended December 31, 2012	For the Year Ended August 31, 2012
Revenues	$ -	$ -
Operating expenses:		
Research and development	8.9	21.4
Selling, general, and administrative	9.0	14.7
Total operating expenses	17.9	36.2
Loss from Operations	(17.9)	(36.2)
Interest expense	(0.1)	(0.0)
Adjustment to the fair value of common stock warrants	(1.5)	(3.2)
Other	0.2	0.7
Net Loss	$ (19.3)	$ (38.6)

Research and Development

For the four months ended December 31, 2012, our research and development expenses consisted primarily of costs associated with the manufacturing and testing of clinical and commercial materials in anticipation for our approval and commercial launch of RP103 for cystinosis, clinical trial research expenses and employee compensation.

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For the year ended August 31, 2012, research and development expenses include medical, clinical, regulatory and scientists' compensation and benefits, lab collaborations, preclinical studies, clinical trials, amortization of intangible assets and allocated human resources and facilities expenses.

Major Program Expenses Recorded as Research and Development

(In millions)	For the Four Months Ended December 31, 2012	For the Year Ended August 31, 2012
RP103: All indications (clinical/pre-commercial)	$ 5.1	$ 18.2
Preclinical programs	0.2	0.0
Other programs	0.2	1.7
R&D personnel and other costs not allocated to programs	3.4	1.5
Total Research and Development Expenses	$ 8.9	$ 21.4

General and Administrative Expenses

For the four months ended December 31, 2012, our general and administrative expenses consisted primarily of expenses for pre-commercial operations requirements for RP103 for the potential treatment of cystinosis, employee compensation, stock compensation for employees and directors, legal fees and investor relations costs. Additional major program expenses include patent fees and patent expenses which were recorded as general and administrative expenses as these fees are to support patent applications (not issued patents) and expenses related to the pre-commercial launch of RP103 for the potential treatment of cystinosis.

For the year ended August 31, 2012, general and administrative expenses included finance, executive and sales and marketing compensation and benefits, pre-commercial expenses, such as reimbursement and marketing studies, corporate costs, such as legal and auditing fees, business development expenses, travel, board of director fees and expenses, investor relations expenses, intellectual property costs associated with filed (but not issued) patents, administrative consulting and allocated human resources and facilities costs.

Major Program Expenses Recorded as General and Administrative Expenses

For the four months ended December 31, 2012 and the fiscal year ended August 31, 2012, our program expenses in general and administrative expenses consisted primarily of pre-commercial launch expenses for RP103, such as market research and market access studies.

(In millions)	For the Four Months Ended December 31, 2012	For the Year Ended August 31, 2012
RP103: All indications (clinical/pre-commercial)	$ 3.2	$ 2.7
Other programs	0.2	0.1
Total Selling, General, and Administrative Expenses	$ 3.4	$ 2.8

Adjustment to the Fair Value of Common Stock Warrants

Adjustment to the fair value of common stock warrants was a loss of approximately $1.5 million for the four months ended December 31, 2012. Adjustment to the fair value of common stock warrants was a loss of approximately $3.2 million for the year ended August 31, 2012.

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Liquidity and Capital Resources

Capital Resources

As of December 31, 2014, we had $149.6 million in cash and cash equivalents, of which $5.4 million is held by our foreign subsidiaries, $29.1 million in current liabilities and $142.5 million of net working capital. During the year ended December 31, 2014, we raised $66 million of net proceeds from modification of our loan agreement with HC Royalty Partners and the issuance of convertible notes, $44.8 million in proceeds after commissions under our at-the-market ("ATM") common stock sales agreement, $1.8 million net proceeds from warrant exercises and $6.8 million net proceeds from stock option exercises and our employee stock purchase plan. We believe that our cash balance will be sufficient to meet our projected operational requirements and obligations at least through 2016.

Under the terms of the HC Royalty loan agreement executed on December 20, 2012, we received $23.4 million in net proceeds from the first tranche of the loan at closing in December 2012. We received an additional $23.7 million in net proceeds in May 2013 from the second tranche upon FDA approval of RP103 for the management of cystinosis. In July 2014, we modified our original December 2012 loan agreement to provide for an additional $10 million in term loan funding. The loan matures on March 31, 2020, bears interest at an annual fixed rate of 8.0% (after the July 2014 modification) and has a synthetic royalty, tiered down, based on a percentage of net product sales. The loan is interest-only until June 2015. In July 2014, we also sold $60 million of convertible senior notes, which bear a fixed interest rate of 8.0% until maturity in August 2019, if not yet converted. The proceeds from the loans are being used primarily to fund the commercialization of PROCYSBI for the management of cystinosis, advance our development programs and for general corporate purposes.

On April 30, 2012, we entered into a Sales Agreement with Cowen and Company, or Cowen, to sell shares of our common stock, with aggregate gross sales proceeds of up to $40 million, from time to time through an "at the market" equity offering program under which Cowen acted as sales agent. We paid a 3% commission to Cowen on all sales pursuant to this Sales Agreement.

On July 3, 2013, we amended and restated the Sales Agreement to increase the aggregate gross sales proceeds that may be raised to $100 million. Cumulatively through December 31, 2014, we sold 12,569,914 shares under the ATM offerings at a weighted-average selling price of $7.96 per share for net proceeds of approximately $97 million. During the three months ended December 31, 2014, we sold 4,970,440 shares under the ATM for net proceeds of approximately $45 million.

As of February 20, 2015, there were warrants exercisable for an aggregate of 334,764 shares of our common stock outstanding.

Future Funding Requirements

We will need to raise additional capital through the sale of either equity or debt or both to fund our operations and to, among other activities, continue to commercialize PROCYSBI and develop RP103 for the potential treatment of other indications. Our future capital requirements may be substantial, and will depend on many factors, including:

- The continuing sales of PROCYSBI in the United States and Europe;
- The ongoing costs of establishing and maintaining sales and marketing capabilities in the United States, Europe and other countries;
- Our ability to negotiate reimbursement and pricing of PROCYSBI in various countries outside of the United States;
- The cost of our manufacturing-related activities in support of PROCYSBI and RP103;
- The cost of activities and outcomes related to the regulatory submission of cysteamine bitartrate delayed-release capsules in Canada;
- The cost of additional clinical trials in order to obtain regulatory approvals for PROCYSBI in non-U.S. and non-European countries;
- The timing and cost of our ongoing clinical programs for RP103, including: evaluating PROCYSBI in treatment-naïve cystinosis patients, and other supportive studies; evaluating RP103 as a potential treatment for HD; evaluating RP103 as a potential treatment for NASH in children; evaluating RP103 as a potential treatment for Leigh syndrome and other mitochondrial disorders;

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- The cost of regulatory submissions, as well as the preparation, initiation and execution of clinical trials in potential new clinical indication using RP103;
- The cost of evaluating and potentially acquiring or in-licensing new drug compound(s) for potential clinical development and commercialization; and
- The cost of filing, surveillance around, prosecuting, defending and enforcing patent claims.

There can be no assurance that we will be successful in raising sufficient funds when needed. Additional financing may not be available in amounts or on terms satisfactory to us or at all.

Research and Development Activities

We plan to conduct further research and development, to support several clinical trials for RP103, improve upon our internal discovery molecules and in-licensed technology and continue business development efforts for our preclinical and other clinical-stage product candidates in the next 12 months. We plan to conduct research and development activities by our own laboratory staff and also by engaging contract research organizations, clinical research organizations and contract manufacturing organizations. We also plan to incur costs for the production of our clinical study drug candidate RP103 for the potential treatment of HD and NASH; for production of RP103 for additional clinical trials in cystinosis; clinical and medical advisors; and consulting and collaboration fees. We anticipate that our research and development costs will increase during the next 12 months primarily due to the addition of new studies in support of cystinosis, HD, pediatric NASH, Leigh syndrome and other indications.

Selling, General and Administrative Activities

Selling, general and administrative costs in the next 12 months will consist primarily of sales activities surrounding the sale of PROCYSBI in the United States and Europe and the commercial launch of PROCYSBI in additional countries in Europe, of legal, business development, tax and accounting fees, patent legal fees, investor relations expenses, board fees and expenses, insurance, rent and facility support expenses. We anticipate that selling, general and administrative expenses will continue to increase in support of PROCYSBI sales growth, as well as an increase in facilities and administrative expenses to support our anticipated growth.

Capital Expenditures

In the next 12 months, we expect to increase our capital expenditures on laboratory and office equipment and computer software and hardware as we continue to increase our staff in 2015.

Contractual Obligations

Contractual Obligations with UCSD Relating to the Acquisition of the DR Cysteamine (RP103) License

Pursuant to our license agreement with UCSD, we are obligated to pay milestone payments (ranging in size for orphan and non-orphan indications) upon the occurrence of certain events during the life of the license agreement. These include a royalty on commercial net sales from products developed pursuant to the agreement, a percentage of sublicense fees, a percentage of sublicense royalties, and a minimum annual royalty. Under the license agreement, we are obligated to fulfill predetermined milestones within a specified number of years from the effective date of the agreement, depending on the indication. Cumulatively, we have expensed approximately $0.9 million in milestone payments to UCSD based upon the initiation of clinical trials in cystinosis, Huntington's disease and NASH and on regulatory filings in cystinosis. In March 2012, we filed an MAA with the EMA, as well as an NDA with the FDA for RP103 for the potential treatment of cystinosis. In conjunction with the achievement of MAA/NDA filing milestone, we paid additional milestone payments to UCSD pursuant to this license. Based on approval of RP103 by the FDA on April 30, 2013 we paid a milestone license of $0.75 million which was capitalized as commercial IP and is being amortized as expense in cost of sales over the life of the patent. Based on approval by the EMA of RP103 on September 6, 2013, we paid a milestone license of $0.5 million which was capitalized as commercial IP and is being amortized as expense in cost of sales over the life of the patent. In 2013, we began paying UCSD royalties based upon our net sales of PROCYSBI. Other future milestones will be payable based on other regulatory approvals and clinical trial milestones.

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Other Contractual Obligations

We have contractual obligations under our capital and operating leases and other obligations related to research and development activities, purchase commitments and licenses. Information about these obligations as of December 31, 2014 is presented in the table below:

(In thousands)	< 1 year	1 - 3 Years	3 - 5 Years	> 5 Years	Total
Debt principal	$ 9,000	$ 24,000	$ 24,000	$ 3,000	$ 60,000
Convertible notes	-	-	60,000	-	60,000
Operating lease obligations	1,553	3,768	3,800	3,329	12,450
Purchase commitments and research and development/clinical	6,979	831	108	300	8,218
Total	$ 17,532	$ 28,599	$ 87,908	$ 6,629	$ 140,668

We maintain several contracts with contract manufacturers, clinical organizations and clinical sites, drug labelers and distributors and research organizations, primarily to assist with clinical research and clinical manufacturing for our cystinosis and HD programs and our NASH clinical collaboration. The future commitments pursuant to these agreements, some of which include estimates of amounts or timing of payments, are included in the table above as research and development and purchase commitments.

We are also subject to contingent payments related to various development activities totaling approximately $17.1 million, which are primarily due upon the achievement of certain development and commercial milestones if such milestones occur before certain dates in the future. These contingent payments are not included in the table above as we cannot reliably predict their timing or occurrence.

In conjunction with our HC Royalty loan agreement, we have contractual interest payments that began in December 2012 at a fixed rate of 10.75% plus a percentage of product revenue. In July 2014, these fixed interest payments were amended to 8.00%. We also issued senior convertible notes which bear fixed interest of 8.00%. The fixed interest amount that remains committed through the term of the amended loan agreement and convertible senior notes is approximately $36.2 million.

Off-Balance Sheet Arrangements

We do not have any outstanding derivative financial instruments, off-balance sheet guarantees, interest rate swap transactions or foreign currency contracts. We do not engage in trading activities involving non-exchange traded contracts.

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ITEM 7A: QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

Market risk represents the risk of changes in the value of market risk sensitive instruments caused by fluctuations in interest rates, foreign exchange rates and commodity prices. We are exposed to various market risks that may arise from adverse changes in market rates and prices, such as foreign exchange rate and interest rate fluctuations. We do not enter into derivatives or other financial instruments for trading or speculative purposes.

Foreign Exchange Risk

A majority of our assets and liabilities are maintained in the United States in U.S. dollars and a majority of our expenditures are transacted in U.S. dollars. We are subject to foreign exchange risk for the operations of Raptor Pharmaceuticals Europe B.V., Raptor Pharmaceuticals France SAS, and Raptor Pharmaceuticals Germany GmbH, which use the Euro as their functional currency. We do not believe that a hypothetical one percentage point fluctuation in the U.S. dollar exchange rate would materially affect our consolidated financial position, results from operations or cash flows as of December 31, 2014. We do not currently hedge our foreign currency transactions.

Interest Rate Risk

As of December 31, 2014, we had approximately $137.9 million in cash equivalent money market accounts, yielding approximately 0.06% per year. A hypothetical one percentage point decline in interest rates would not have materially affected our consolidated financial position, results of operations or cash flows as of December 31, 2014.

ITEM 8: FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

The information required to be filed in this item appears on pages 91 to 120 of this Annual Report on Form 10-K.

Documents filed as part of this Annual Report on Form 10-K:

Financial Statements

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PART II – FINANCIAL INFORMATION

ITEM 9: CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

ITEM 9A: CONTROLS AND PROCEDURES

Evaluation of Disclosure Controls and Procedures

Disclosure controls and procedures are controls and other procedures that are designed to ensure that information required to be disclosed in our reports filed or submitted under the Securities Exchange Act of 1934, as amended, is recorded, processed, summarized and reported, within the time periods specified in the Securities and Exchange Commission's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed in our reports filed under the Exchange Act is accumulated and communicated to management, including our principal executive officer and our principal financial officer, as appropriate, to allow timely decisions regarding required disclosure. As of the end of the period covered by this report, the Company carried out an evaluation under the supervision and with the participation of its management, including the Company's Chief Executive Officer ("CEO") and its Chief Financial Officer ("CFO"), of the effectiveness of the design and operation of the Company's disclosure controls and procedures in ensuring that material information required to be disclosed in the Company's reports filed or submitted under the Exchange Act, has been made known to them in a timely fashion. Based on this evaluation, the CEO and CFO concluded that the Company's disclosure controls and procedures were not effective as of December 31, 2014 due to a material weakness in our internal control over financial reporting related to our inventory costing and overhead allocations for our commercial product PROCYSBI, which is disclosed below. Notwithstanding the identified material weakness, management of the Company does not believe that these deficiencies had an adverse effect on our reported operating results or financial condition and management has determined that the financial statements and other information included in this Annual Report on Form 10-K and other periodic filings present fairly in all material respects the financial position and results of operations at and for the periods presented in accordance with the accounting principles generally accepted in the United States of America ("GAAP").

Management's Annual Report on Internal Control over Financial Reporting

Management of the Company is responsible for establishing and maintaining adequate internal control over financial reporting as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act. The Company's internal control over financial reporting is designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. The Company's internal control over financial reporting includes those policies and procedures that (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the Company; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the Company are being made only in accordance with authorizations of management and directors of the Company; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of the Company's assets that could have a material effect on the consolidated financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. All control systems have inherent limitations so that no evaluation of controls can provide absolute assurance that all control issues are detected. A control system, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the internal control system are met. We are continuously seeking to improve the efficiency and effectiveness of our operations and of our internal controls. This results in refinements to processes throughout our organization. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Under the supervision and with the participation of our management, we assessed the effectiveness of the Company's internal control over financial reporting as of December 31, 2014, based on the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission ("COSO") in the 2013 *Internal Control-Integrated Framework*. Based on the results of our assessment, we concluded that there was a material weakness in the design and operating effectiveness of our internal control over financial reporting related to our inventory costing and overhead allocations for our commercial product PROCYSBI as of December 31, 2014. A material weakness is defined as a deficiency or a combination of deficiencies, in internal control over financial reporting such that there is a reasonable possibility that a material misstatement of our annual or interim financial statements will not be prevented or detected on a timely basis.

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During the year ended December 31, 2014, we determined that certain management review controls, including those designed to provide oversight over our inventory costing and tracking systems were not effective. Our findings related to both the design and operating effectiveness of these controls. Although certain adjustments identified during the year related to a variety of accounts and were not material, we concluded that these control deficiencies could lead to misstatements in the aforementioned accounts and related disclosures, which would give rise to a reasonable possibility that a material misstatement of the consolidated financial statements would not be prevented or detected. Accordingly, management has determined that these control deficiencies collectively constitute a material weakness. Given this material weakness, management concluded that the Company did not maintain effective internal control over financial reporting as of December 31, 2014, based on the criteria in the 2013 *Internal-Control Integrated Framework* issued by the COSO.

Grant Thornton LLP, an independent registered public accounting firm, has audited the effectiveness of the Company's internal control over financial reporting as of December 31, 2014 as stated in their report, which is referenced in the index appearing under Item 8.

Material Weakness and Remediation Activities

As part of our assessment of internal control over financial reporting as of December 31, 2014, during the fourth quarter of 2014, we determined that our reviews of our inventory costing and overhead allocations for our commercial product PROCYSBI were not performed at a sufficiently detailed level to detect errors in our inventory and related accounts.

With the oversight of management and our Audit Committee, we have initiated actions to address the root causes of the material weakness identified in 2014. These following actions are planned to be implemented in 2015.

- We will implement additional automated controls related to our standard costing overhead model, add additional requirements to our tolerances, and add additional and more precise general and management review controls to ensure that all available information is properly considered and reconciled.
- We will add additional personnel as needed to support our inventory supply chain process, including personnel in senior level oversight roles to improve the precision and effectiveness of the review function throughout the company.

The material weakness will not be considered remediated until the remedial controls operate for a sufficient period.

ITEM 9B: OTHER INFORMATION

None.

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PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by Item 10 is incorporated herein by reference to the definitive Proxy Statement to be filed with the SEC pursuant to Regulation 14A within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

ITEM 11. EXECUTIVE COMPENSATION

The information required by Item 11 is incorporated herein by reference to the definitive Proxy Statement to be filed with the SEC pursuant to Regulation 14A within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The information required by Item 12 is incorporated herein by reference to the definitive Proxy Statement to be filed with the SEC pursuant to Regulation 14A within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

The information required by Item 13 is incorporated herein by reference to the definitive Proxy Statement to be filed with the SEC pursuant to Regulation 14A within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

ITEM 14. PRINCIPAL ACCOUNTING FEES AND SERVICES

The information required by Item 14 is incorporated herein by reference to the definitive Proxy Statement to be filed with the SEC pursuant to Regulation 14A within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

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PART IV

ITEM 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES

The information required to be filed in this item appears on pages 91 to 120 of this Annual Report on Form 10-K.

(a) Documents filed as part of this Annual Report on Form 10-K:

(1) Index list to Consolidated Financial Statements:

(2) Schedule II is included on page 121 of this report. All other schedules are omitted because they are not required or the required information is included in the financial statements or notes thereto.

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Exhibits

The following exhibits are filed as part of, or incorporated by reference into this Annual Report on Form 10-K:

		Incorporated by Reference			
Exhibit Number	**Exhibit Description**	**Form**	**Date**	**Exhibit Number**	**Filed Here with**
2.1	Agreement and Plan of Merger and Reorganization, dated June 7, 2006, among Axonyx Inc., Autobahn Acquisition, Inc. and TorreyPines Therapeutics, Inc.	S-4	7/25/2006	Annex A	
2.2	Amendment No. 1 to Agreement and Plan of Merger and Reorganization, dated August 25, 2006, among Axonyx Inc., Autobahn Acquisition, Inc. and TorreyPines Therapeutics, Inc.	S-4/A	8/25/2006	Annex A	
2.3	Agreement and Plan of Merger and Reorganization, dated July 27, 2009, among ECP Acquisition, Inc., Raptor Pharmaceuticals Corp. and TorreyPines Therapeutics, Inc.	8-K	7/28/2009	2.1	
3.1	Certificate of Incorporation of the Registrant	8-K	10/10/2006	3.1	
3.2	Amended and Restated Bylaws of the Registrant	8-K	2/26/2014	3.1	
3.3	Certificate of Amendment to the Articles of Incorporation of Axonyx Inc., filed with the Secretary of State of the State of Nevada, effecting an 8-for-1 reverse split of the Registrant's common stock and changing the name of the Registrant from Axonyx Inc. to TorreyPines Therapeutics, Inc.	8-K	10/10/2006	3.3	
3.4	Articles of Conversion of TorreyPines Therapeutics, Inc., filed with the Secretary of State of the State of Nevada, changing the state of incorporation of the Registrant	8-K	10/10/2006	3.4	
3.5	Certificate of Conversion of TorreyPines Therapeutics, Inc., filed with the Secretary of State of the State of Delaware	8-K	10/10/2006	3.5	
3.6	Certificate of Amendment to Certificate of Incorporation of TorreyPines Therapeutics, Inc.	8-K	10/5/2009	3.1	
3.7	Certificate of Merger of ECP Acquisition, Inc. with and into Raptor Pharmaceuticals Corp.	8-K	10/5/2009	3.2	
4.1	Specimen common stock certificate of the Registrant	8-K	10/5/2009	4.7	
4.2(a)	Rights Agreement, dated as of May 13, 2005, between Registrant and The Nevada Agency and Trust Company, as Rights Agent	8-K	5/16/2005	99.2	
4.2(b)	Amendment to Rights Agreement, dated as of June 7, 2006, between Registrant and The Nevada Agency and Trust Company, as Rights Agent	8-K	6/12/2006	4.1	
4.2(c)	Amendment to Rights Agreement, dated as of October 3, 2006, between Registrant and The Nevada Agency and Trust Company, as Rights Agent	10-K	3/29/2007	4.19	
4.2(d)	Amendment to Rights Agreement, dated as of July 27, 2009, to the Rights Agreement dated May 13, 2005 between Registrant and American Stock Transfer and Trust Company (replacing The Nevada Agency and Trust Company)	8-K	7/28/2009	4.1	
4.2(e)	Amendment to Rights Agreement, dated August 6, 2010, by and between Registrant and American Stock Transfer & Trust Company, LLC	8-K	8/10/2010	4.2	
4.3	Form of Warrant, dated September 27, 2005, issued to Oxford Financial and Silicon Valley Bank	10-K	3/29/2007	4.16	
4.4*	Warrant, dated December 14, 2007, issued to Flower Ventures, LLC	10QSB**	4/15/2008	4.1	

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4.5*	Warrant Agreement Amendment, dated December 17, 2009, between Flower Ventures, LLC and the Registrant	10-Q	4/9/2010	4.15	
10.1#	TorreyPines Therapeutics, Inc. 2006 Equity Incentive Plan	8-K	10/4/2006	10.1	
10.2#	Form of Stock Option Agreement under TorreyPines Therapeutics, Inc. 2006 Equity Incentive Plan	8-K	10/4/2006	10.2	
10.3#	2006 Equity Incentive Plan of Raptor Pharmaceuticals Corp., as amended	S-8**	2/28/2007	4.3	
10.4#	Amendment to 2006 Equity Incentive Plan of Raptor Pharmaceuticals Corp.	10-K/A**	12/23/2008	10.5	
10.5#	Raptor Pharmaceutical Corp. 2010 Stock Incentive Plan	DEF14A	2/5/2010	Appendix A	
10.6#	Amendments to the Raptor Pharmaceutical Corp. 2010 Stock Incentive Plan	S-8	4/26/2011	4.15	
10.7#	Form of Award Agreement under the Raptor Pharmaceutical Corp. 2010 Stock Incentive Plan	8-K	9/28/2011	10.1	
10.8#	Amendment to the Raptor Pharmaceutical Corp. 2010 Stock Incentive Plan	8-K	7/25/2013	10.1	
10.9	Securities Purchase Agreement, dated December 17, 2009, between the investors signatories thereto and the Registrant	8-K	12/18/2009	10.1	
10.10	Securities Purchase Agreement, dated August 9, 2010, among the investors signatory thereto and the Registrant	8-K	8/10/2010	10.1	
10.11	Securities Purchase Agreement, dated August 9, 2010, among the investors signatory thereto and the Registrant	8-K	8/10/2010	10.2	
10.12	Registration Rights Agreement, dated April 16, 2010, between Lincoln Park Capital Fund, LLC and the Registrant	8-K	4/22/2010	10.2	
10.13	Registration Rights Agreement, dated August 12, 2010, among the signatories thereto and the Registrant	8-K	8/13/2010	10.3	
10.14#	Employment Agreement, dated May 15, 2006, between Dr. Todd Zankel and Raptor Pharmaceuticals Corp.	8-K**	5/26/2006	10.6	
10.15#	First Amendment to Employment Agreement, dated January 1, 2009, between Dr. Todd Zankel and Raptor Pharmaceuticals Corp.	8-K**	1/5/2009	10.3	
10.16#	Employment Agreement, dated September 7, 2007, between Thomas E. Daley and Raptor Therapeutics Inc.	10-QSB**	1/14/2008	10.1	
10.17#	First Amendment to Employment Agreement, dated January 1, 2009, between Thomas E. Daley and Raptor Pharmaceuticals Corp.	8-K**	1/5/2009	10.4	
10.18#	Offer Letter, dated April 8, 2009, between and Dr. Patrice Rioux and Raptor Therapeutics Inc.	8-K**	4/14/2009	10.1	
10.19++#	Offer Letter, dated January 1, 2011, between Patrick Reichenberger and Raptor Therapeutics Inc.	10-K	11/14/2011	10.17	
10.20++#	Employment Agreement, dated April 15, 2012, between Henk Doude van Troostwijk and Raptor Pharmaceuticals Europe B.V.	10-Q	7/10/2012	10.1	
10.21++#	Employment Agreement, dated September 10, 2012, between Kim R. Tsuchimoto and the Registrant	8-K	9/12/2012	10.3	
10.22#	Employment Agreement, dated September 25, 2012, between Kathy Powell and the Registrant	8-K	10/1/2012	10.1	
10.23++	Research and License Agreement, dated May 10, 2004, between TPTX, Inc. and Life Science Research Israel Ltd.	8-K	10/10/2006	10.2	

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10.24	Asset Purchase Agreement, dated October 17, 2007, between Convivia, Inc., Raptor Therapeutics, Inc. and Raptor Pharmaceuticals Corp.	10QSB**	1/14/2008	10.3	
10.25	Merger Agreement, dated December 14, 2007, between Encode Pharmaceuticals, Inc., Raptor Therapeutics, Inc. and Raptor Pharmaceuticals Corp.	10QSB/A**	4/15/2008	10.1	
10.26++	Pharmaceutical Development Services Agreement, dated January 7, 2008, between Raptor Therapeutics Inc. and Patheon Pharmaceuticals Inc.	10QSB/A**	4/15/2008	10.2	
10.27	Form Indemnity Agreement	8-K	12/15/2009	10.1	
10.28++	Manufacturing Services Agreement, dated November 15, 2010, between Patheon Pharmaceuticals Inc. and Raptor Therapeutics, Inc.	POS AM	11/23/2010	10.53	
10.29++	API Supply Agreement, dated November 15, 2010, between Cambrex Profarmaco Milano and Raptor Therapeutics Inc.	POS AM	11/23/2010	10.54	
10.30++	Cooperative Research and Development Agreement for Extramural-PHS Clinical Research, dated December 15, 2011, between the U.S. Department of Health and Human Services, as represented by the National Institute of Diabetes and Digestive and Kidney Diseases, an institute or center of the National Institutes of Health, and Raptor Therapeutics Inc.	10-Q	4/9/2012	10.1	
10.31++	Second Amendment to License Agreement, effective October 30, 2012, between The Regents of the University of California and Raptor Therapeutics, Inc.	10-KT	3/14/2013	10.37	
10.32++	Wholesale Product Purchase Agreement, dated April 3, 2013, between Accredo Health Group, Inc. and Raptor Pharmaceuticals Inc.	10-Q	8/9/2013	10.1	
10.33++	Pharmacy Services Agreement, dated April 3, 2013, between Accredo Health Group, Inc. and Raptor Pharmaceuticals Inc.	10-Q	8/9/2013	10.2	
10.34	Office Lease, dated April 18, 2013, between Hamilton Marin, LLC and Raptor Pharmaceuticals Corp.	10-Q	8/9/2013	10.3	
10.35	First Amendment to Lease, dated June 10, 2013, between Hamilton Marin, LLC and Raptor Pharmaceuticals Corp.	10-Q	8/9/2013	10.4	
10.36++	Amendment to Manufacturing Services Agreement, dated April 5, 2012, between Patheon Pharmaceuticals Inc. and Raptor Therapeutics, Inc.	10-Q	8/9/2013	10.5	
10.37++	Second Amendment to Manufacturing Services Agreement, dated June 21, 2013, between Patheon Pharmaceuticals Inc. and Raptor Therapeutics, Inc.	10-Q	8/9/2013	10.6	
10.38	Convertible Note Purchase Agreement, dated as of July 1, 2014, among Registrant, as Issuer, HealthCare Royalty Partners II, L.P., HCRP Overflow Fund, L.P. and MOLAG Healthcare Royalty, LLC, each as Holder, and the Guarantors party thereto	8-K	7/2/2014	10.1	
10.39#	Amended and Restated Employment Agreement, dated as of July 7, 2014, by and between Julie Anne Smith and Registrant	8-K	7/8/2014	10.1	
10.40#	Transition and Separation Agreement, dated as of July 7, 2014, by and between Christopher Starr, Ph.D. and Registrant	8-K	7/8/2014	10.1	
10.41	Second Amended and Restated Sales Agreement, dated as of August 21, 2014, between Registrant and Cowen and Company, LLC	8-K	8/21/2014	10.1	
10.42++	Amended and Restated Loan Agreement, dated as of July 1, 2014, by and among Healthcare Royalty Partners II, L.P., Registrant and the Guarantors party thereto	8-K	8/21/2014	10.1	
10.43#	Separation Agreement, dated as of October 21, 2014, by and between Georgia Erbez and Registrant	8-K	10/24/2014	10.1	
10.44#	Executive Employment Agreement, dated as of January 2, 2015, by and between Michael Smith and Registrant	8-K	1/7/2015	10.1	

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10.45#	Raptor Pharmaceutical Corp. 2015 Employment Commencement Stock Incentive Plan				X
10.46#	Form of Stock Option Agreement under Raptor Pharmaceutical Corp. 2015 Employment Commencement Stock Incentive Plan				X
10.47#	Executive Employment Agreement, dated as of October 21, 2014, by and between David Happel and Registrant				X
10.48#	Executive Employment Agreement, dated as of January 2, 2015, by and between Krishna Polu, M.D. and Registrant				X
10.49	Third Amendment to License Agreement, dated as of March 1, 2013, between The Regents of the University of California and Raptor Pharmaceuticals, Inc.				X
10.50	Fourth Amendment to License Agreement, dated as of December 16, 2013, between The Regents of the University of California and Raptor Pharmaceuticals, Inc.				X
21.1	Subsidiaries of the Registrant				X
23.1	Consent of Grant Thornton LLP, Independent Registered Public Accounting Firm to the Registrant				X
23.2	Consent of Burr Pilger Mayer, Inc., Former Independent Registered Public Accounting Firm to the Registrant				X
24.1	Power of Attorney (included in the signature page hereto)				X
31.1	Certification of Julie Anne Smith, Chief Executive Officer and Director				X
31.2	Certification of Michael P. Smith, Chief Financial Officer, Secretary and Treasurer				X
32.1	Certification of Julie Anne Smith, Chief Executive Officer and Director, and of Michael P. Smith, Chief Financial Officer, Secretary and Treasurer				X
101.INS	XBRL Instance Document				X
101.SCH	XBRL Taxonomy Extension Schema Document				X
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document				X
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document				X
101.LAB	XBRL Taxonomy Extension Labels Linkbase Document				X
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document				X

* The Raptor Pharmaceuticals Corp. warrants set forth in Exhibits 4.4 and 4.5 have been converted into warrants of the Registrant and the exercise price of such warrants and number of shares of common stock issuable thereunder have been converted as described in Item 1.01 (under the section titled, "Background") of the Registrant's Current Report on Form 8-K, filed on October 5, 2009.

** Incorporated by reference from the indicated filing of Raptor Pharmaceuticals Corp. rather than that of the Registrant.

# Indicates a management contract or compensatory plan or arrangement.

++ Certain information omitted pursuant to a request for confidential treatment filed separately with and granted by the SEC.

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SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

RAPTOR PHARMACEUTICAL CORP.

Dated: March 2, 2015

By: /s/ MICHAEL SMITH
Michael Smith
Chief Financial Officer, Secretary and Treasurer
(Principal Financial Officer)

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Julie A. Smith and Michael Smith, his or her attorney-in-fact, with the power of substitution, for him or her in any and all capacities, to sign any amendments to this Annual Report on Form 10-K and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, hereby ratifying and confirming all that each of said attorneys-in-fact, or his or her substitute or substitutes, may do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated:

Signatures	Title	Date
/s/ Julie A. Smith Julie A. Smith	Chief Executive Officer and Director (Principal Executive Officer)	March 2, 2015
/s/ Michael Smith Michael Smith	Chief Financial Officer, Secretary and Treasurer (Principal Financial Officer and Principal Accounting Officer)	March 2, 2015
/s/ Raymond W. Anderson Raymond W. Anderson	Director	March 2, 2015
/s/ Suzanne L. Bruhn Suzanne L. Bruhn, Ph.D.	Director	March 2, 2015
/s/ Richard L. Franklin Richard L Franklin, M.D., Ph.D.	Director	March 2, 2015
/s/ Georges Gemayel Georges Gemayel, Ph.D.	Director	March 2, 2015
/s/ Llew Keltner Llew Keltner, M.D., Ph.D.	Director	March 2, 2015
/s/ Gregg Lapointe Gregg Lapointe	Director	March 2, 2015
/s/ Erich Sager Erich Sager	Director	March 2, 2015
/s/ Christopher M. Starr Christopher M. Starr, Ph.D.	Director	March 2, 2015

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RAPTOR PHARMACEUTICAL CORP.

CONSOLIDATED FINANCIAL STATEMENTS,

REPORTS OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

For Inclusion in Annual Report on Form 10-K Filed With

Securities and Exchange Commission

December 31, 2014

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RAPTOR PHARMACEUTICAL CORP.

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REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Board of Directors and Stockholders
of Raptor Pharmaceutical Corp.

We have audited the accompanying consolidated balance sheets of Raptor Pharmaceutical Corp. (a Delaware corporation) and subsidiaries (the "Company") as of December 31, 2014 and 2013, and the related consolidated statements of operations and comprehensive loss, stockholders' equity (deficit), and cash flows for the years then ended and for the four month period ended December 31, 2012. Our audits of the basic consolidated financial statements included the financial statement schedule listed in the index appearing under Item 15(a)(2). These financial statements and financial statement schedule are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements and financial statement schedule based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of Raptor Pharmaceutical Corp. and subsidiaries as of December 31, 2014 and 2013, and the results of their operations and their cash flows for the years then ended and for the four month period ended December 31, 2012 in conformity with accounting principles generally accepted in the United States of America. Also in our opinion, the related financial statement schedule, when considered in relation to the basic consolidated financial statements taken as a whole, presents fairly, in all material respects, the information set forth therein.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the Company's internal control over financial reporting as of December 31, 2014, based on criteria established in the 2013 *Internal Control—Integrated Framework* issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO), and our report dated March 2, 2015 expressed an adverse opinion thereon.

/s/ GRANT THORNTON LLP
San Francisco, California
March 2, 2015

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REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Board of Directors and Stockholders of
Raptor Pharmaceutical Corp.

We have audited the internal control over financial reporting of Raptor Pharmaceutical Corp. (a Delaware corporation) and subsidiaries (the "Company") as of December 31, 2014, based on criteria established in the 2013 *Internal Control—Integrated Framework* issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting, included in the accompanying Management's Annual Report on Internal Control over Financial Reporting ("Management's Report"). Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit.

We conducted our audit in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

A material weakness is a deficiency, or combination of control deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of the Company's annual or interim financial statements will not be prevented or detected on a timely basis. The following material weakness has been identified and included in management's assessment: management has determined that its reviews of inventory costing and overhead allocations for its commercial product, PROCYSBI, were not performed at a sufficiently detailed level to detect errors in inventory and related accounts.

In our opinion, because of the effect of the material weakness described above on the achievement of the objectives of the control criteria, the Company has not maintained effective internal control over financial reporting as of December 31, 2014, based on criteria established in the 2013 *Internal Control—Integrated Framework* issued by COSO.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the consolidated financial statements of the Company as of and for the year ended December 31, 2014. The material weakness identified above was considered in determining the nature, timing, and extent of audit tests applied in our audit of the 2014 consolidated financial statements, and this report does not affect our report dated March 2, 2015 which expressed an unqualified opinion on those financial statements.

We do not express an opinion or any other form of assurance on management's statements referring to corrective actions to be taken after December 31, 2014 relative to the aforementioned material weakness in internal control over financial reporting.

/s/ GRANT THORNTON LLP
San Francisco, California
March 2, 2015

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REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Board of Directors and Stockholders of Raptor Pharmaceutical Corp.

We have audited the accompanying consolidated statements of comprehensive loss, shareholders' equity (deficit), and cash flows of Raptor Pharmaceutical Corp. and its subsidiaries (the "Company") (a development stage enterprise) for each of the two years in the period ended August 31, 2012. These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these consolidated financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the results of operations and cash flows of Raptor Pharmaceutical Corp. and its subsidiaries for each of the two years in the period ended August 31, 2012, in conformity with accounting principles generally accepted in the United States of America.

Burr Pilger Mayer, Inc.
San Francisco, California
November 13, 2012

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RAPTOR PHARMACEUTICAL CORP.
CONSOLIDATED BALANCE SHEETS
(In Thousands, except shares and per share data)

	December 31, 2014	December 31, 2013
ASSETS		
Current assets:		
Cash and cash equivalents	$ 149,613	$ 83,052
Restricted cash	1,562	500
Accounts receivable	7,455	6,181
Inventories	9,134	3,000
Prepaid expenses and other	3,841	3,566
Total current assets	171,605	96,299
Noncurrent assets:		
Fixed assets, net	5,880	1,810
Goodwill	3,275	3,275
Intangible assets, net	2,974	3,213
Other assets	5,332	4,129
Total Assets	$ 189,066	$ 108,726
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 2,550	$ 5,264
Accrued liabilities	16,859	13,128
Common stock warrant liability	711	7,066
Deferred revenue	-	4,698
Note payable, current portion	9,000	-
Total current liabilities	29,120	30,156
Noncurrent liabilities:		
Note payable, net of current portion	51,000	50,000
Convertible notes	60,000	-
Total liabilities	140,120	80,156
Stockholders' equity:		
Preferred stock, $0.001 par value per share, 15,000,000 shares authorized, zero shares issued and outstanding	-	-
Common stock, $0.001 par value per share, 150,000,000 shares authorized, 68,861,366 and 61,614,576 shares issued and outstanding at December 31, 2014 and 2013, respectively	69	62
Additional paid-in capital	306,832	234,246
Accumulated other comprehensive loss	(60)	(383)
Accumulated deficit	(257,895)	(205,355)
Total stockholders' equity	48,946	28,570
Total Liabilities and Stockholders' Equity	$ 189,066	$ 108,726

The accompanying notes are an integral part of these consolidated financial statements.

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RAPTOR PHARMACEUTICAL CORP.
CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(In thousands, except shares and per share data)

	For the Year Ended December 31,		For the Four Months Ended December 31,	For the Year Ended August 31,
	2014	2013	2012	2012
Revenues	$ 69,497	$ 16,872	$ -	$ -
Cost of sales	9,416	1,653	-	-
Gross profit	60,081	15,219	-	-
Operating expenses:				
Research and development	43,477	29,177	8,963	21,443
Selling, general and administrative	56,654	37,948	8,971	14,723
Total operating expenses	100,131	67,125	17,934	36,166
Loss from operations	$ (40,050)	$ (51,906)	$ (17,934)	$ (36,166)
Interest income	76	188	160	340
Interest expense	(13,971)	(6,832)	(83)	(3)
Foreign currency transaction gain	261	8	113	145
(Loss) gain on short-term investments	-	(128)	(64)	213
Adjustment to fair value of common stock warrants	(1,148)	(10,747)	(1,484)	(3,173)
Other income	2,346	-	-	-
Net loss before provision for income taxes	(52,486)	(69,417)	(19,292)	(38,644)
Provision for income taxes	(54)	-	-	-
Net Loss	$ (52,540)	$ (69,417)	$ (19,292)	$ (38,644)
Other comprehensive income (loss):				
Foreign currency translation gain (loss)	323	(268)	(65)	(52)
Comprehensive Loss	$ (52,217)	$ (69,685)	$ (19,357)	$ (38,696)
Net loss per share:				
Basic and diluted	$ (0.83)	$ (1.20)	$ (0.37)	$ (0.80)
Weighted-average shares outstanding:				
Basic and diluted	63,213,504	57,860,366	51,736,956	48,084,633

The accompanying notes are an integral part of these consolidated financial statements.

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RAPTOR PHARMACEUTICAL CORP.
CONSOLIDATED STATEMENT OF STOCKHOLDERS' EQUITY (DEFICIT)
(In thousands, except shares and per share data)

	Common Stock		Additional Paid In	Accumulated Other Comprehensive	Accumulated	
	Shares	Amount	Capital	Income (Loss)	Deficit	Total
Balance at August 31, 2011	**35,569**	**$ 36**	**$ 73,817**	**$ 2**	**$ (78,002)**	**$ (4,147)**
Net loss	-	-	-	-	(38,644)	(38,644)
Other comprehensive income (loss)	-	-	-	(52)	-	(52)
Issuance of common stock:						-
Follow-on public offering, net of offering costs	11,500	12	42,822	-	-	42,834
At-the-market financing facility, net of offering costs	1,508	1	7,323	-	-	7,324
Exercise of common stock options	160	-	366	-	-	366
Exercise of common stock warrants	1,831	2	5,011	-	-	5,013
Reclassification of the fair value of warrant liabilities upon exercise	-	-	9,482	-	-	9,482
Stock-based compensation	-	-	4,559	-	-	4,559
Balance at August 31, 2012	**50,568**	**51**	**143,380**	**(50)**	**(116,646)**	**26,735**
Net loss	-	-	-	-	(19,292)	(19,292)
Other comprehensive income (loss)	-	-	-	(65)	-	(65)
Issuance of common stock:						-
At-the-market financing facility, net of offering costs	1,153	1	5,946	-	-	5,947
Exercise of common stock options	79	-	192	-	-	192
Exercise of common stock warrants	625	-	1,843	-	-	1,843
Reclassification of the fair value of warrant liabilities upon exercise			2,345			2,345
Stock-based compensation	-	-	2,239	-	-	2,239
Balance at December 31, 2012	**52,425**	**52**	**155,945**	**(115)**	**(135,938)**	**19,944**
Net loss	-	-	-	-	(69,417)	(69,417)
Other comprehensive income (loss)	-	-	-	(268)	-	(268)
Issuance of common stock:						-
At-the-market financing facility, net of offering costs	4,939	5	38,389	-	-	38,394
Exercise of common stock options	651	1	2,474	-	-	2,475
Exercise of common stock warrants	3,600	4	10,322	-	-	10,326
Reclassification of the fair value of warrant liabilities upon exercise			20,086		-	20,086
Stock-based compensation	-	-	7,030	-	-	7,030
Balance at December 31, 2013	**61,615**	**62**	**234,246**	**(383)**	**(205,355)**	**28,570**
Net loss	-	-	-	-	(52,540)	(52,540)
Other comprehensive income (loss)	-	-	-	323	-	323
Issuance of common stock:						-
Employee stock purchase plan	21	-	179	-	-	179
At-the-market financing facility, net of offering costs	4,970	4	44,459	-	-	44,463
Exercise of common stock options	1,643	2	6,574	-	-	6,576
Exercise of common stock warrants	612	1	1,825	-	-	1,826
Reclassification of the fair value of warrant liabilities upon exercise	-	-	7,503	-	-	7,503
Stock-based compensation	-	-	12,046	-	-	12,046
Balance at December 31, 2014	**68,861**	**$ 69**	**$ 306,832**	**$ (60)**	**$ (257,895)**	**$ 48,946**

The accompanying notes are an integral part of these consolidated financial statements.

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RAPTOR PHARMACEUTICAL CORP.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(In Thousands)

	For the Year Ended December 31,		For the Four Months Ended December 31,	For the Year Ended August 31,
	2014	2013	2012	2012
Cash flows from operating activities:				
Net loss	$ (52,540)	$ (69,417)	$ (19,292)	$ (38,644)
Adjustments to reconcile net loss to net cash used in operating activities:				
Stock-based compensation expense	12,046	7,030	2,239	4,559
Fair value adjustment of common stock warrants	1,148	10,747	1,484	3,173
Amortization of intangible assets	239	193	49	146
Depreciation of fixed assets	798	244	42	65
Realized loss (gain) on disposal of fixed assets	219	(12)	-	-
Loss on short-term investments	-	128	64	-
Write-off of intangible assets and other intellectual property	-	-	-	900
Amortization of debt issuance cost	1,626	433	-	-
Changes in assets and liabilities:				
Accounts receivable	(1,274)	(6,181)	-	-
Inventories	(6,134)	(3,000)	-	-
Prepaid expenses and other assets	572	(2,028)	1,580	(2,695)
Accounts payable	(2,714)	(114)	3,081	754
Accrued liabilities	3,731	10,683	(593)	403
Deferred revenue	(4,698)	4,698	-	(10)
Net cash used in operating activities	(46,981)	(46,596)	(11,346)	(31,349)
Cash flows from investing activities:				
Net purchase of fixed assets	(5,086)	(1,586)	(57)	(385)
Purchase of short-term investments	-	(147)	(6,853)	(45,307)
Sale of short-term investments	-	22,114	-	30,000
Intangible assets	-	(1,250)	-	-
Change in restricted cash	(1,062)	(337)	6	(54)
Net cash (used in) provided by investing activities	(6,148)	18,794	(6,904)	(15,746)
Cash flows from financing activities:				
Proceeds from sale of common stock, net	-	-	-	42,834
Proceeds from sale of common stock under ATM agreement	44,463	38,394	5,947	7,324
Proceeds from the exercise of common stock warrants	1,826	10,326	1,843	5,013
Proceeds from the exercise of common stock options and ESPP	6,755	2,475	192	366
Proceeds from issuance of debt	70,000	25,000	25,000	-
Debt issuance costs	(3,521)	(1,260)	(1,959)	-
Offering costs	(156)	(126)	25	18
Net cash provided by financing activities	119,367	74,809	31,048	55,555
Effect of exchange rates on cash and cash equivalents	323	(268)	(65)	(52)
Net increase in cash and cash equivalents	66,561	46,739	12,733	8,408
Cash and cash equivalents, beginning of period	83,052	36,313	23,580	15,172
Cash and Cash Equivalents, End of Period	$ 149,613	$ 83,052	$ 36,313	$ 23,580
Supplemental cash flow information:				
Interest paid	$ 11,654	$ 5,412	$ 83	$ 3
Income taxes paid	$ 176	$ 2	$ -	$ -
Supplemental disclosure of non-cash financing activities:				
Fair value of warrant liability reclassified to equity upon exercise	$ 7,503	$ 20,086	$ 2,345	$ 9,482

The accompanying notes are an integral part of these consolidated financial statements.

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RAPTOR PHARMACEUTICAL CORP.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS
December 31, 2014

1. NATURE OF OPERATIONS AND BUSINESS RISKS

The accompanying consolidated financial statements reflect the financial position and results of operations of Raptor Pharmaceutical Corp. (the "Company" or "Raptor") and have been prepared in accordance with the accounting principles generally accepted in the United States of America ("GAAP").

Raptor is a biopharmaceutical company focused on developing and commercializing life-altering therapeutics that treat debilitating and often fatal diseases. The Company's first product, PROCYSBI® (cysteamine bitartrate) delayed-release capsules ("PROCYSBI"), received marketing approval from the U.S. Food and Drug Administration ("FDA") on April 30, 2013 for the management of nephropathic cystinosis in adults and children six years and older. In Europe, PROCYSBI® gastro-resistant hard capsules of cysteamine (as mercaptamine bitartrate), received marketing authorization on September 6, 2013 from the European Commission ("EC"), for marketing in the European Union ("EU") as an orphan medicinal product for the management of proven nephropathic cystinosis. PROCYSBI received seven years of market exclusivity as an orphan drug in the United States and ten years of market exclusivity as an orphan drug in the EU. The Company commenced commercial sales of PROCYSBI in the United States in mid-June 2013, in Europe in April 2014. For at least the near term, the Company's ability to generate revenues is entirely dependent upon sales of PROCYSBI in the United States for the management of nephropathic cystinosis in adults and children six years and older and in the EU for the management of proven nephropathic cystinosis.

Raptor's pipeline includes its proprietary delayed-release form of cysteamine, or RP103 and its proprietary oral 4-methylpyrazole, or Convivia™. Raptor currently has product candidates in clinical development designed to potentially treat Huntington's disease ("HD"), non-alcoholic steatohepatitis ("NASH") in children, Leigh syndrome and other mitochondrial disorders and aldehyde dehydrogenase deficiency ("ALDH2"). Raptor's preclinical programs are based upon bioengineered novel drug candidates that are designed to target cancer and other diseases.

The Company is subject to a number of risks, including: the level of commercial sales of PROCYSBI in the United States and Europe; the ability to successfully launch PROCYSBI in other international markets; uncertainty whether the Company's research and development efforts will result in expanded labeling for PROCYSBI and commercialization for RP103 in various indications or additional commercial products; competition from other organizations; reliance on licensing the proprietary technology of others; uncertain patent protection; and the need to raise capital through equity and/or debt financings. Funding may not be available when needed if at all or on terms acceptable to the Company. If the Company exhausts its cash reserves and is unable to obtain adequate financing, it may be required to curtail planned operating expenditures, including its development programs.

Change in Fiscal Year End

On December 4, 2012, Raptor's Board of Directors approved a change in its fiscal year end from August 31 to December 31. The change became effective at the end of the four months ended December 31, 2012. All references to "fiscal years" or "years" prior to this change refer to the twelve-month fiscal period covering September 1 through August 31, and each year after December 31, 2012, the fiscal year covers January 1 through December 31.

Basis of Presentation

The Company's consolidated financial statements include the accounts of the Company's direct and indirect wholly owned subsidiaries, Raptor Pharmaceuticals Inc., formerly known as Raptor Therapeutics Inc. which merged with Raptor Discoveries Inc. in December 2012 prior to changing its name, and Raptor European Products, LLC, such subsidiaries incorporated in Delaware on August 1, 2007, and February 14, 2012, respectively, and Raptor Pharmaceuticals Europe B.V. (“BV”), Raptor Pharmaceuticals France SAS (“SAS”), Raptor Pharmaceuticals Germany GmbH (“GMBH”) and RPTP European Holdings C.V. (“CV”), domiciled in the Netherlands on December 15, 2009, in France on October 30, 2012, in Germany on October 16, 2013 and in the Cayman Islands on February 16, 2012, respectively. All inter-company accounts have been eliminated. Net assets in foreign countries totaled $5.8 million at December 31, 2014.

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2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Use of Estimates

The preparation of financial statements in conformity with U.S. GAAP requires management to make certain estimates and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent assets and liabilities as of the dates of the consolidated financial statements and the reported amounts of revenues and expenses during the reporting period. Actual results could differ from those estimates.

Functional Currency

The Company's consolidated functional currency is the U.S. dollar. BV, SAS, and GMBH, the Company's Dutch subsidiary, French subsidiary, and German Subsidiary, respectively, use the European Euro as their functional currency. The CV subsidiary, a Cayman-based subsidiary, uses the dollar as its functional currency. At each quarter end, each foreign subsidiary's balance sheets are translated into U.S. dollars based upon the quarter-end exchange rate, while their statements of operations and comprehensive loss are translated into U.S. dollars based upon an average exchange rate during the period.

Segment Information

The Company has determined that it operates in only one segment, as it only reports profit and loss information on an aggregate basis to its chief operating decision maker. The Company's long-lived assets maintained outside the United States are not material.

Fair Value of Financial Instruments

The carrying amounts of certain of the Company's financial instruments including cash equivalents, restricted cash, accounts payable, accrued liabilities, note payable and capital lease liability approximate fair value due either to length of maturity or interest rates that approximate prevailing market rates. The warrant liability is carried at fair value, which is determined using the Black-Scholes option valuation model at the end of each reporting period.

Cash and Cash Equivalents

The Company considers all highly liquid investments with original maturities of three months or less, when purchased, to be cash equivalents. The Company maintains cash and cash equivalents, which consist principally of money market funds, with high credit quality financial institutions. Such amounts exceed Federal Deposit Insurance Corporation insurance limits. Restricted cash represents certificates of deposit and compensating balances required by the Company's U.S. and European banks as collateral for credit cards and for access to a value-added tax deferral program. As of December 31, 2014, the Company had $149.6 million in cash and cash equivalents, of which $5.4 million was held by its foreign subsidiaries.

Revenue Recognition and Accounts Receivable

The Company recognizes revenue in accordance with the Financial Accounting Standards Board ("FASB") Accounting Standards Codification (“ASC”) 605, *Revenue Recognition*, when the following criteria have been met: persuasive evidence of an arrangement exists; delivery has occurred and risk of loss has passed; the seller's price to the buyer is fixed or determinable and collectability is reasonably assured. The Company determines that persuasive evidence of an arrangement exists based on written contracts that define the terms of the arrangements. Pursuant to the contract terms, the Company determines when title to products and associated risk of loss has passed on to the customer. The Company assesses whether the fee is fixed or determinable based on the payment terms associated with the transaction and whether the sales price is subject to refund or adjustment. The Company assesses collectability based primarily on the customer's payment history and creditworthiness.

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PROCYSBI is currently available for U.S. distribution from the Company's U.S. specialty pharmacy partner, the Accredo Health Group, Inc. ("Accredo") which is currently the Company's only U.S. customer and ships directly to patients. The Company's distributor in the EU is the Almac Group, Ltd. PROCYSBI is not available in U.S. retail pharmacies. Prior authorization of coverage by patients' commercial insurance plans, Raptor's patient assistance program ("PAP") or government payors is a prerequisite to the shipment of PROCYSBI to U.S. patients. Prior to the third quarter of 2014, revenue was recognized in the United States once the product had been shipped by the specialty pharmacy to patients because the Company had not yet been able to reasonably estimate the third-party payor mix and resulting rebates based on its lack of sufficient historical data. Beginning July 2014, the Company was able to reasonably estimate and determine sales allowances; therefore the Company began recognizing PROCYSBI revenue at the point of sale to the specialty pharmacy, which resulted in the one-time non-recurring recognition of an additional $4.4 million in net revenues during the quarter ended September 30, 2014. Revenue is currently recognized in the EU once confirmed orders from the pharmacies have been shipped and invoiced for payment by the distributor on the Company’s behalf.

The Company records revenue net of expected discounts, distributor fees, and rebates, including government rebates such as Medicare and Medicaid in the United States. Allowances are recorded as a reduction of revenue at the time product sales are recognized. Allowances for government rebates and discounts are established based on the actual payor and payor mix information, which is known in the United States at the time of shipment to the distributor and in Germany at the time of shipment to the pharmacy, and the government-mandated discount rates applicable to government-funded programs. The allowances are adjusted to reflect known changes in the factors that may impact such allowances in the quarter the changes are known.

Trade accounts receivable are recorded net of product sales allowances for prompt-payment discounts and chargebacks. Estimates for chargebacks and prompt-payment discounts are based on contractual terms and the Company's expectations regarding the utilization rates.

Inventories and Cost of Sales

Inventories are stated at the lower of cost or market price, with cost determined on a first-in, first-out basis. Inventories are reviewed periodically to identify slow-moving inventory based on sales activity, both projected and historical, as well as product shelf-life. Prior to the approval of PROCYSBI by the FDA on April 30, 2013 and in Europe, prior to the approval by the EC on September 6, 2013, the Company recorded the purchase of raw materials and the manufacturing costs relating to PROCYSBI as research and development expense. Subsequent to FDA and EC approval, the Company began capitalizing these costs and manufacturing overhead as commercial inventory. Upon launching PROCYSBI in mid-June 2013 in the United States and April 2014 in the EU, the Company began recognizing cost of sales. Cost of sales includes the cost of inventory sold or reserved; manufacturing, manufacturing overhead and supply chain costs; product shipping and handling costs; and amortization of licensing approval milestone payments and licensing royalties payable to the University of California, San Diego ("UCSD").

Prepaid Expenses and Other

Prepaid expenses consists primarily of advance vendor payments which will be expensed within one year from the balance sheet date, including $0.5 million prepaid to the National Institute of Diabetes and Digestive and Kidney Diseases (“NIDDK”) which is part of the National Institutes of Health. Such amounts relate to a clinical trial being conducted under a Cooperative Research and Development Agreement (“CRADA”) with the NIDDK, and are being recorded to research and development expense over the estimated term of the trial. See *Note 13* for additional information on future payments due under the CRADA. Other assets consist primarily of amounts receivable for vendor refunds, stock option exercises, and VAT tax refunds, including $0.7 million from Cambrex for API purchase refunds and $0.2 million from the FDA for PDUFA filing fee refunds.

Fixed Assets

Fixed assets, which mainly consist of leasehold improvements, office furniture, lab equipment and computer hardware and software, are stated at cost. Depreciation is computed using the straight-line method over the related estimated useful lives, except for leasehold improvements and capital lease equipment, which are depreciated over the shorter of the useful life of the asset or the lease term. Significant additions and improvements that have useful lives estimated at greater than one year are capitalized, while repairs and maintenance are charged to expense as incurred.

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Goodwill and Intangible Assets

Intangible assets primarily include the intellectual property and other rights relating to DR Cysteamine (currently developed as RP103) and to an out-license acquired in a 2009 merger. The intangible assets related to RP103 are amortized using the straight-line method over the estimated useful life of 20 years, which is the life of the intellectual property patents. The 20-year estimated useful life is also based upon the typical development, approval, marketing and life cycle management timelines of pharmaceutical drug products.

Goodwill represents the excess of the purchase price over the fair value of tangible and identified intangible net assets of businesses acquired. Goodwill is not amortized, but is evaluated for impairment on an annual basis or more often when impairment indicators are present. The Company has one reporting unit. Therefore, the Company's consolidated net assets, including existing goodwill and other intangible assets, are considered to be the carrying value of the reporting unit. If the carrying value of the reporting unit is in excess of its fair value, an impairment may exist, and the Company must perform the second step of the analysis, in which the implied fair value of the goodwill is compared to its carrying value to determine the impairment charge, if any. If the estimated fair value of the reporting unit exceeds the carrying value of the reporting unit, goodwill is not impaired and no further analysis is required.

The Company makes judgments about the recoverability of purchased intangible assets with finite lives whenever events or changes in circumstances indicate that impairment may exist. Recoverability of purchased intangible assets with finite lives is measured by comparing the carrying amount of the asset to the future undiscounted cash flows the asset is expected to generate. Impairment, if any, is measured as the amount by which the carrying value exceeds the fair value of the impaired asset.

Common Stock Warrant Liabilities

The Company issued warrants that contain conditional obligations that may require the Company to transfer cash to settle the warrants upon the occurrence of certain fundamental transactions. Therefore, the Company has classified the warrants as liabilities. The Company re-measures the liability at the end of every reporting period with the change in value reported in the Company's consolidated statements of operations and comprehensive loss. At the exercise date, the fair values of these warrants are re-measured and reclassified to equity.

Note Payable

Note payable consists of a loan agreement with HealthCare Royalty Partners II, L.P. ("HC Royalty"), as lender, which was amended effective July 1, 2014. The amendment qualified as a modification of debt in accordance with ASC 470-50, Debt – Modifications and Extinguishments, as the Company determined it did not result in substantially different terms. The amended loan requires quarterly interest payments at an annual fixed interest rate of 8.0% of outstanding principal and includes a synthetic royalty component based on net product sales, including PROCYSBI, in a calendar year. The amended loan is a senior secured obligation of the Company.

Note payable is carried at its unpaid principal balance. The fixed and royalty interest under both agreements were recognized as interest expense as incurred.

Convertible Notes

Convertible notes include unsecured convertible senior notes and are carried at their unpaid principal balance. Interest on the notes is payable quarterly and the notes mature on August 1, 2019. If converted by a holder, upon conversion, the holder of the notes would receive shares of the Company’s common stock.

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Debt Issuance Costs

Debt issuance costs are expenses associated with the issuance of the loan agreements with HC Royalty and the convertible notes. Debt issuance costs which were capitalized are being amortized over the life of the respective debt to interest expense using the interest method. Debt issuance costs are a component of *Other Assets* on the Company's consolidated balance sheets.

Other Income

In 2014, we recorded other income of $2.3 million related to disgorgement of alleged short-swing profits under Section 16(b) of the Securities Exchange Act of 1934 from a stockholder. This amount is recorded as *Other Income* on the Company's consolidated financial statements.

Net Loss per Share

Net loss per share is calculated by dividing net loss by the weighted-average shares of common stock outstanding during the period. Diluted net loss per share is calculated by dividing net loss by the weighted-average shares of common stock outstanding and potential shares of common stock during the period. For all periods presented, potentially dilutive securities are excluded from the computation of fully diluted net loss per share as their effect is anti-dilutive. Potentially dilutive securities include:

	Year Ended December 31,		For the Four Months Ended December 31,	For the Year Ended August
	2014	2013	2012	31, 2012
Warrants to purchase common stock	334,764	946,370	4,562,772	5,187,772
Options to purchase common stock	8,857,961	8,217,674	7,790,794	6,124,823
Convertible debt	3,428,571	-	-	-
Total Potentially Dilutive Securities	12,621,296	9,164,044	12,353,566	11,312,595

Comprehensive Loss

The components of comprehensive loss include net loss and foreign currency translation adjustments.

Stock-Based Compensation

Stock Option Plan

Compensation costs related to the Company's stock option plan are measured at the grant date based on the fair value of the equity instruments awarded and are recognized over the period during which an employee is required to provide service in exchange for the award, or the requisite service period, which is usually the vesting period. The compensation expense for stock-based compensation awards is reduced by an estimate for forfeitures.

The Company recognizes expense associated with stock options issued to third parties, including consultants, based upon the fair value of such awards on the date the options vest.

Employee Stock Purchase Plan

In July 2014, the Company's shareholders approved the Raptor Pharmaceutical Corp. 2013 Employee Stock Purchase Plan ("ESPP"). Up to 1,000,000 shares may be issued pursuant to the ESPP. The purpose of the ESPP is to give the Company's employees an opportunity to acquire an equity interest in the Company through the purchase of shares of common stock at a discount. The ESPP allows eligible employees to purchase common stock at 85% of its fair value, subject to certain limits. Fair value as defined under the ESPP is the lesser of the closing market price of the common stock on the first day of the offering period or the last day of the offering period, which is a six-month period beginning on each May 15 and November 15.

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Research and Development

Research and development costs are charged to expense as incurred. Research and development expenses primarily include salaries and benefits for medical, clinical, regulatory, quality, pharmacovigilance and research personnel, preclinical studies, clinical trials, and certain commercial drug manufacturing expenses prior to obtaining marketing approval.

Advertising Expenses

The Company expenses advertising costs, including promotional expenses, as incurred. For the years ended December 31, 2014 and 2013, the four months ended December 31, 2012 and the fiscal year ended August 31, 2012, advertising expenses were $1.4 million, $3.7 million, $1.3 million and $0.6 million, respectively.

Income Taxes

Income taxes are recorded under the liability method, under which deferred tax assets and liabilities are determined based on the difference between the financial statement and tax bases of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to affect taxable income. Valuation allowances are established when necessary to reduce deferred tax assets to the amount expected to be realized. Based on the weight of available evidence, including cumulative losses since inception and expected future losses, the Company has determined that it is more likely than not that the deferred tax asset amount will not be realized and therefore a full valuation allowance has been provided on the Company's net deferred tax assets.

The Company identifies uncertain tax positions and discloses any potential tax liability on its financial statements. The Company recognizes interest and/or penalties related to income tax matters as a component of income tax expense. As of December 31, 2014, there were no accrued uncertain tax positions or interest and penalties related to uncertain tax positions.

The Company files U.S. Federal, California, various other state and other income tax returns and various foreign country income tax returns. The Company is currently not subject to any income tax examinations. Due to the Company's net operating losses ("NOLs"), generally all tax years remain open.

Reclassifications

Certain amounts previously reported under specific financial statement captions have been reclassified to be consistent with the current period presentation.

Recent Accounting Pronouncements

In May 2014, the FASB issued Accounting Standards Update (“ASU”) 2014-09, *Revenue from Contracts with Customers*, which outlines a single comprehensive model for entities to use in accounting for revenue arising from contracts with customers and supersedes most current revenue recognition guidance, including industry-specific guidance. The core principle of the revenue model is that “an entity recognizes revenue to depict the transfer of promised goods or services to customers in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services.” In applying the revenue model to contracts within its scope, the Company will: identify the contract(s) with a customer, identify the performance obligations in the contract, determine the transaction price, allocate the transaction price to the performance obligations in the contract, and recognize revenue when (or as) the entity satisfies a performance obligation. This ASU is effective for interim and annual periods beginning after December 15, 2016 and early adoption is not permitted. The Company does not believe the adoption of this ASU will have a material impact on its consolidated financial statements.

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In June 2014, the FASB issued ASU 2014-12, *Accounting for Share-Based Payments When the Terms of an Award Provide That a Performance Target Could Be Achieved after the Requisite Service Period.* The ASU requires that a performance target that affects vesting, and that could be achieved after the requisite service period, be treated as a performance condition. A reporting entity should apply existing guidance in Topic 718 as it relates to awards with performance conditions that affect vesting to account for such awards. This ASU is effective for interim and annual periods beginning after December 15, 2015 and early adoption is permitted. The Company does not anticipate the adoption of this ASU will have a material impact on its consolidated financial statements.

In August 2014, the FASB issued ASU No. 2014-15, *Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern,* which provides guidance on determining when and how reporting entities must disclose going-concern uncertainties in their financial statements. The ASU requires management to perform interim and annual assessments of an entity's ability to continue as a going concern within one year of the date of issuance of the entity's financial statements (or within one year after the date on which the financial statements are available to be issued, when applicable). Further, an entity must provide certain disclosures if there is "substantial doubt about the entity's ability to continue as a going concern." This ASU is effective for annual periods ending after December 15, 2016, and interim periods thereafter; early adoption is permitted.

3. FAIR VALUE MEASUREMENT

The Company uses a fair value approach to value certain assets and liabilities. Fair value is the price that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. As such, fair value is a market-based measurement that should be determined based on assumptions that market participants would use in pricing an asset or liability. The Company uses a fair value hierarchy, which distinguishes between assumptions based on market data (observable inputs) and an entity's own assumptions (unobservable inputs). The hierarchy consists of three levels:

- Level 1 –Quoted market prices in active markets for identical assets or liabilities;
- Level 2 –Inputs other than level one inputs that are either directly or indirectly observable; and
- Level 3 –Unobservable inputs developed using estimates and assumptions, which are developed by the reporting entity and reflect those assumptions that a market participant would use.

Determining which category an asset or liability falls within the hierarchy requires significant judgment. The Company evaluates its hierarchy disclosures each reporting period. The following table presents the assets and liabilities recorded that are reported at fair value on our consolidated balance sheets on a recurring basis.

Assets and Liabilities Measured at Fair Value on a Recurring Basis

(In thousands) **December 31, 2014**	**Level 1**	**Level 2**	**Level 3**	**Total**
Assets				
Cash equivalents (1)	$ 137,938	$ -	$ -	$ 137,938
Total	$ 137,938	$ -	$ -	$ 137,938
Liabilities				
Common stock warrants	$ -	$ -	$ 711	$ 711
Total	$ -	$ -	$ 711	$ 711

December 31, 2013	**Level 1**	**Level 2**	**Level 3**	**Total**
Assets				
Cash equivalents (1)	$ 70,627	$ -	$ -	$ 70,627
Total	$ 70,627	$ -	$ -	$ 70,627
Liabilities				
Common stock warrants	$ -	$ -	$ 7,066	$ 7,066
Total	$ -	$ -	$ 7,066	$ 7,066

(1) Cash equivalents represent the fair value of the Company's investments in money market funds at December 31, 2014 and 2013.

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Certain of the Company's common stock warrants are classified as liabilities and are, therefore, re-measured using the Black-Scholes option valuation model at the end of each reporting period with the change in value reported in the Company's consolidated statements of operations and comprehensive loss.

The following table presents a reconciliation of the Company's recurring fair value measurements categorized within Level 3 of the fair value hierarchy (liability-classified common stock warrants).

Changes in Level 3 Liabilities Measured at Fair Value on a Recurring Basis – Common Stock Warrants

	Year Ended December 31,		For the Four Months Ended December 31,	For the Year Ended August 31,
(In thousands)	**2014**	**2013**	**2012**	**2012**
Beginning fair value	$ 7,066	$ 16,405	$ 17,266	$ 23,575
Change in fair value recognized in earnings	1,148	10,747	1,484	3,173
Exercises	(7,503)	(20,086)	(2,345)	(9,482)
Ending Fair Value	$ 711	$ 7,066	$ 16,405	$ 17,266

Effect of Raptor's Stock Price and Volatility Assumptions on the Calculation of Fair Value of Warrant Liabilities

As discussed above, the Company uses the Black-Scholes option pricing model as its method of valuation for warrants that are subject to warrant liability accounting. The determination of fair value as of the reporting date is affected by Raptor's stock price as well as assumptions regarding a number of subjective variables. These variables include, but are not limited to, expected stock price volatility over the term of the security and risk-free interest rate. The primary factors affecting the fair value of the warrant liability are the Company's stock price and volatility.

The following table presents the carrying value and fair value of certain financial liabilities that are recorded on the Company’s consolidated balance sheets.

Fair Value of Certain Financial Liabilities

(In thousands) **December 31, 2014**	**Carrying Value**	**Fair Value**
Liabilities		
Note payable	$ 60,000	$ 65,522
Convertible notes	60,000	56,760

4. INVENTORIES

Inventories consist of raw materials, work-in-process and finished goods related to the manufacture of PROCYSBI. Raw materials include the Company's active pharmaceutical ingredient ("API"), cysteamine bitartrate. Work-in-process includes third party manufacturing and associated labor costs relating to the Company's personnel directly involved in the production process. Also included in inventories are raw materials that may be used for clinical trials, which are charged to research and development (“R&D”) expense when consumed.

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Inventories are summarized as follows:

(In thousands)	December 31, 2014	December 31, 2013
Raw materials	$ 6,290	$ 2,469
Work-in-process	721	-
Finished goods	2,123	531
Total Inventories	$ 9,134	$ 3,000

5. FIXED ASSETS

Fixed assets consisted of:

(In thousands)	December 31, 2014	December 31, 2013	Estimated useful lives
Assets under construction	$ 2,393	$ 102	-
Office furniture	2,198	605	7 years
Laboratory equipment	1,373	1,132	5 years
Computer hardware and software	815	646	3 years
Leasehold improvements	470	-	Lease term
Total at cost	7,249	2,485	
Less: accumulated depreciation	(1,369)	(675)	
Total Fixed Assets, Net	$ 5,880	$ 1,810	

Depreciation expense for the years ended December 31, 2014 and 2013, the four months ended December 31, 2012 and the year ended August 31, 2012 was $798 thousand, $244 thousand, $42 thousand, and $65 thousand, respectively.

6. INTANGIBLE ASSETS AND GOODWILL

On December 14, 2007, the Company acquired the intellectual property and other rights to develop RP103 to treat various clinical indications from UCSD by way of a merger with Encode Pharmaceuticals, Inc., a privately held development stage company ("Encode"), which held the intellectual property license with UCSD. The fair value of the intangible assets at the time of acquisition was approximately $2.6 million.

Pursuant to the license agreement with UCSD, the Company is obligated to pay milestone payments upon the occurrence of certain events, royalties on net sales from products developed pursuant to the license agreement and a percentage of sublicense fees or royalties, if any. The Company is obligated to fulfill predetermined milestones within a specified number of years from the effective date of the license agreement, depending on the indication. To the extent that the Company fails to perform any of its obligations under the agreement, UCSD may terminate the license or otherwise cause the license to become non-exclusive.

In May 2013, the Company announced that the FDA has approved PROCYSBI (cysteamine bitartrate) delayed release capsules for the management of nephropathic cystinosis in adults and children 6 years and older. Subsequently, the Company announced that the EC has approved PROCYSBI® gastro-resistant hard capsules of cysteamine (as mercaptamine bitartrate) as an orphan medicinal product for the management of proven nephropathic cystinosis for marketing in the EU. In conjunction with these approvals, the Company paid milestone payments to UCSD during the second and third quarters of 2013 of $0.8 million and $0.5 million, respectively, pursuant to this license, which were capitalized as intangible assets.

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A summary of intangibles acquired is as follows:

(In thousands)	Useful Life (Years)	December 31, 2014	December 31, 2013
Intangible asset (IP license for RP103) related to the Encode merger	20.0	$ 2,620	$ 2,620
Intangible assets (UCSD license - FDA and EC approval milestones)	20.0	1,250	1,250
Other intangible assets	16.0	240	240
Total intangible assets		4,110	4,110
Less accumulated amortization		(1,136)	(897)
Intangible Assets, Net		$ 2,974	$ 3,213

The intangible assets related to RP103 are being amortized over an estimated useful life of 20 years, which is the life of the intellectual property patents. The 20 year estimated useful life is also based upon the typical development, approval, marketing and life cycle management timelines of pharmaceutical drug products. Other intangible assets are being amortized using the straight-line method over an estimated useful life of 16 years, which is the life of the intellectual property patents.

As of August 31, 2012, the Company had determined that its acquired in-process research and development asset was impaired and wrote off the $0.9 million carrying amount to research and development expense. During the years ended December 31, 2014 and 2013, and the four months ended December 31, 2012, there was no intangible asset impairment recognized.

During the years ended December 31, 2014 and 2013, the four months ended December 31, 2012 and the fiscal year ended August 31, 2012, the Company amortized $239 thousand, $193 thousand, $49 thousand, and $146 thousand, respectively, of intangible assets.

Amortization expense for intangible assets for each of the next five years is as follows:

(In thousands)	Amortization Expense
2015	$ 238
2016	238
2017	238
2018	238
2019	238

The Company tested the carrying value of goodwill for impairment as of December 31, 2014 and determined that there was no impairment.

7. ACCRUED LIABILITIES

Accrued liabilities consisted of:

(In thousands)	December 31, 2014	December 31, 2013
Personnel-related costs	$ 6,879	$ 4,443
Rebates and other sales deductions	3,231	2,325
Clinical trials and research and development costs	2,522	1,661
License royalty payable	972	564
Royalty-based interest payable	369	1,255
Manufacturing costs	284	294
Other	2,602	2,586
Total Accrued Liabilities	$ 16,859	$ 13,128

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8. NOTE PAYABLE

On December 20, 2012, the Company entered into a loan agreement with HC Royalty, as lender, under which it agreed to borrow $50.0 million in two $25.0 million tranches. The Company received $23.4 million in net proceeds from the first tranche of the loan at closing in December 2012 and an additional $23.7 million in net proceeds in May 2013 from the second tranche upon FDA approval of PROCYSBI.

In July 2014, the Company entered into an amended and restated loan agreement with HC Royalty which revised the terms of the 2012 loan agreement between the Company and HC Royalty, and also provided for an additional $10 million in term loan funding. The interest rate was revised to an annual fixed rate of 8.0%, compared to the original interest rate of 10.75%. The loan also contains a synthetic royalty component based on net product revenues, including PROCYSBI, in a calendar year, and such royalty is payable quarterly. The variable royalty rate under the amended and restated loan agreement has been revised to 8.0% on the first $50 million of revenue and 2.0% on revenue in excess of $50 million. The first quarterly principal payment of $3 million is due in June 2015. All term loans under the amended and restated loan agreement mature on March 31, 2020. The loan and the Company's obligation to make payments thereunder shall terminate immediately when all payments received by HC Royalty equal $120.0 million.

Prior to July 1, 2014, with respect to the first $25.0 million tranche, for each calendar year (prorated for any portion thereof), the loan bore a royalty rate of 6.25% of the first $25.0 million of product net revenues, 3.0% of product net revenues for such calendar year in excess of $25.0 million and up to $50.0 million, and 1.0% of product net revenues for such calendar year in excess of $50.0 million, payable quarterly. Prior to July 1, 2014, with respect to the second $25.0 million tranche, for each calendar year (prorated for any portion thereof), the loan bore a royalty rate of 6.0% of the first $25.0 million of net product revenues for such calendar year, 3.0% of product net revenues for such calendar year in excess of $25.0 million and up to $50.0 million, and 1.0% of product net revenues for such calendar year in excess of $50.0 million, payable quarterly.

The Company's amended and restated loan agreement with HC Royalty includes affirmative and negative covenants, including the use of commercially reasonable efforts to exploit RP103 in specific markets and compliance with laws, as well as restrictions on mergers and sales of assets, incurrence of liens, incurrence of indebtedness and transactions with affiliates and other requirements. To secure the performance of the Company's obligations under the loan, the Company granted a security interest to HC Royalty in substantially all of its assets, the assets of its domestic subsidiaries and a pledge of stock of certain of its domestic subsidiaries. The Company's failure to comply with the terms of the loan and related documents, the occurrence of a change of control of the Company or the occurrence of an uncured material adverse effect on the Company or the occurrence of certain other specified events, will result in an event of default under the loan that, if not cured or waived, could result in the acceleration of the payment of all of its indebtedness, as well as prepayment penalties, to HC Royalty and interest thereon. Under the terms of the security agreement, in an event of default, the lender can potentially take possession of, foreclose on, sell, assign or grant a license to use, the Company's pledged collateral and assign and transfer the pledged stock of certain of its subsidiaries.

The Company received marketing approval of PROCYSBI from the FDA on April 30, 2013 and commenced shipment of PROCYSBI during June 2013, and as a result, royalties became payable to HC Royalty based upon net revenues of PROCYSBI. Interest expense on the loan, excluding amortization of debt issuance costs, for the years ended December 31, 2014 and 2013 and the four months ended December 31, 2012 was approximately $10.6 million, $6.8 million and $0.1 million, respectively.

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The following table presents contractual principal payments of the note payable at December 31, 2014.

(In thousands)	Note Principal Payments
2015	$ 9,000
2016	12,000
2017	12,000
2018	12,000
2019	12,000
2020 and thereafter	3,000
Total	$ 60,000

Unamortized debt issuance costs on the loan agreement totaled $2.3 million and $2.8 million at December 31, 2014 and 2013, respectively. Amortization expense was $1.0 million and $0.4 million for the years ended December 31, 2014 and 2013, respectively, and a nominal amount for the four months ended December 31, 2012.

9. CONVERTIBLE NOTES

In July 2014, the Company sold $60 million aggregate principal amount of 8.0% convertible senior notes due 2019 to HC Royalty and other purchasers. These convertible notes require quarterly interest distributions at a fixed coupon rate equal to 8.0% until maturity or conversion, which will be no later than August 1, 2019. The convertible senior notes are convertible at the option of the holder at a conversion rate of 57.14 common shares per $1,000 principal amount of convertible senior notes at issuance (equivalent to a conversion price of $17.50 per common share), subject to adjustment in certain events. Upon conversion of these convertible senior notes by a holder, the holder will receive shares of the Company’s common stock.

In addition, the Company may elect to exercise the optional redemption, as defined in the note purchase agreement, in which case the convertible senior notes will convert into shares of common stock if the price of the common stock is at or above 175% of the applicable conversion price over a 30 consecutive day period. Upon the occurrence of a “change of control”, as defined in the note purchase agreement, the holders may require the Company to repurchase all or a portion of the notes for cash at 100% of the principal amount of the notes being purchased, plus a repayment premium and any accrued and unpaid interest. To secure the performance of the Company's obligations under the convertible notes agreement, the Company has assigned certain of its assets as collateral.

Interest expense on convertible notes, excluding amortization of debt issuance costs, was $2.1 million for the year ended December 31, 2014. Unamortized debt issuance costs on these convertible notes totaled $2.8 million at December 31, 2014. Amortization expense for the year ended December 31, 2014 was $0.2 million.

10. CAPITAL STRUCTURE

Preferred Stock

At December 31, 2014, the Company was authorized to issue 15,000,000 shares of $0.001 par value per share of preferred stock. There were no shares issued and outstanding.

Common Stock

At December 31, 2014, the Company was authorized to issue 150,000,000 shares of $0.001 par value per share of common stock. Each holder of common stock is entitled to vote on all matters and is entitled to one vote for each share held. As of December 31, 2014 and 2013, there were 68,861,366 and 61,614,576 shares, respectively, of the Company's common stock issued and outstanding.

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Stockholder Rights Plan

The Company's stockholder rights plan entitles the holder of each outstanding share of common stock of the Company to one stock purchase right (a "Right"). Each Right entitles the registered holder to purchase from the Company one thousandth of a share of the Company's Series A Participating Preferred Stock (the "Preferred Shares") at a price of $15 per one one-thousandth of a Preferred Share (the "Purchase Price"), once the Rights become exercisable. The Rights will not be exercisable until the earlier of either (a) 10 days after the public announcement that a person, together with all affiliates or associates of such person, has become an "Acquiring Person" by obtaining beneficial ownership of 15% or more of the Company's outstanding common stock, or (b) 10 business days (or a later date determined by the Board before any person or group becomes an Acquiring Person) after a person or group of affiliated or associated persons begins a tender or exchange offer which, if completed, would result in that person or group of affiliated or associated persons becoming an Acquiring Person. Each one one-thousandth of a share preferred stock, if issued, will have the same voting power as one one-hundred thirty-sixth (1/136th) of a share of common stock and will entitle holders to a per share payment equal to the payment made on one one-hundred thirty-sixth (1/136th) of a share of common stock, so that one full share of preferred stock would be entitled to receive a payment one one-hundred thirty-sixth (1/136th) of 1,000 times the per share payment to a share of common stock, provided that shares of the Company's common stock are exchanged via merger, consolidation or a similar transaction. The Rights will expire on May 13, 2015 or on an earlier date if the Company redeems or exchanges the Rights.

Common Stock and Warrants Issuance in Connection with the Sale of Units in a Private Placement

On August 21, 2009, Raptor entered into a securities purchase agreement pursuant to which the Company issued shares and warrants for aggregate gross proceeds of approximately $2.4 million. All warrants issued in connection with the August 2009 private placement have been exercised or expired as of December 31, 2014.

2009 Merger and NASDAQ Listing

On September 29, 2009, the Company, formerly known as TorreyPines Therapeutics, Inc. ("TorreyPines") and Raptor Pharmaceutical Corp. ("RPC") completed a reverse merger. The Company changed its name to "Raptor Pharmaceutical Corp." and commenced trading on September 30, 2009 on the NASDAQ Capital Market under the ticker symbol "RPTP". Effective February 29, 2012, the Company's common stock commenced trading on the NASDAQ Global Market. In connection with the merger, the Company assumed all of the TorreyPines stock options and warrants outstanding at the time of the merger. The remaining warrants outstanding are exercisable at $157.08 per share and expire on September 26, 2015.

Common Stock and Warrants Issuance in Connection with the Sale of Units in a Registered Direct Offering

On December 17, 2009, the Company entered into a Placement Agent Agreement (the "2009 Placement Agent"), pursuant to a registered direct offering (the "Direct Offering") of up to 3,748 units (the "Units"), consisting of (i) 3,748 shares of the Company's common stock, (ii) warrants to purchase an aggregate of up to 1,874 shares of the Company's common stock (and the shares of common stock issuable from time to time upon exercise of such warrants) (the "Series A Warrants"), and (iii) warrants to purchase an aggregate of up to 1,874 shares of the Company's common stock (and the shares of common stock issuable from time to time upon exercise of such warrants) (the "Series B Warrants," and collectively with the Series A Warrants, the "Investor Warrants"). All warrants issued in connection with the December 2009 direct offering have been exercised or expired as of December 31, 2014.

Common Stock Issuance in Connection with an Equity Line

On April 16, 2010, the Company signed a purchase agreement with Lincoln Park Capital Fund, LLC ("LPC"), together with a registration rights agreement, whereby LPC agreed to purchase up to $15.0 million of the Company's common stock over a 25 month period.

The purchase price of the shares issued to LPC under the purchase agreement was based on the prevailing market prices of the Company's shares at the time of sale without any fixed discount. The Company controlled the timing and amount of any sales of shares to LPC. LPC did not have the right or the obligation to purchase any shares of the Company's common stock on any business day that the purchase price of the Company's common stock was below $1.50 per share.

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2010 Private Placement

On August 9, 2010, the Company entered into a securities purchase agreement for the private placement (the "2010 Private Placement") of the Company's common stock and warrants to purchase its common stock, at a purchase price of $3.075 per unit, with each unit comprised of one share of common stock and a warrant to purchase one share of common stock. Each warrant, exercisable for 5 years from August 12, 2010, has an exercise price of $3.075 per share.

2011 Follow-on Public Offering

On September 13, 2011, the Company closed an underwritten public offering of shares of the Company's common stock at a price to the public of $4.00 per share. The shares sold in the offering included 10.0 million shares of common stock plus an additional 1.5 million shares of common stock pursuant to the exercise by the underwriters of the over-allotment option the Company granted to them. Total gross proceeds to the Company in the offering (including in connection with the sale of the shares of common stock pursuant to the exercise of the over-allotment option) totaled $46.0 million, before underwriting discounts and commissions. The offering resulted in net proceeds to the Company of approximately $42.8 million after deduction of underwriting discounts of 6% and other offering expenses paid by the Company.

Common Stock Issuance under At-The-Market ("ATM") Agreement

On April 30, 2012, the Company entered into an "At-the-Market" ("ATM") Sales Agreement with Cowen and Company, LLC ("Cowen"), under which the Company may, at its discretion, sell its common stock with a sales value of up to a maximum of $40 million through ATM sales on the NASDAQ Stock Market. Cowen acts as sole sales agent for any sales made under the ATM and receives a 3% commission on gross proceeds. The common stock is being sold at prevailing market prices at the time of the sale of common stock, and, as a result, prices may vary.

On July 3, 2013, the Company and Cowen amended and restated the Sales Agreement (the "Amended and Restated Sales Agreement") to increase the aggregate gross sales proceeds that may be raised to $100 million. Cumulatively through December 31, 2014, we sold 12,569,914 shares under the ATM offerings at a weighted-average selling price of $7.96 per share for net proceeds of approximately $97 million.

Sales in the ATM offerings are being made pursuant to the prospectus supplement dated April 30, 2012, as amended by Amendment No. 2 dated July 3, 2013, which supplements the Company's prospectus dated February 3, 2012, filed as part of the shelf registration statement that was declared effective by the Securities and Exchange Commission ("SEC") on February 3, 2012, and pursuant to the prospectus supplement dated August 21, 2014, which supplements the Company’s prospectus dated May 12, 2014, filed as part of the automatic shelf registration statement filed with the SEC on May 12, 2014. We did not sell any shares under ATM offerings during the nine months ended September 30, 2014. During the years ended December 31, 2014 and 2013, the Company sold approximately 5.0 million and 4.9 million shares, respectively, under ATM offerings at a weighted-average selling price of $9.29 and $8.09 per share, respectively, for proceeds of approximately $45 million and $38.8 million net of commissions, respectively. During the four month period ended December 31, 2012 and fiscal year ended August 31, 2012, the Company sold approximately 1.2 million shares and 1.5 million shares, respectively, at a weighted-average selling price of $5.10 and $5.34 per share, respectively, for net proceeds of approximately $6.0 million and $7.4 million, net of commissions, respectively. As of December 31, 2014, the Company did not have any remaining shares available under the ATM for future sales of the Company's common stock.

Common Stock Warrants

During the year ended December 31, 2014, the Company received approximately $1.8 million from the exercise of warrants in exchange for the issuance of 611,606 shares of the Company's common stock.

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The following table reflects the number of common stock warrants outstanding as of December 31, 2014.

	Number of Shares Exercisable	Exercise Price	Expiration Date
Issued in connection with Encode merger	233,309	$ 2.87	12/13/2015
TorreyPines warrants assumed in 2009 Merger	3,503	157.08	9/26/2015
Issued to placement agent in Aug. 2010	97,952	3.08	8/12/2015
Total Warrants Outstanding	334,764	$ 4.54(1)	

(1) Weighted-average exercise price

The warrants issued by the Company in the August 2010 private placement and the December 2009 equity financing contain a conditional obligation that may require the Company to transfer assets to repurchase the warrants upon the occurrence of potential future events. Under ASC 480, a financial instrument that may require the issuer to settle the obligation by transferring assets is classified as a liability. Therefore, the Company has classified the warrants from both financings as liabilities and marks them to fair value at each period end. All warrants issued in connection with the December 2009 equity financing have been exercised or expired as of December 31, 2014.

A Black-Scholes option-pricing model was used to obtain the fair value of the warrants issued in the December 2009 and August 2010 equity financings. The following table presents the assumptions used at December 31, 2014 and 2013.

	August 2010 Private Placement Investors and Placement Agent		December 2009 Equity Financing Series A
	December 31,		December 31,
	2014	2013	2013
Fair value (in thousands)	$ 711	$ 6,933	$ 133
Black-Scholes inputs:			
Stock price	$ 10.28	$ 13.02	$ 13.02
Exercise price	$ 3.08	$ 3.08	$ 2.45
Risk free interest rate	0.12%	0.33%	0.13%
Volatility	95.00%	95.00%	95.00%
Expected term (years)	0.50	1.75	1.00
Dividend	-	-	-

For the years ended December 31, 2014 and 2013, the four months ended December 31, 2012 and the fiscal year ended August 31, 2011, the Company recorded losses of approximately $1.1 million, $10.7 million, $1.5 million, and $3.2 million, respectively, in its consolidated statements of operations and comprehensive loss from changes in the fair values of liability-classified warrants.

11. STOCK-BASED COMPENSATION

Stock Incentive Plans

In February 2010, the Company's Board of Directors approved, and in March 2010 Raptor's stockholders approved, the Raptor Pharmaceutical Corp. 2010 Stock Incentive Plan, as subsequently amended and approved by its stockholders in March 2011 ("Amended Plan"). On July 23, 2013, the Company, held its 2013 Annual Meeting of Stockholders (the "Annual Meeting"). At the Annual Meeting, Raptor's stockholders approved an amendment to the Amended Plan, which among other things, increased the authorized share reserve by 3,000,000 shares to an aggregate of 11,936,383 shares.

On November 25, 2014, as a key requirement of the Company's strategy of strengthening its leadership team and employee base, continuing the expansion of its commercial activities into new territories, and increasing the expansion of its product development programs, the Company's Board of Directors approved the Raptor Pharmaceutical Corp. 2014 Employment Commencement Stock Incentive Plan. The plan was approved pursuant to Rule 5635(c)(4) of the Nasdaq Global Select Market for equity grants to induce new employees to enter into employment with the Company. Up to 2,400,000 shares may be issued under this plan.

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As of December 31, 2014, there were 3,970,685 shares remaining available for issuance under both plans.

Stock options are granted to recognize the contributions made by its employees, independent contractors, consultants and directors, to provide those individuals with additional incentive to devote themselves to the Company's future success and to improve its ability to attract, retain and motivate individuals upon whom its growth and financial success depends. Employee stock options generally vest over four years with a six-month clift-vesting period. In general, all options are exercisable over a period not to exceed the contractual term of ten years from the date the stock options are granted at prices not less than the fair market value of the Company's common stock on the grant date. The Company has and may grant options with different vesting terms from time to time.

The following table presents components of stock-based compensation recorded in our consolidated statements of operations and comprehensive loss.

	Year Ended December 31,		For the Four Months Ended December 31,	For the Year Ended August 31,
(In thousands)	**2014 (1)**	**2013**	**2012**	**2012**
Cost of goods sold	$ 188	$ -	$ -	$ -
Research and development	2,191	1,550	453	926
General and administrative	9,554	5,480	1,786	3,633
Total Stock-Based Compensation Expense	$ 11,933	$ 7,030	$ 2,239	$ 4,559

(1) Stock-based compensation for the year ended December 31, 2014 does not include expense associated with the ESPP program of $113 thousand.

Stock-based compensation expense was based on the Black-Scholes option-pricing model assuming the following:

Period (1)	Risk-free interest rate	Expected life of stock option	Annual Volatility
Year ended December 31, 2014	0.0025% to 2.13%	6 years	67 to 68%
Four months ended December 31, 2013	0.68% to 0.7%	5 years	95%
Year ended August 31, 2012	0.68% to 1.2%	5 to 6 years	121 to 125%

(1) Dividend rate is 0% for all periods presented.

The compensation expense for stock-based compensation awards includes an estimate for forfeitures and is recognized over the requisite service period of the options, which is typically the period over which the options vest, using the straight-line method.

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A summary of the activity in the 2014 Employment Commencement Stock Incentive Plan, the 2010 Equity Incentive Plan, as amended, the 2006 Equity Compensation Plan, as amended, and the Company's other stock option plans, is as follows:

	For the Year Ended					
	December 31, 2014			December 31, 2013		
	Option Shares		Weighted-average Exercise Price	Option Shares		Weighted-average Exercise Price
Beginning balance	8,217,674		$ 6.05	7,790,794		$ 5.79
Granted	3,356,946		12.03	1,187,500		9.21
Exercised	(1,643,464)		4.00	(651,386)		3.80
Canceled	(1,073,195)		14.22	(109,234)		34.89
Outstanding Balance at Year End	8,857,961		7.71	8,217,674		6.05

The number of options outstanding, vested and expected to vest as of December 31, 2014 was 8,390,147 and the weighted-average remaining contractual life was 6.8 years. The aggregate intrinsic value and the weighted-average intrinsic value of stock options outstanding, vested and expected to vest as of December 31, 2014 was $33.7 million and $7.57 per option, respectively. The number of options outstanding, vested and expected to vest as of December 31, 2013 was 8,109,622 and the weighted-average remaining contractual life was 7.6 years. The aggregate intrinsic value and the weighted-average intrinsic value of stock options outstanding, vested and expected to vest as of December 31, 2013 was $71.8 million and $8.85 per option, respectively.

As of December 31, 2014, the options outstanding under all of the Company's stock option plans consisted of the following:

	Options Outstanding			Options Vested and Exercisable		
Range of Exercise Price	Number of Options Outstanding	Weighted- average Remaining Contractual Life	Weighted-average Exercise Price	Number of Options Exercisable	Weighted-average Remaining Contractual Life	Weighted-average Exercise Price
$0 to $3.00	669,848	3.56	$ 2.61	669,848	3.56	$ 2.61
$3.01 to $5.00	1,357,975	5.09	3.80	1,249,480	4.86	3.72
$5.01 to $6.00	3,061,116	6.29	5.27	2,255,570	6.12	5.25
$6.01 to $8.00	738,872	8.37	7.11	273,306	7.95	6.90
$8.01 to $10.00	1,064,603	9.66	8.96	40,528	9.35	8.63
$10.01 to $14.00	568,696	8.84	12.42	121,481	7.50	12.76
$14.01 to $18.00	1,368,019	7.94	14.97	513,782	7.03	14.86
$18.01 to $965.00	28,832	1.57	100.58	28,832	1.57	100.58
Total	8,857,961	6.88	7.71	5,152,827	5.70	6.32

The aggregate intrinsic value of stock options outstanding as of December 31, 2014 was $34.5 million. The aggregate intrinsic value of stock options exercisable as of December 31, 2014 was $26.6 million.

At December 31, 2014, the total unrecognized compensation cost was approximately $21.5 million. The weighted-average period over which it is expected to be recognized is approximately 2.85 years.

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The following table presents details on the stock options granted and exercised.

(In thousands, except per share data)	Year Ended December 31, 2014	Year Ended December 31, 2013	For the Four Months Ended December 31, 2012	For the Year Ended August 31, 2012
Weighted-average fair value per share of options granted	$ 6.50	$ 5.33	$ 3.84	$ 4.62
Aggregate intrinsic value of options exercised	11,920	5,979	228	602

In the year ended December 31, 2014, the Company incurred $1.3 million of incremental stock compensation costs associated with modifications to two directors' and two employees' stock option grants. These modifications included the acceleration of unvested shares and an extended period to exercise vested options.

Employee Stock Purchase Plan

The ESPP allows a maximum of 1,000,000 shares of common stock to be purchased in aggregate for all employees. During 2014, the Company issued 21,280 shares under the ESPP. As of December 31, 2014, there were approximately 978,720 shares reserved for future issuance under the ESPP.

The assumptions used to estimate the per share fair value of stock purchase rights granted under the ESPP were as follows:

Period [1]	Risk-free interest rate	Expected life of stock option	Annual Volatility
Year ended December 31, 2014	0.01% to 0.16%	4 to 6 months	62% to 67%

(1) Dividend rate is 0%.

12. INCOME TAXES

The Company had losses before income taxes for domestic and foreign operations as follows:

(In thousands)	Year Ended December 31, 2014	Year Ended December 31, 2013	For the Four Months Ended December 31, 2012	For the Year Ended August 31, 2012
Domestic loss	$ 15,463	$ 33,966	$ 12,510	$ 26,642
Foreign loss	37,023	35,451	6,782	12,002
Loss before Income Taxes	$ 52,486	$ 69,417	$ 19,292	$ 38,644

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The provision for income taxes differs from the amount estimated by applying the statutory federal income tax rate to loss before taxes. The following is a reconciliation of the statutory federal and state rates to the effective rates, for the years ended December 31, 2014 and 2013, the four months ended December 31, 2012, and the fiscal year ended August 31, 2012.

Reconciliation of Statutory Tax Rate to Effective Tax Rate

	Year Ended December 31,		For the Four Months Ended December 31,	For the Year Ended August 31,
(In thousands)	**2014**	**2013**	**2012**	**2012**
Federal tax (benefit) at statutory rate	(34.00)%	(34.00)%	(34.00)%	(34.00)%
State tax (benefit) at statutory rate, net of federal tax benefit	(7.10)%	0.72%	(3.72)%	(2.77)%
Change in valuation allowance	14.51%	20.86%	12.22%	12.38%
Research and development credits	(2.34)%	(14.92)%	-%	(2.68)%
Fair market value of warrants	-%	5.27%	2.62%	2.80%
Intangible asset basis allocation	2.77%	-%	8.69%	7.66%
Stock-based compensation - ISO	-%	1.08%	3.93%	3.96%
Tax attributes not benefited	-%	6.07%	-%	-%
Foreign losses not benefited	27.11%	14.94%	10.38%	9.98%
Other	(0.95)%	(0.02)%	(0.12)%	2.67%
Effective Tax Rate	0%	0%	0%	0%

Components of our net deferred tax assets are presented in the following table.

Deferred Tax Assets

	December 31,	
(In thousands)	**2014**	**2013**
Net operating loss carryforwards	$ 22,480	$ 18,797
Capitalized start-up costs	11,057	11,256
Stock option expense	4,435	1,909
Research credits	20,951	19,281
Fixed assets and intangible assets	1,565	4,813
Accruals	1,434	1,224
Inventory	1,200	186
Other	124	65
Valuation allowance	(63,246)	(57,531)
Deferred Tax Assets, Net	$ -	$ -

As of December 31, 2014, the Company had net operating loss carryforwards for U.S. federal, U.S. state and foreign income tax purposes of approximately $51.5 million, $115.0 million and $2.9 million, respectively, which expire beginning after the year 2022, 2016 and 2021, respectively. As of December 31, 2014, the Company had federal and state research and development credits of $20.0 million and $1.4 million, respectively. The federal credits expire beginning after the year 2026 and the state credits have no expiration.

As of December 31, 2014, the Company's net operating loss carryforwards for federal and state income tax purposes include approximately $7.5 million on a gross basis, respectively, of losses attributable to stock option tax expense deductions.

The valuation allowance increased approximately $5.7 million during the period ending December 31, 2014, primarily as a result of current year losses and tax credits.

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Utilization of the Company's net operating loss may be subject to substantial annual limitation due to the ownership change limitations provided by the Internal Revenue Code and similar state provisions. Such an annual limitation could result in the expiration of the net operating loss before utilization.

The Company has analyzed its tax positions in all of the federal, state and foreign jurisdictions where it is required to file income tax returns, as well as all open tax years in these jurisdictions.

As of December 31, 2014, the Company had no unrecognized tax benefits and has recorded no liability related to uncertain tax positions. The Company did not record a change in its unrecorded tax benefits during the year ended December 31, 2014, and expects no change in its unrecorded tax benefits in the next 12 months.

Due to net operating loss and research credit carryforwards, substantially all of the Company's tax years, from 2001 through 2014, remain open to U.S. federal and state tax examinations.

The Company is not aware of any pending income tax audits. Significant components of the Company's deferred tax assets for income tax purposes are net operating loss carryforwards, capitalized start-up costs, and stock-based compensation and research credits. Due to the Company's lack of earning history, any deferred assets recorded have been fully offset by a valuation reserve.

The Company's practice is to recognize interest and/or penalties related to income tax matters as a component of income tax expense. As of December 31, 2014, there were no accrued interest and penalties related to uncertain tax positions.

13. COMMITMENTS AND CONTINGENCIES

Contractual Obligations with UCSD Relating to the Acquisition of the DR Cysteamine (RP103) License

Pursuant to the license agreement with UCSD, the Company is obligated to pay milestone payments upon the occurrence of certain events, royalties on net sales from products developed pursuant to the license agreement and a percentage of sublicense fees or sublicense royalties, if any. The Company is obligated to fulfill predetermined milestones within a specified number of years from the effective date of the license agreement, depending on the indication. Cumulatively, the Company has expensed $2.2 million in milestone payments to UCSD based upon the initiation of clinical trials in cystinosis, Huntington's disease and NASH fand on regulatory filings in cystinosis. To the extent that the Company fails to perform any of its obligations under the license agreement, then UCSD may terminate the license or otherwise cause the license to become non-exclusive.

Leases

In April 2013, the Company executed a seven-year lease for its corporate office facilities in Novato, California. The Company took occupancy of such facilities at the end of June 2013. On June 10, 2013, the Company amended the lease to add space to accommodate its research laboratory and relocated to this space in July 2014. The Company records such rent on a straight-line basis.

In October 2014, the Company executed a three-year lease for its European sales, marketing and administrative headquarters in Utrecht, Netherlands. The Company records such rent on a straight-line basis.

Rent expense for the Company's current and previous facilities was approximately $1.3 million, $0.6 million, $0.1 million, and $0.2 million for the years ended December 31, 2014 and 2013, the four months ended December 31, 2012 and the fiscal year ended August 31, 2012, respectively. Leasehold improvements for our offices are amortized into expense over the lease term. There were $470 thousand of unamortized leasehold improvements at December 31, 2014. For the years ended December 31, 2014 and 2013, the four months ended December 31, 2012 and the fiscal year ended August 31, 2012, the Company recognized a negligible amount of leasehold amortization expense.

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RAPTOR PHARMACEUTICAL CORP.
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The following table presents our future lease commitments at December 31, 2014:

(In thousands)	Future Lease Payments
2015	$ 1,553
2016	1,867
2017	1,901
2018	1,871
2019	1,929
2020 and thereafter	3,329
Total	$ 12,450

14. QUALIFYING THERAPEUTIC DISCOVERY PROJECT GRANT

In October 2010, the Company was awarded a tax grant under the U.S. Government's Qualifying Therapeutic Discovery Project for five of its research programs including its cystinosis, Huntington's disease and NASH clinical programs and its HepTide™ and WntTide™ preclinical cancer research programs. The Company was granted an aggregate of approximately $1.1 million for all five programs of which, as of August 31, 2011, it had received approximately $0.9 million. The Company recorded the $0.8 million of proceeds as a contra-research and development expense during the first two quarters of fiscal year 2011. During the fiscal year ended August 31, 2012, the Company received approximately $162 thousand pursuant to the government program funding guidelines and the remaining balance of approximately $36 was drawn but was returned to the government in March 2012 along with an additional $28 thousand as recapture tax because the Company had not incurred the amount originally estimated as qualified expenses for its WntTide™ program, which was the basis for the program funding. The Company recorded the contra-expense upon receipt of the grant proceeds.

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December 31, 2014

15. QUARTERLY RESULTS OF OPERATIONS (UNAUDITED)

The following table presents selected unaudited quarterly results of operations in conjunction with the consolidated financial statements and related notes contained elsewhere in this Annual Report on Form 10-K. These unaudited results were prepared on the same basis as the Company's audited consolidated financial statements. The Company's quarterly operating results have fluctuated in the past and may continue to do so in the future as a result of a number of factors, including, but not limited to, the timing and amounts of its revenues and the timing and nature of research and development activities.

	Quarterly Data 2014			
(In millions, except per share data, unaudited)	**March 31, 2014**	**June 30, 2014**	**September 30, 2014**	**December 31, 2014**
Net sales	$ 12.1	$ 16.3	$ 23.8	$ 17.3
Gross profit	10.8	15.3	19.8	14.0
Net loss	(14.9)	(12.7)	(6.0)	(18.9)
Net loss per share, basic and diluted	(0.24)	(0.20)	(0.10)	(0.29)

	Quarterly Data 2013			
(In millions, except per share data, unaudited)	**March 31, 2013**	**June 30, 2013**	**September 30, 2013**	**December 31, 2013**
Net sales	$ -	$ -	$ 6.7	$ 10.2
Gross profit	-	(0.4)	6.2	9.5
Net loss	(15.9)	(24.1)	(17.3)	(12.1)
Net loss per share, basic and diluted	(0.30)	(0.43)	(0.29)	(0.20)

	Quarterly Data for the Four Months Ended December 31, 2012
(In millions, except per share data, unaudited)	**November 30, 2012 (1)**
Net loss	$ (13.4)
Net loss per share, basic and diluted	(0.26)

	Quarterly Data 2012			
(In millions, except per share data, unaudited)	**November 30, 2011**	**February 29, 2012**	**May 31, 2012**	**August 31, 2012**
Net loss	$ (11.4)	$ (14.0)	$ (3.0)	$ (10.2)
Net loss per share, basic and diluted	(0.25)	(0.29)	(0.06)	(0.21)

(1) The Company changed its fiscal year end to December; the four-month transition period included one quarterly report on Form 10-Q for the three months ended November 30, 2012.

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RAPTOR PHARMACEUTICAL CORP.
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December 31, 2014

Schedule II: Valuation and Qualifying Accounts

Valuation Allowance for Deferred Tax Assets

(In millions)	Year Ended December 31, 2014	Year Ended December 31, 2013	Four Months Ended December 31, 2012	Fiscal Year Ended August 31, 2012
Balance at beginning of year	$ 58	$ 43	$ 41	$ 36
Additions to charged to expenses/other accounts	5	15	2	5
Net (deductions) recoveries	-	-	-	-
Balance at end of year	$ 63	$ 58	$ 43	$ 41

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2015

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to

Commission File Number: 000-25571

RAPTOR PHARMACEUTICAL CORP.

(Exact name of registrant as specified in its charter)

Delaware	86-0883978
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)

7 Hamilton Landing, Suite 100, Novato, CA 94949
(Address of Principal Executive Offices)

(415) 408-6200
(Registrant's telephone number)

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	Name of Each Exchange on Which Registered
Common Stock, $0.001 par value	The NASDAQ Global Select Market

Securities registered under Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company.

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act.) Yes ☐ No ☒

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant as of June 30, 2015 (the last business day of the registrant's most recently completed second quarter) was $1,267 million.

The number of shares of the registrant's common stock outstanding, par value $0.001, on February 22, 2016 was 85,243,864.

The documents incorporated by reference are as follows: Portions of the registrant's definitive Proxy Statement to be filed with the Securities and Exchange Commission under Regulation 14A within 120 days after the end of registrant's fiscal year covered by this Annual Report are incorporated by reference into Part III.

RAPTOR PHARMACEUTICAL CORP.

2015 Form 10-K Annual Report

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FORWARD-LOOKING STATEMENTS

Forward-Looking Statements

In this Annual Report on Form 10-K, in our other filings with the Securities and Exchange Commission, or the SEC, and in press releases and other public statements by our officers throughout the year, we make or will make statements that plan for or anticipate the future. These "forward-looking statements," within the meaning of the Private Securities Litigation Reform Act of 1995, include statements about our future business plans and strategies, as well as other statements that are not historical in nature. These forward-looking statements are based on our current expectations.

In some cases, these statements can be identified by the use of terminology such as "believes," "expects," "anticipates," "plans," "may," "might," "will," "could," "should," "would," "projects," "anticipates," "predicts," "intends," "continues," "estimates," "potential," "opportunity" or the negative of these terms or other comparable terminology. All such statements, other than statements of historical facts, including, but not limited to:

- statements regarding our financial condition and future results of operations;
- projected revenues from sales of PROCYSBI, QUINSAIR or future product candidates;
- business strategies and operating efficiencies or synergies;
- our products' competitive positions;
- potential clinical efficacy of our product candidates;
- growth opportunities for existing intellectual properties and technologies;
- patient market size for our products and product candidates, and market adoption of our products by patients and physicians;
- timing of or costs of our clinical trials;
- plans and objectives of management,
- markets for our securities;
- the impact of changes in laws and accounting standards;
- our ability to repay our notes or raise capital in the public markets; and
- our estimates of the timing of our need to raise capital.

These and other prospective matters, involve substantial risks and uncertainties and constitute forward-looking statements for the purpose of the safe harbor provided by Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. You should not place undue reliance on these statements, which only reflect information available as of the date that they were made. Our business' actual operations, performance, developments and results might differ materially from any forward-looking statement due to various known and unknown risks, uncertainties, assumptions and contingencies, including those described in the section titled "Risk Factors" in Part I, Item 1A of this Annual Report on Form 10-K as well as other documents we file with the SEC. In light of the significant uncertainties inherent in such forward-looking statements, you should not regard the inclusion of this information as a representation by us or any other person that the results or conditions described in those statements or our objectives and plans will be achieved.

All subsequent forward-looking statements attributable to us or any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to herein. Unless required by U.S. federal securities laws and the rules and regulations of the SEC, we do not undertake any obligation and disclaim any intention to update or release publicly any revisions to these forward-looking statements after the filing of this Annual Report on Form 10-K to reflect later events or circumstances or to reflect the occurrence of unanticipated events or for any other reason.

PART I

1. BUSINESS

You should read the following discussion in conjunction with our consolidated financial statements as of December 31, 2015, and the notes to such consolidated financial statements included elsewhere in this Annual Report on Form 10-K.

Unless otherwise stated or the context requires otherwise, for the period from and after the effective time of the 2009 Merger (as described below under "Corporate Information"), all references in this Annual Report on Form 10-K to the "Company," "we," "our," "us," "Raptor" and similar references refer to the company formerly known as TorreyPines Therapeutics, Inc. and now known as Raptor Pharmaceutical Corp. and its direct and indirect wholly-owned subsidiaries Raptor Pharmaceuticals Inc., Raptor European Products, LLC, RPTP European Holdings C.V., Raptor Pharmaceuticals Europe B.V., Raptor Pharmaceuticals France SAS and Raptor Pharmaceuticals Germany GmbH.

Corporate History

In September 2009, our subsidiary merged with and into Raptor Pharmaceutical Corp., a Delaware corporation, or RPC, pursuant to which the stockholders of RPC received shares of our common stock in exchange for their shares of stock and RPC survived as our wholly-owned subsidiary. This merger is referred to herein as the 2009 Merger. Immediately prior to the 2009 Merger, we changed our corporate name from "TorreyPines Therapeutics, Inc." to "Raptor Pharmaceutical Corp." At the time of the 2009 Merger, RPC had two principal subsidiaries, Raptor Discoveries, a development-stage research and development company, and Raptor Therapeutics, which focused on developing clinical-stage drug product candidates through to commercialization and, in connection with the 2009 Merger, these two subsidiaries became our subsidiaries. In December 2012, the two principal subsidiaries were merged and currently operate under the name Raptor Pharmaceuticals Inc. Due to the amount of our stock issued to the stockholders of RPC in the 2009 Merger, RPC was treated as the "accounting acquirer" in the merger, and its board of directors and officers managed and operated the combined company. In December 2011, we merged RPC with and into us and it ceased to exist as a separate company. TorreyPines Therapeutics was incorporated in July 1997 under the name "Axonyx, Inc." and RPC was incorporated in May 2006 under the name "Highland Clan Creations Corp."

Overview

We are a biopharmaceutical company focused on developing and commercializing transformative treatments for people affected by rare and debilitating diseases.

Our first commercial product, PROCYSBI® (cysteamine bitartrate) delayed-release capsules ("PROCYSBI"), received marketing approval from the U.S. Food and Drug Administration ("FDA") on April 30, 2013 for the management of nephropathic cystinosis in adults and children six years and older. On August 14, 2015, we received FDA approval for the expanded use of PROCYSBI to treat children two to six years of age with nephropathic cystinosis. In Europe, PROCYSBI® gastro-resistant hard capsules of cysteamine (as mercaptamine bitartrate), received marketing authorization on September 6, 2013 from the European Commission ("EC"), for marketing in the European Union ("EU") as an orphan medicinal product for the management of proven nephropathic cystinosis. The EU marketing authorization allows us to commercialize PROCYSBI in the 28 Member States of the EU plus Norway, Liechtenstein and Iceland (which are not EU Member States but are part of the European Economic Area or EEA). PROCYSBI received seven years of market exclusivity, through 2020 for patients six years and older as an orphan drug in the United States and ten years of market exclusivity, through 2023, as an orphan drug in Europe. Recently, PROCYSBI received orphan drug designation for the treatment of patients ages two years to six years, through 2022. We commenced commercial sales of PROCYSBI in the United States in June 2013 and in Europe in April 2014. For at least the near term, our ability to generate revenue is dependent upon sales of PROCYSBI in the United States for the management of nephropathic cystinosis in adults and children two years and older and in the EU for the management of proven nephropathic cystinosis.

As of December 31, 2015, insurers of U.S. commercial patients reimburse Raptor for PROCYSBI therapy at a Wholesale Acquisition Cost, or WAC, price for PROCYSBI of $17,812.50 per bottle of 250 75-mg capsules and $4,275.00 per bottle of 60 25-mg capsules. Prices for PROCYSBI therapy vary among patients because doses are individually based on a patient's weight. In September 2013, we executed an agreement to participate in the U.S. State Medicare/Medicaid rebate program, which is reflected in our net revenues in mandatory rebates on reimbursements for patients receiving state Medicare and Medicaid insurance coverage. As of December 31, 2015, our price to German, Swiss and Austrian pharmacies was €5,850.23 per bottle of 250 75-mg capsules and €468.02 per bottle of 60 25-mg capsules.

In October 2015, we acquired various assets and rights related to levofloxacin solution for inhalation, a pharmaceutical product also known as "MP-376" and commercially as "QUINSAIR," from Tripex Pharmaceuticals, LLC ("Tripex"). QUINSAIR received marketing authorization by the EC for treating chronic lung infection caused by the bacteria Pseudomonas aeruginosa in adults who

have cystic fibrosis in March 2015 and Health Canada in June 2015 for the management of cystic fibrosis in patients aged 18 years or older with chronic pulmonary *Pseudomonas aeruginosa* infections. QUINSAIR is the first inhaled fluoroquinolone approved for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis 18 years old and older. We plan to launch QUINSAIR in Europe in the first half of 2016 and Canada later in 2016. We plan to discuss the path to potential approval in the same indication in the United States with the FDA in 2016. We will also pursue a clinical program for the development of MP-376 in non-cystic fibrosis related bronchiectasis in 2016 and are planning to do work in preparation to support further clinical development of MP-376 in nontuberculous mycobacteria. QUINSAIR is not approved in the United States, and we may not market or commercialize QUINSAIR in the United States for any indication unless we receive FDA approval, which we may not be able to obtain.

Cysteamine Mechanism of Action

Cysteamine, or 2-aminoethanethiol, the active pharmaceutical ingredient in PROCYSBI, is a molecule generated naturally in human cells during the metabolism of cysteine. Cysteamine is used to construct the key enzymatic cofactor involved in energy produced from sugars and lipids. Cysteamine's uniquely reactive properties result in a number of physiological effects when given in pharmaceutical doses.

- Antioxidation – Cysteamine is known to increase levels of a key cellular antioxidant, glutathione. Glutathione is composed of the amino acids gamma-glutamate, cysteine and glycine. The availability of cysteine is the major rate-limiting factor in glutathione production. Cysteamine may release cysteine in the circulation, or from within the cell. Cysteamine has been shown to activate the NRF2 pathway, which leads to the increased expression of a wide variety of proteins involved in antioxidation which may help to reduce oxidative stress in CNS, hepatic and mitochondrial disorders.
- Proteostasis – Heat shock proteins, or HSPs, are chaperones that play an important role in protein-protein interactions such as folding and assist in the establishment of proper protein conformation. Proper protein folding may also prevent unwanted protein aggregation. By helping to stabilize partially unfolded proteins, HSPs aid in transporting proteins across membranes within the cell. HSPs are typically produced by cells in response to stress or injury, or other metabolic imbalance. HSPs are part of a cell's mechanism for protein maintenance. The presence of cysteamine within a cell has been shown to increase transcription of certain HSPs that are key components to the cell's ability to maintain the integrity of proteins.
- Anti-fibrosis – Cysteamine blocks TGF-β signaling and thereby inhibits the production and proliferation of myofibroblasts. It also inhibits formation of three cross-links in collagen protein, each of which exacerbate formation of fibrotic tissue: gamma-glutamyl peptide bonds, formed by transglutaminase; oxidized lysyl-lysine conjugates, formed by lysyl oxidase; and inter-chain disulfide bonds.
- Transcription inhibition-Cysteamine inhibits transcription of a variety of collagens and basement membrane-related proteins:
- Metal chelation – In vitro studies have shown that cysteamine chelates metals, including copper, zinc and iron. High doses of cysteamine can lead to copper depletion, implying that chelation effects also occur in vivo.
- Induction of DNA repair mechanisms – Cysteamine has been known for over sixty years to mitigate the effects of radiation by upregulating cell cycle checkpoints and repair mechanisms.

MARKETED PRODUCT

PROCYSBI®

PROCYSBI is an approved therapy for the management of nephropathic cystinosis, a rare, life-threatening metabolic lysosomal storage disorder that causes the rapid, toxic accumulation of cystine in all cells, tissues and organs in the body. PROCYSBI capsules contain cysteamine bitartrate in the form of innovative microspheronized beads that are individually coated to create delayed and extended-release properties, allowing patients to maintain consistent therapeutic systemic drug levels over a 12-hour dosing period. The enteric-coated beads are pH sensitive and bypass the stomach for dissolution and absorption in the more alkaline environment of the proximal small intestine. Randomized controlled clinical trials and extended treatment with PROCYSBI therapy demonstrated consistent cystine depletion as monitored by levels of the biomarker (and surrogate marker), white blood cell cystine.

About Nephropathic Cystinosis

We estimate that there are approximately 500 patients diagnosed with cystinosis living in the United States and an estimated 2,000 worldwide. Nephropathic cystinosis comprises 95% of known cases of cystinosis. In these patients, elevated cystine leads to cellular dysfunction and death; without treatment, the disease is usually fatal by the end of the first decade of life. Cystinosis is progressive, eventually causing irreversible tissue damage and multi-organ failure, including kidney failure, blindness, muscle wasting

and premature death. Nephropathic cystinosis is usually diagnosed in infancy after children present with symptoms including markedly increased urination, thirst, dehydration, gastrointestinal distress, failure to thrive, rickets, photophobia and kidney symptoms specific to Fanconi syndrome. Management of cystinosis requires lifelong therapy.

Cystine depletion is the only approved treatment strategy for nephropathic cystinosis. Committed adherence and persistence to cystine depletion therapy is critical to achieve optimal clinical outcomes. Failure to adhere to prescribed dosing of cystine depletion therapy results in disease progression, including kidney failure leading to dialysis and kidney transplantation, muscle wasting and in most cases, premature death. Even brief interruptions in daily therapy can permit toxic accumulation of cystine, exposing tissues to renewed, progressive deterioration.

In addition to the population of patients who have already been identified, we believe that a number of patients with atypical phenotypic presentation and end-stage renal disease have their condition as a result of undiagnosed late-onset nephropathic cystinosis, and would benefit from treatment with PROCYSBI. We currently are collaborating with the Marshfield Clinic to develop an algorithm to identify late onset cystinosis patients.

APPROVED PRODUCT IN CANADA AND EUROPE

QUINSAIR®

QUINSAIR is a formulation of the antibiotic drug levofloxacin, suitable for inhalation via a nebulizer. This route of delivery allows higher concentrations of drug in the lung sputum than can be achieved via systemic (e.g. oral) administration. QUINSAIR, as approved, is administered twice daily in 28-day cycles, using a hand-held nebulizer with a disposable handset known as the Zirela ® device, manufactured by our partner PARI Pharma GmbH, and configured specifically for use with QUINSAIR.

QUINSAIR is the first fluoroquinolone inhaled antibiotic to be approved in Canada and the EU for the treatment of chronic pulmonary infections due to *Pseudomonas aeruginosa* in cystic fibrosis (CF) patients. QUINSAIR was approved in the EU and Canada on the basis of three randomized, controlled studies, one Phase 2 and two Phase 3. In the EU, QUINSAIR is eligible for "new data" regulatory exclusivity of ten years after approval, a period which is concurrent with, and independent from, the period of any applicable patent.

We intend to discuss filing of a New Drug Application ("NDA") with the FDA in 2016 for the treatment of *Pseudomonas aeruginosa* infection in CF based on the studies that were the basis for EU and Canadian marketing approvals. Depending on the feedback we receive, we may submit an NDA which, if approved, would enable us to market QUINSAIR in the United States.

About Pseudomonas aeruginosa infection in Cystic Fibrosis

CF is a rare, life-threatening genetic disease affecting approximately 70,000 people worldwide. CF is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Defective or missing CFTR protein causes poor flow of salt and water into or out of the cell in several organs, including the lungs. This leads to the buildup of abnormally thick secretions that can cause chronic lung infections and progressive lung damage in many patients that eventually leads to death.

Patients with CF are highly susceptible to colonization with bacterial infections of the lung, largely because their pulmonary mucous secretions are thicker, stickier, and more difficult to expectorate than those of healthy individuals. This creates an environment in the lung that favors bacterial proliferation. As of 2014, approximately 50% of all patients with CF in the US were colonized with *Pseudomonas aeruginosa*, a gram-negative bacterial infection. Infection rates climb as patients age, with over 80% of patients colonized by adulthood. In the EU, infection rates vary significantly from country to country, with a median of approximately 35% of patients colonized. These infections are currently treated primarily with inhaled antibiotics, including tobramycin, an aminoglycoside-class antibiotic sold by Novartis Pharmaceuticals Corporation as TOBI® or in dry-powder-inhalation format as TOBI Podhaler® and sold by others in generic form, and aztreonam, a monobacter-class antibiotic which is marketed in an inhaled formulation by Gilead Sciences, Inc. under the tradename Cayston®. Both tobramycin and aztreonam are primarily effective against gram-negative bacteria such as *Pseudomonas aeruginosa*. However, the prevalence of multi-drug-resistant *Pseudomonas aeruginosa* is growing. Thus, we believe there is an unmet need that might be addressed with a new class of inhaled antibiotic such as the fluoruquinolone class that levofloxacin represents.

CLINICAL DEVELOPMENT

RP103 Clinical Development

Huntington's Disease

Huntington's Disease ("HD") is a rare, inherited neurodegenerative disorder caused by an autosomal dominant mutation in a gene called huntingtin (Htt). The huntingtin gene encodes a protein that is also called "huntingtin." Expansion of a CAG triplet repeat beyond the normal range within the huntingtin gene results in a mutant form of the protein, which gradually damages cells in the brain. HD causes neuronal degeneration in the cerebral cortex and basal ganglia, which play a key role in movement and behavior control. The cumulative damage to these areas results in the hallmark symptoms of HD: a triad of movement, cognitive and neuropsychiatric symptoms which progress gradually in severity over 15-20 years, eventually causing severe physical and mental disability and premature death. The symptoms of HD usually become evident between ages 35-44 years, but the onset can also begin from childhood to late life (>75 years). The treatment options for HD patients are very limited, with no approved drugs that modify disease course. Recommended treatment strategies consist of drugs for symptomatic relief of chorea, an involuntary motor movement (with tetrabenazine, XENAZINE®, approved by the FDA) and mood disorder associated with HD as well as a variety of physical, occupational and dietary therapies.

RP103, enteric-coated delayed-release cysteamine bitartrate, is currently being evaluated as a potentially neuroprotective treatment for HD. Centre Hospitalier Universitaire d'Angers ("CHU d'Angers") in France, is conducting a Phase 2/3 clinical trial of RP103, referred to as CYST-HD (Clinicaltrials.gov Identifier:NCT02101957). This trial comprises an 18-month blinded, placebo-controlled phase, followed by an 18-month open-label phase in which all patients transitioned to RP103 and an extension phase for subjects who finished the 36 month trial and wish to continue on RP103. The primary endpoint of the trial was change from the baseline of the Total Motor Score ("TMS") of the Unified Huntington's Disease Rating Scale ("UHDRS") between RP103 and placebo treated patients. TMS, a validated rating scale, is comprised of approximately 15 different tests that evaluate gross and small motor function in patients with HD. The trial commenced in October 2010, with full enrollment achieved in June 2012. The study enrolled primarily Stage 1 patients showing early disease symptoms with a UHDRS TMS >5, Total Functional Capacity > 10 and a CAG repeat > 38. Due to the length of the study and the characteristic continuous progression of the disease, patients were allowed to continue their normal medication regime including taking antidepressants antipsychotics and neuroleptics. Tetrabenazine is approved as a treatment for chorea associated with HD, and chorea is a single measurement included in the TMS.

CYST-HD: 18 months results

In February 2014, we announced top line results from the planned 18-month analysis of the study. A total of 96 patients with HD were randomized to treatment with RP103 or placebo. A total of 89 patients completed the initial 18-month phase. A mixed model analysis of all 96 patients enrolled in the trial showed a trend towards slower progression of TMS in patients treated with RP103 versus those patients on placebo after 18 months treatment (4.51 vs. 6.68 respectively, p=0.19). While the results did not reach statistical significance, an overall positive trend was observed.

Patients were not stratified in the study based on concomitant medication use at baseline. We performed post-hoc statistical analyses to assess whether the TMS results were impacted by the effect of tetrabenazine on chorea. In 66 patients not taking tetrabenazine (32 under placebo and 34 under RP103), the results showed a statistically significant difference in the change in total motor score of 2.84 points of progression in the RP103 treatment arm versus 6.78 for the placebo group (p= 0.03).

There were no new or unusual variations from RP103's clinical safety profile with 48 of 52 patients experiencing at least one adverse event ("AE") during the 18-month interim evaluation versus 38 of 44 under placebo. There were slightly more patients under RP103 than under placebo reporting at least one gastrointestinal AE (61.5% RP103 versus 45.5% placebo), which consisted mostly of nausea, vomiting, abdominal pain, constipation, headache and breath odor. There were five patients treated with RP103 who experienced serious adverse events ("SAEs") compared with four patients treated with placebo. At the 18-month time point, seven patients had discontinued treatment, six in the RP103 arm and one in placebo. Three patients receiving RP103 discontinued for SAEs including one for lymphopenia, one for repetitive faintness and one for elevated liver enzymes. One SAE in the placebo group, anxiety, resulted in discontinuation.

CYST-HD: 36 months results

In December 2015, we announced top line results from the planned 36-month analysis of the study, which included subjects who crossed over from placebo to open-label treatment at the completion of month 18. The study examined the effect of RP103 in Huntington's disease subjects treated earlier, beginning at Month 0 (RP103/RP103) compared to subjects with a delayed start to treatment, beginning at Month 18 (placebo/RP103). The primary efficacy endpoint for this analysis was the change from baseline at 36 months in the TMS component of the UHDRS between placebo/RP103 and RP103/RP103-treated subjects. Analysis of this endpoint was also completed in the open-label phase of the study at 36 months. Key secondary endpoints evaluating function included

the UHDRS-TFC and Independence Scale. 88 subjects entered the open-label period and 78 subjects completed 36 months of treatment. The full analyses set included all randomized subjects from Month 0 to Month 36.

An evaluation of the change in the progression of the UHDRS-TMS at Month 36 from baseline in the full analyses set in the trial showed a 25% slower progression [10.0 (1.7) vs. 13.3 (1.8), respectively; p=0.18] in patients treated earlier with RP103 relative to those patients on a delayed start. In a completers analysis, these effects were more pronounced with a 35% slower progression [9.2(1.7) vs. 14.1(1.9), respectively p=0.06] in the earlier treatment with RP103 relative to those patients on a delayed start. The 25% treatment effect in TMS favoring subjects treated with RP103 for the full 36 months as compared to the placebo/RP103 arm, while not statistically significant, is regarded by clinical leaders in the field as clinically meaningful**.** These effects on the TMS were consistent with improvements in functional measures including the UHDRS-TFC and the Independence Scale. A 23% slowing in the rate of decline in TFC [-2.0 (0.33) vs. -2.6 (0.35); p=0.25] and a 46% slowing in the rate of deterioration on the Independence Scale [-6.9(1.45) vs. -12.7 (1.54); p=0.008] was observed, favoring earlier treatment relative to a delayed start of RP103. Subjects who completed the 36 months study period are allowed to continue receiving RP103 under an extension phase of the CYST-HD clinical trial.

The safety profile observed for RP103 after completion of the 36 month study was generally consistent with what has been previously reported. The most common adverse events included nausea, vomiting, diarrhea, headache and breath odor. Three deaths due to suicide occurred during the open-label period, including two deaths that occurred in subjects in the placebo/RP103 group and one death in the RP103/RP103 group. Deaths due to suicide were generally consistent with background rates, with over 25% of patients with Huntington's disease attempting suicide at least once and accounting for 5% to 7% of deaths, per published estimates. Suicides have not been observed in any other RP103 clinical trials or in any patients on clinical or commercial drug.

Regulatory Update

We initiated regulatory discussions with the FDA and the EMA in 2014 based on the 18-month data and most recently received feedback from the EMA in the fourth quarter of 2015 through a Scientific Advice procedure. The outcome of these interactions with both agencies indicated that additional data from a confirmatory study would be required to support an application for marketing authorization. We intend to update both regulatory agencies with the 36-month data and to discuss a trial design that would support marketing authorization.

Under our amended collaboration agreement with CHU d'Angers, we supply RP103 and placebo capsules for the clinical trial and open-label extension study and fund the third-party statistical analysis of clinical trial data in exchange for regulatory and commercial rights to the clinical trial data. Clinical expenses of the study are covered by a grant from the Programme Hospitalier de Recherche Clinique, which is funded by the French government.

In 2008, we received FDA orphan drug designation for cysteamine formulations, including RP103, for the potential treatment of HD. We have received orphan drug designation in the EU for the treatment of HD .

RP103 Mechanism in Huntington's Disease

In HD, mutant Htt aggregate formation and processing leads to neuronal, mitochondrial, cellular stress and dysfunction and death. The metabolism of cysteamine boosts systemic cysteine, which may induce several beneficial stress responses, including the production of glutathione, that in aggregate reduce cellular oxidative stress. A major deficiency of cystathionine c-lyase (CSE), the principal generator of endogenous cysteine from cystathionine, has been shown to mediate neurodegeneration in HD. The ability of CSE and cysteine to reverse oxidative stress and lethality in HD cells suggests that cysteine supplementation and intracellular mobilization through cysteamine therapy might be beneficial in treating HD. Through inhibition of intracellular enzymes, such as transglutaminase, cysteamine inhibits protein aggregation, which are known to form in HD. Cysteamine also increases transcription and production of certain heat shock proteins, which may assist in clearing or repairing misfolded Htt and other proteins in neuronal cells. Cysteamine and its dimer cystamine have been shown in preclinical studies to increase levels of brain derived neurotropic factor, or BDNF. BDNF is induced by cortical neurons and helps support survival, growth and differentiation of new neurons and synapses. Two master genes, huntingtin, or Htt, and huntingtin-associated protein, or Hap1, govern BDNF axonal transport and secretion. Expression of the BDNF gene is reduced in both Alzheimer's and HD patients, and HD patients are believed to be deficient in BDNF. The BDNF gene may play a role in the regulation of stress response and in the biology of mood disorders. Finally, cysteamine's metal-chelating properties may assist in removing excess copper, a metal that has shown increased accumulation in brains of people with HD as well as other neurodegenerative disorders.

Mitochondrial Disorders including Leigh Syndrome

Leigh syndrome is a severe neurological disorder caused by genetic defects in mitochondrial or nuclear DNA affecting respiratory chain function that typically results in death within the first decade of life. The condition causes increased production of reactive oxygen species that disrupt mitochondrial electron transport and affect cellular function in a variety of tissues. Typically observed during the first year of life, Leigh syndrome is characterized by a failure to thrive, lack of coordination, involuntary and sustained muscle contraction, muscle wasting and multiple organ failure. The incidence of Leigh syndrome and similar mitochondrial disorders in the United States is estimated to be 1 in 40,000 newborns.

RP103 as a Treatment for Mitochondrial Disorders including Leigh Syndrome

In June 2014, we initiated a Phase 2 study in the United States designed to evaluate the safety, tolerability and efficacy of RP103 as a potential treatment for Leigh syndrome and other mitochondrial disorders. RP103 potentially increases mitochondrial glutathione which may act as a scavenging agent of reactive oxygen species and thereby reduce the mitochondrial oxidative stress typically associated with these disorders.

The clinical plan includes an open label, 24 week, Phase 2a study in 24 patients (up to a maximum of 32 patients). Patients with Leigh syndrome are expected to comprise approximately two-thirds of the enrolled population in the study. Employing a statistical plan based on an adaptive design, we will conduct interim analyses after four patients and again after 12 patients have completed the study. The primary endpoint of the study will be the change from baseline in the Newcastle Pediatric Mitochondrial Disease Scale, at 24 weeks. Secondary endpoints will include observations of myopathy, dystonia, seizures, motor development, dyskinesia, quality of life and activities of daily living. An interim analysis based on four subjects was conducted at the end of 2015. Evaluation of the safety data revealed no unexpected adverse events or adverse safety signal. Study enrollment is ongoing with data collection from 12 subjects for the second interim analysis per the statistical analysis plan expected inthe first quarter of 2016.

MP-376 Clinical Development

In addition to CF, MP-376 has development potential in two additional orphan diseases with significant unmet need: non-CF bronchiectasis (BE) and nontuberculous mycobacteria (NTM) lung infections. Currently, few therapeutic options exist for patients with these diseases. BE is characterized by abnormal dilatation and destruction of lung bronchi and bronchioles due to chronic recurring infection and long-term inflammation, which leads to frequent hospitalizations. NTM are a group of microbes that cause severe and recurrent lung infections, often in individuals who are immune-compromised or who have structural lung disease, such as bronchiectasis. We are evaluating the therapeutic potential of MP-376 in these indications and intend to pursue clinical programs in 2016 in non-CF related bronchiectasis and are also planning to do work in preparation to support further clinical development of MP-376 in NTM.

About non-CF Bronchiectasis (BE)

BE is a disease in which airways lose elasticity over time, which impairs the lung's ability to clear out mucus,creating a highly favorable environment for bacteria. These bacterial infections typically result in inflammation that further damages bronchial tissue, creating a negative feedback loop and significant loss of lung function. BE can be due to a variety of causes, including but not limited to chronic obstructive pulmonary disease (COPD), smoking history, autoimmune disease, and triggering bacterial or viral infection.

Current standard of care is to reduce the number of exacerbations requiring critical care, with reduction of bacterial load considered to be highly important as a preventative measure. No antibiotic product is approved currently. There is some evidence suggesting that drugs of the macrolide class are effective in treating infections in the context of BE, but these are associated with rapid development of bacterial resistance as well as side effects including hepatotoxicity, hearing loss, and cardiovascular events.

In *in vitro* studies, levofloxacin has demonstrated the ability to eradicate bacterial colonies of several types that are found with high frequency in the non-CF BE population. In addition, randomized, controlled studies have been conducted with inhaled ciprofloxacin, another drug in the same fluoroquinolone class as levofloxacin, showing increased time to exacerbations and improvements in bacterial load when compared to placebo. Levofloxacin is, in general, as potent as, or more potent in *in vitro* assays than ciprofloxacin. Thus, we believe it is a favorable candidate for development in BE.

About Non-Tuberculous Mycobacterium Infections (NTM)

NTM is a bacterial infection of the lung caused by bacteria of the *mycobacterium* family, but which do not result in tuberculosis. Infections of this type frequently result in progressive loss of lung function, and can be life-threatening if not treated. Symptoms of NTM include fever, weight loss, cough, lack of appetite, night sweats, and loss of energy. Approximately 60,000 patients exist in the United States, with another 30,000 found in the EU.

No treatment is currently approved specifically for use in NTM. Treatment guidelines suggest high doses of systemic (usually oral) antibiotics be used, typically with multiple active agents in a "cocktail" to cover a variety of bacterial strains. These regimens have a high rate of failure to clear the infection, and also cause significant side effects such as gastrointestinal distress, hearing impairment, flu-like reactions, and liver toxicity. Surgical resection of lung tissue is recommended in particularly symptomatic cases.

In *in vitro* studies, levofloxacin (the active agent in MP-376) has demonstrated the ability to inhibit bacterial colonies of several types that are found with high frequency in the NTM population, including *m. abcessis* and *m. kansasii*. Based on these results, and the demonstrated ability of MP-376 to reach certain concentrations in lung sputum of patients, as well as on feedback from medical providers and opinion leaders, we believe development of MP-376 for the treatment of this disease is appropriate.

Preclinical Product Candidates

Our preclinical programs include RP105 and RP106 being developed for a variety of rare diseases.

Future Activities

We expect that our near-term efforts will be focused on:

- Increasing product uptake and sales of PROCYSBI in the United States and continuing to provide comprehensive reimbursement and adherence support to commercial cystinosis patients in the United States;
- Increasing market penetration and sales of PROCYSBI in current markets in Europe, negotiating pricing and reimbursement in specific European countries, and accelerating launch in additional countries in Europe;
- Seeking approval for PROCYSBI from Health Canada;
- Launching QUINSAIR in Europe and Canada for treatment of chronic lung infection with *Pseudomonas aeruginosa* in CF patients;
- Pursuing NDA approval from the FDA for marketing of QUINSAIR in U.S. for treatment of *Pseudomonas aeruginosa* infection in CF patients;
- Pursuing clinical trials of MP-376 in non-CF BE;
- Design of a pediatric study of MP-376 for eradication of first infection with *Pseudomonas aeruginosa* in CF patients;
- Work in preparation to support further clinical development of MP-376 in NTM;
- Continuing a clinical trial to evaluate PROCYSBI in cysteamine-naïve cystinosis patients, as well as other supporting trials in underdeveloped markets;
- Screening for undiagnosed and unidentified late-onset adult nephropathic cystinosis patients;
- Supporting clinical programs and developing clinical and regulatory strategies for the use of RP103 as a potential treatment of HD;
- Supporting clinical programs evaluating RP103 for the potential treatment of mitochondrial disorders;
- Supporting our novel preclinical programs;
- Identifying promising in-licensing product and drug development candidates; and
- Exploring strategic partnerships for HD or our other potential product candidates.

Corporate Information

We are incorporated under the laws of the State of Delaware and our business was founded in May 2006. Our principal executive office is located at 7 Hamilton Landing, Suite 100, Novato, CA 94949. Our phone number is (415) 408-6200.

Intellectual Property

IP Protection for RP103 for Our Products and Product Candidates

We seek to protect our proprietary technology and other intellectual property that we believe is important to our business, including by seeking, maintaining and defending patents. We also rely on trade secrets and know-how to protect our business. We own certain of these intellectual property rights and have obtained licenses under other of our intellectual property rights.

Our intellectual property portfolio is directed to the composition of matter, or COM, the method of use, or MOU, and the composition for use, or CFU, of a formulation/pharmaceutical composition for our products, our product candidates, and other proprietary technologies and processes related to our product development candidates. As of February 25, 2016, our patent portfolio includes the patents and patent applications described below, which we own or have exclusively licensed from third parties, along with any patents that may issue from these patents and applications in the future.

With respect to PROCYSBI, we own, or exclusively license from the University of California,San Diego ("UCSD"), five issued patents and three pending patent applications in the United States, and own, or exclusively license from UCSD, three issued foreign patents, and numerous pending foreign patent applications directed to the formulation/composition, the MOU, and the CFU, of PROCYSBI for the treatment of cystinosis.

With respect to RP103 for indications other than nephropathic cystinosis, including HD and mitochondrial disorders, we own or hold, by exclusive license, six issued US patents and 18 foreign patents, as well as numerous pending applications in the United States and foreign jurisdictions.

IP Protection for QUINSAIR and MP-376

With respect to QUINSAIR, we currently hold seven issued U.S. patents, a Canadian patent and a European patent application that is allowable and is expected to issue in 2016.

General IP Protection

These patents will expire from 2019 to 2031, and additional patents issuing from pending patent applications or others that may be filed, if they issue, will expire after the standard 20-year term, subject to available patent term adjustments.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the date of filing the non-provisional application. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office in granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier-filed patent.

In addition, extensions of the term of a patent that covers an FDA-approved drug are available in the United States, in order to compensate for the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent, based on the length of time the drug is under regulatory review, subject to certain limitations. Similar extensions are available in Europe and other foreign jurisdictions for patents that cover an approved drug. We expect to apply for available patent term extensions for patents covering our product candidates.

Despite the measures we take to protect our intellectual property, any of our patents or other proprietary rights could be challenged, invalidated, infringed or misappropriated or our intellectual property may not prove sufficient to provide us a competitive market advantage. See *"Risk Factors-Risks Related to Intellectual Property and Competition"*.

Trademarks

Our trademark portfolio consists of several registered U.S. trademarks covering our company and our subsidiaries' names, the names of our products and services programs (which are additionally registered in additional territories as necessary to protect our rights to the names). Our trademark RAPTOR is registered in the United States, in the EU and internationally generally and is currently pending registration in several other jurisdictions. Our trademark PROCYSBI is registered in the United States, the EU and several additional jurisdictions. It is pending registration in Canada. Our trademark QUINSAIR is registered in the EU and is pending registration in Canada and the United States.

All third-party trademarks and trade names identified in this Annual Report on Form 10-K are the property of their respective owners.

License Agreement with UCSD

In December 2007, by way of a merger with Encode Pharmaceuticals, Inc., ("Encode") we acquired certain patent rights licensed to Encode by UCSD pursuant to a license agreement dated October 2007, later amended in February 2008, amended and restated in December 2012, and further amended in March 2013 and December 2013. Pursuant to this agreement, we obtained an exclusive, worldwide, sublicenseable license under certain patent rights and know-how controlled by UCSD for the commercial development, use and sale, for human therapeutic purposes, of products covered by such patents or incorporating such know-how,

including RP103. This license is exclusive with respect to the licensed patent rights and non-exclusive with respect to the licensed know-how. Under the agreement, UCSD is obligated to diligently prosecute and maintain the licensed patent rights, conditioned upon our continued fulfillment of our obligation to reimburse UCSD for related costs incurred.

Pursuant to the license agreement, we are obligated to pay milestone payments (ranging in size for orphan and non-orphan indications), up to an aggregate total of $6,275,000, upon the occurrence of certain specified development-, regulatory- and commercial-related events during the term of the agreement. To date, we have paid UCSD approximately $2.2 million in total milestone payments. We are also obligated to pay UCSD a royalty on commercial net sales of licensed products, on a country-by-country basis, ranging in the low single-digit to mid-single-digit percentages, based on whether the licensed product sold is covered by the licensed patent rights in such country, as well as a percentage of sublicensing fees and sublicensing royalties we receive under the agreement, if any. In 2013, we began paying UCSD royalties based upon our net sales of PROCYSBI.

Unless earlier terminated, our license agreement with UCSD will expire upon the later of (i) on a country-by-country basis, the expiration of the last to expire of the licensed patent rights (in the applicable country), and (ii) ten years from the first commercial sale of any royalty-bearing product. We may terminate the agreement at any time upon a specified period of prior written notice to UCSD. In the event of our breach of an obligation under the agreement, which breach is not cured within a specified number of days after receiving notice of such from UCSD, UCSD may terminate the agreement or choose to convert the license into a non-exclusive license with respect to the indication for which we are in breach. We are currently behind in our developmental diligence obligations with respect to HD and non-alcoholic steatohepatitis under this agreement and are in discussions with UCSD to amend the agreement to conform to the product development timeline we expect to achieve. The agreement will immediately terminate if we file a claim asserting that any of the licensed patent rights are invalid or unenforceable.

Asset Purchase Agreement with Tripex

Asset Purchase Agreement

On August 20, 2015, we entered into an Asset Purchase Agreement with Tripex to purchase MP-376 or QUINSAIR and related intellectual property. At the closing of the asset acquisition pursuant to the Amended and Restated Asset Purchase Agreement dated October 2, 2015, which amended agreement provided for the assets to be acquired by our subsidiary, we made an upfront payment to Tripex of $35,370,000 in cash consideration, subject to certain deductions, and issued various Tripex stockholders 3,448,001 shares of our common stock. As additional consideration, Tripex may become entitled to receive contingent payments from us upon the achievement of certain milestones and variable royalty payments on the net sales of QUINSAIR-related products.

The contingent payments include:

- a one-time variable payment which may be as low as $40 million and up to $80 million if the FDA approves QUINSAIR for the treatment of *Pseudomonas aeruginosa* infections in cystic fibrosis with certain conditions for each level of payment;
- a one-time payment of $20 million if a second-indication registrational trial milestone for QUINSAIR is achieved;
- up to four milestone payments, totaling up to $250 million in the aggregate, payable upon achievement of first commercial sale of QUINSAIR in the United States and/or the European Union for up to two approved label indications in addition to cystic fibrosis; and
- certain royalties would become payable by us to Tripex based on net sales of QUINSAIR-related products by us and our sublicensees.

At our election, portions of the milestone payments may be paid in the form of shares of our common stock. In addition, in a change of control, the party acquiring us may be required to prepay portions of certain of our contingent payments if, after the change of control event, we have not met certain diligence obligations pertaining to QUINSAIR.

We are obligated to engage in specified levels of effort to undertake activities relevant to the contingent payments, each of which will be subject to various exceptions to performance.

PARI Letter Agreement

Under the purchase agreement with Tripex, we assumed rights and certain obligations under the Development and License Agreement, dated as of February 11, 2006, between PARI Pharma GmbH, a German corporation (“PARI”), and Mpex Pharmaceuticals, Inc., a prior owner of QUINSAIR. Pursuant to the Development and License Agreement, PARI granted Mpex a worldwide royalty-bearing license to develop, sell and otherwise exploit pharmaceutical preparations formulated for delivery via pulmonary administration, and the parties agreed to perform joint evaluation, research and development of potential formulations of

drug compounds for pulmonary delivery with customized PARI nebulizer devices. QUINSAIR was developed pursuant to the Development and License Agreement, and will continue to be developed and commercialized subject to the terms and conditions of the Development and License Agreement, as amended by the PARI Amendment (as defined and described below).

On August 20, 2015, we entered into a Letter Agreement with PARI, which provided that PARI and Raptor would enter into Amendment No. 1 to the Development and License Agreement (the "PARI Amendment") following the closing of our acquisition of QUINSAIR from Tripex. The PARI Amendment was entered into on October 4, 2015. Pursuant to the Development and License Agreement, as amended by the PARI Amendment, we will make payments due to PARI upon the achievement of milestones related to regulatory approval and commercialization activities. We are required to comply with diligence milestones related to development and commercialization of QUINSAIR in the United States, to spend a specified minimum amount per year on development activities in the United States until filing of the NDA for QUINSAIR in the United States, and will pay PARI tiered single digit royalties on net sales of QUINSAIR for a specified time period. We will have the right to buy down the royalties under certain conditions by paying an amount determined through a defined net present value calculation. The PARI Amendment further provides that in the event that we decide to cease the development or commercialization of QUINSAIR for exclusive delivery via the PARI nebulizer device in the United States, PARI shall have the right, in its sole discretion, to develop, and/or license its technology for use with other inhaled fluoroquinolones within the United States.

Orphan Drug Designation

We have been granted Orphan Drug Designation from the FDA for use of PROCYSBI to manage cystinosis for patients six years of age and older and separately in the pediatric population for two to six year olds, and the use of RP103 to potentially treat HD, pancreatic cancer and Batten Disease. The Orphan Drug Act of 1983 generally provides incentives, including marketing exclusivity, user fee waivers and tax benefits, to companies that undertake development and marketing of products to treat relatively rare diseases, which are defined as diseases for which there is a patient population of fewer than 200,000 persons in the United States or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. A drug that receives orphan drug designation may receive up to seven years of exclusive marketing in the United States for that indication, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity or where the manufacturer is unable to assure sufficient product quantity. A drug may be entitled to an additional six months of exclusive marketing if it satisfies the requirements for pediatric exclusivity; we have applied for this additional six-month pediatric extension for PROCYSBI. See also "Orphan Designation and Exclusivity" and "Pediatric Studies and Exclusivity" below.

PROCYSBI has also been granted Orphan Drug Designation and awarded 10 years of data exclusivity and marketing protection by the EC for treatment of cystinosis, and RP103 has been granted Orphan Drug Designation by the EC for the treatment of HD. QUINSAIR has been awarded 10 years of data exclusivity and marketing protection by the EC for the treatment of *Pseudomonas aeruginosa* infection in CF patients and has been awarded Orphan Drug Designation by the FDA.

Competition

Cystinosis

Other than PROCYSBI, we are aware of two pharmaceutical products currently approved to treat cystinosis. Cystagon® (immediate-release cysteamine bitartrate capsules), is a systemic cystine-depleting therapy for cystinosis in the United States manufactured by Mylan N.V., and by Orphan Europe SARL in markets outside of the United States. Cystagon was approved by the FDA in 1994 and by the EC in 1997. Cystaran® (cysteamine ophthalmic solution) was approved by FDA in 2012 for treatment of corneal crystal accumulation in patients with cystinosis and is marketed by Sigma Tau Pharmaceuticals, Inc.

While we believe that PROCYSBI will continue to be well received in the market, Cystagon remains on the market and we expect it will compete with PROCYSBI for the foreseeable future. We are not aware of any pharmaceutical company with an active program to develop an alternative therapy for cystinosis. Academic researchers in the United States and Europe are pursuing gene therapy and stem cell therapy, as well as pro-drug and pegylated drug approaches as alternatives to cysteamine bitartrate. We believe that the development timeline to an approved product for these approaches is many years with substantial uncertainty.

Huntington's Disease

We are not aware of any approved available treatments to slow the progression of HD. There is only one approved treatment available for specific symptoms of HD, Xenazine® to treat uncontrollable movements (chorea) that result from the disease. There are several pharmaceutical companies pursuing potential cures and disease modifying treatments for HD, as well as numerous academic

and foundation sponsored research efforts. Our product candidate, RP103, is in late-stage clinical development with the goal of slowing motor deterioration with potentially neuroprotective properties through specifically targeting deficient BDNF.

Companies with HD product candidates in development include Prana Biotechnology, Omeros, Teva (and formerly Auspex and Neurosearch), Ionis Pharmaceuticals/Roche, Eli Lilly & Co. and Pfizer. Several other companies have drug candidates in preclinical development. Additionally, nutritional supplements including creatine and coenzyme Q10 have been investigated as potential treatments for HD. The Huntington Study Group sponsors numerous studies of potential therapies for HD, including the recently completed trials evaluating coenzyme Q10 and the antibiotic minocycline.

- ***Pseudomonas Aeruginosa Infection in CF Patients***

Currently, there are three products approved in the United States for treatment of chronic *Pseudomonas aeruginosa* lung infections in patients with CF. Tobramycin solution for inhalation is sold by Novartis as TOBI®, and is now also available as a generic from multiple sources. TOBI Podhaler®, a dry-powder inhalation formulation of tobramycin, is also sold by Novartis. Gilead Sciences sells Cayston®, a nebulized formulation of aztreonam. In the EU, an additional competitor, colistimethate, is available in addition to the products currently available in the United States.

Other programs that are in development for treatment of chronic pulmonary infections in CF patients include the inhaled amikacin product developed by Insmed, Inc., an inhaled vancomycin under development by Savara Pharmaceuticals and the tobramycin/fosfomycin treatment under development by CuRx, Inc.

- ***BE and NTM***

No products are currently labeled for treatment of either non-CF BE or pulmonary NTM. Systemic antibiotics, labeled for other diseases, are frequently used off-label as first-line treatment. However, several inhaled antibiotic products are currently in development for either BE or NTM, including Insmed's Arikayce (tm) (liposomal amikacin for inhalation), AG Bayer's ciprofloxacin dry powder for inhalation, and Aradigm's two inhaled ciprofloxacin product candidates, one of which has been licensed to Grifols, Inc.

Government Regulations of the Biotechnology Industry

Human therapeutic products are subject to extensive regulation by governmental authorities in the United States and foreign countries. Governmental authorities govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling, and import and export of pharmaceutical products. The nature and extent to which such regulation will apply to us will vary depending on the nature of any drug product candidates developed. Failure to comply with applicable governmental requirements may subject a company to a variety of administrative or judicial sanctions, such as refusal to approve pending applications, a clinical hold, warning letters, recall or seizure of products, partial or total suspension of production, withdrawal of the product from the market, injunctions, fines, civil penalties or criminal prosecution.

Governmental agency approval is required before any new unapproved drug or dosage form, including a new use of a previously approved drug, can be marketed in each jurisdiction in which the product is marketed. We anticipate that all of our drug product candidates will require regulatory approval by governmental agencies prior to commercialization.

In particular, human therapeutic products are subject to rigorous preclinical and clinical testing and other approval procedures of the FDA and similar regulatory authorities in other countries. Various federal statutes and regulations also govern or influence testing, manufacturing, safety, labeling, storage, record-keeping and marketing related to such products. The process of obtaining these approvals and the subsequent compliance with the appropriate federal statutes and regulations requires substantial time and financial resources.

Before obtaining regulatory approvals for the commercial sale of any of our products under development, we must demonstrate through preclinical studies and clinical trials that the product is safe and efficacious for use in each target indication. The results from preclinical studies and early clinical trials might not be predictive of results that would be obtained in large-scale testing. Our clinical trials might not successfully demonstrate the safety and efficacy of any product candidates or result in marketable products, and failure can occur at any point in the testing process.

In order to clinically test, manufacture and market products for therapeutic use, we will have to comply with mandatory procedures and safety and effectiveness standards established by various regulatory bodies. In the United States, the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act, as amended, or FDCA, and the regulations promulgated thereunder, and

other federal and state statutes and regulations govern, among other things, the testing, manufacture, labeling, storage, record keeping, approval, advertising, and promotion of our current and proposed product candidates. Product development and approval within this regulatory framework takes a number of years and involves the expenditure of substantial resources.

The steps required by the FDA before new drug products may be marketed in the United States include:

- Completion of extensive preclinical laboratory and animal studies performed in accordance with the FDA's Good Laboratory Practice, or GLP, regulations;
- The submission to the FDA of a request for authorization to conduct clinical trials in an investigational new drug application, or IND, which must become effective before clinical trials may commence;
- Approval by an independent institutional review board, or IRB, or ethics committee representing each clinical site before each clinical study may be initiated;
- Completion of adequate and well-controlled human clinical trials to establish and confirm the safety and efficacy of a drug candidate for the proposed indication;
- Completion of process validation, quality product release and stability;
- Submission to the FDA of a new drug application, or NDA, for the drug candidate for marketing approval;
- Potential review of the product application by an FDA advisory committee, where appropriate and if applicable;
- Satisfactory completion of an FDA pre-approval inspection of the manufacturing facilities where the proposed product is produced to assess compliance with the FDA's current Good Manufacturing Practice, or cGMP, requirement and to assure that the facilities, methods and controls are adequate to preserve the drugs' identity, strength and purity; and
- Review and approval of the NDA by the FDA before the product may be sold commercially.

The pre-clinical and clinical testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that approvals for our product candidates will be granted on a timely basis, if at all. Preclinical testing includes laboratory evaluation and characterization of the safety and efficacy of a drug and its chemistry, formulation, stability and toxicity, as well as animal studies to assess the characteristics and potential safety and efficacy of the product. Preclinical testing results are submitted to the FDA as a part of an IND. Some pre-clinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises concerns or questions relating to one or more proposed clinical trials and places a trial on clinical hold, including concerns that human research subjects will be exposed to unreasonable health risks. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, the submission of an IND may not result in FDA authorization to commence a clinical trial. A separate submission to an existing IND must also be made for each successive clinical trial conducted during product development. Further, an independent IRB, covering each site proposing to conduct the clinical trial must review and approve the plan for any clinical trial and informed consent information for subjects before the trial commences at that site and it must monitor the study until completed.

Clinical trials involve the administration of an investigational drug to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Sponsors of clinical trials generally must register and report, at the NIH-maintained website ClinicalTrials.gov, key parameters of certain clinical trials. For purposes of an NDA submission and approval, human clinical trials are typically conducted in the following sequential phases, which may overlap or be combined. Phase 1 represents the initial administration of the drug to a small group of humans, either patients or healthy volunteers, typically to test for safety (adverse effects), dosage tolerance, absorption, distribution, metabolism, excretion and clinical pharmacology, and, if possible, to gain early evidence of effectiveness. Phase 2 involves studies in a small sample of the actual intended patient population to assess the efficacy of the drug for a specific indication, to determine dose tolerance and the optimal dose range and to gather additional information relating to safety and potential adverse effects. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more extensive Phase 3 clinical trials. Once an investigational drug is found to have some efficacy and an acceptable safety profile in the targeted patient population, Phase 3 studies are initiated to further establish clinical safety and efficacy of the therapy in a broader sample of the general patient population, in order to determine the overall risk-benefit ratio of the drug and to provide an adequate basis for any physician labeling. During all clinical studies, we must adhere to GCP or good clinical practices, standards. The results of the research and product development, manufacturing, preclinical studies, clinical studies and related information are submitted in an NDA to the FDA.

The FDA, the IRB or the clinical study sponsor may suspend or terminate a clinical study at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Additionally, some clinical studies are overseen by an independent group of qualified experts organized by the clinical study sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a study may move forward at designated check points based

on access to certain data from the study. We may also suspend or terminate a clinical study based on evolving business objectives and/or competitive climate. The process of completing clinical testing and obtaining FDA approval for a new drug is likely to take a number of years and require the expenditure of substantial resources. If an application is submitted, there can be no assurance that the FDA will review and approve the NDA.

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, detailed investigational new drug product information is submitted to the FDA in the form of an NDA requesting approval to market the product for one or more indications. Under federal law, the submission of most NDAs is subject to a substantial application user fee. Applications for orphan drug products are exempt from the NDA user fees, unless the application includes an indication for other than a rare disease or condition.

An NDA must include all relevant data available from pertinent preclinical and clinical studies, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls and proposed labeling, among other things. Data can come from company-sponsored clinical studies intended to test the safety and effectiveness of a use of a product, or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and effectiveness of the investigational new drug product to the satisfaction of the FDA.

Under federal law, the submission of an NDA is subject to a substantial application user fee, and the manufacturer and/or sponsor under an approved NDA are also subject to annual product and establishment user fees. The FDA has 60 days from its receipt of an NDA to determine whether the application will be accepted for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. The FDA may request additional necessary information rather than accept an NDA for filing. In this event, the NDA must be resubmitted with the additional information and may be subject to payment of additional user fees. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission has been accepted for filing, the FDA begins an in-depth substantive review.

The FDA's goal is to review the application within 10 months after it accepts the application for filing, or, if the application relates to an unmet medical need in a serious or life-threatening indication, six months after the FDA accepts the application for filing. The review process is often significantly extended by FDA requests for additional information or clarification. In addition, an application may be referred to an advisory committee, which is a panel of independent experts, to review, evaluate and provide a recommendation to the FDA as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it typically follows such recommendations and considers them carefully when making approval decisions.

Before obtaining FDA approval for each product, the FDA typically will inspect the facility or facilities where the product is manufactured and will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP requirements. Following approval, each product manufacturing establishment must be registered with the FDA and its quality control and manufacturing procedures must continue to conform and adhere at all times to the FDA's cGMP regulations. The FDA and other government agencies regularly inspect manufacturing facilities for compliance with these requirements. If, as a result of these inspections, the FDA determines that any equipment, facilities, laboratories or processes do not comply with applicable FDA regulations and conditions of product approval, the FDA may seek civil, criminal or administrative sanctions and/or remedies against us, including the suspension of the manufacturing operations. Manufacturers must expend substantial time, money and effort in the area of production and quality control to ensure full technical compliance with these standards.

In some cases, the FDA may condition approval of an NDA for a product candidate on the sponsor's agreement to conduct additional clinical trials to further assess the drug's safety and effectiveness after NDA approval. Such post-approval trials are typically referred to as Phase 4 studies. In addition, even after initial FDA approval has been obtained, further studies would be required to gain approval for the use of a product as a treatment for clinical indications other than those for which the product was initially tested and approved. Once an NDA is approved, a product will be subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to drug/device listing, recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. Results of post-marketing programs, including Phase 4 clinical studies or post-market surveillance, might limit or expand the further marketing of the products. Further, if there are any modifications to the drug, including changes in indication, manufacturing process, labeling or a change in manufacturing facility, submission and approval of an NDA supplement might be required. Drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and generally require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP or QSR and impose reporting and documentation

requirements upon us and any third-party manufacturers that we may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP or QSR compliance.

Failure to comply with applicable FDA requirements may result in a number of consequences that could materially and adversely affect us. Failure to adhere to approved trial standards and GCPs in conducting clinical trials could cause the FDA to place a clinical hold on one or more studies which would delay research and data collection necessary for product approval. Noncompliance with GCPs could also have a negative impact on the FDA's evaluation of an NDA. Failure to adhere to GCPs, cGMPs and other applicable requirements could result in FDA enforcement action and in civil and criminal sanctions, including but not limited to fines, seizure of product, refusal of the FDA to approve product approval applications, withdrawal of approved applications, and prosecution. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical studies to assess new safety risks; or imposition of distribution restrictions or other restrictions under a Risk Evaluation and Mitigation Strategies, or REMS, program.

The FDA strictly regulates marketing, labeling, advertising, and promotion of products that are placed on the market pursuant to a number of complex regulations which include, among others, standards for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities, and promotional activities involving the internet. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability. Indeed, the FDA has very broad enforcement authority under the FFDCA, and failure to abide by these regulations can result in penalties, including the issuance of a warning letter directing entities to correct deviations from FDA standards, a requirement that future advertising and promotional materials be pre-cleared by the FDA, and state and federal civil and criminal investigations and prosecutions.

Whether or not FDA approval has been obtained, approval of a product by regulatory authorities in foreign countries must be obtained prior to the commencement of marketing of the product in those countries. The requirements governing the conduct of clinical trials and product approvals vary widely from country to country, and the time required for approval might be longer or shorter than that required for FDA approval. Although there are some procedures for unified filings for some European countries, in general, each country at this time has its own procedures and requirements. There can be no assurance that any foreign approvals would be obtained.

In addition to the regulatory framework for product approvals, we and our collaborative partners must comply with federal, state and local laws and regulations regarding occupational safety, laboratory practices, the use, handling and disposition of radioactive materials, environmental protection and hazardous substance control, and other local, state, federal and foreign regulations. All facilities and manufacturing processes used by third parties to produce our drug candidates for clinical use in the United States must conform with cGMPs. These facilities and practices are subject to periodic regulatory inspections to ensure compliance with cGMP requirements. Their failure to comply with applicable regulations could extend, delay, or cause the termination of clinical trials conducted for our drug candidates or of manufacturing and sale of any of our products approved for sale. We cannot accurately predict the extent of government regulation that might result from future legislation or administrative action.

Expedited Review and Accelerated Approval Programs

A sponsor may seek approval of its product candidate under programs designed to accelerate FDA's review and approval of NDAs. For example, Fast Track Designation may be granted to a drug intended for treatment of a serious or life-threatening disease or condition that has potential to address unmet medical needs for the disease or condition. The key benefits of fast track designation are the eligibility for priority review, rolling review (submission of portions of an application before the complete marketing application is submitted), and accelerated approval, if relevant criteria are met. Based on results of clinical studies submitted in an NDA, upon the request of an applicant, the FDA may grant the NDA priority review designation, which sets the target date for FDA action on the application at six months after the FDA accepts the application for filing. Priority review is granted where there is evidence that the proposed product would be a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition. If criteria are not met for priority review, the application is subject to the standard FDA review period of 10 months after FDA accepts the application for filing. Priority review designation does not change the scientific/medical standard for approval or the quality of evidence necessary to support approval.

Under the accelerated approval program, the FDA may approve an NDA on the basis of either a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Post-marketing studies or completion of ongoing studies after marketing approval are generally required to verify the drug's clinical benefit in relationship to the surrogate endpoint or ultimate outcome in relationship to the clinical benefit. In addition, the Food and Drug Administration Safety

and Innovation Act, or FDASIA, which was enacted and signed into law in 2012, established the new Breakthrough Therapy designation. A sponsor may seek FDA designation of its product candidate as a Breakthrough Therapy if the drug is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

European Union Drug Review and Approval

In the EEA (which is comprised of the 28 Member States of the European Union plus Norway, Iceland and Liechtenstein), medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. There are two types of MA:

The Community MA, which is issued by the European Commission through the Centralized Procedure, based on the opinion of the CHMP of the EMA, is valid throughout the entire territory of the EEA. The Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products, and medicinal products containing a new active substance indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes and auto-immune and viral diseases. The Centralized Procedure is optional for products containing a new active substance not yet authorized in the EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU.

National MAs, which are issued by the competent authorities of the Member States of the EEA and only cover their respective territory, are available for products not falling within the mandatory scope of the Centralized Procedure. Where a product has already been authorized for marketing in a Member State of the EEA, this National MA can be recognized in other Member States through the Mutual Recognition Procedure. If the product has not received a National MA in any Member State at the time of application, it can be approved simultaneously in various Member States through the Decentralized Procedure.

Under the above described procedures, before granting the MA, the EMA or the competent authorities of the Member States of the EEA make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy.

Orphan Drug Designation and Exclusivity

The Orphan Drug Act provides incentives for the development of products intended to treat rare diseases or conditions. Under the Orphan Drug Act, the FDA may grant orphan designation to a drug intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making a drug product available in the United States for this type of disease or condition will be recovered from sales of the product. If a sponsor demonstrates that a drug is intended to treat rare diseases or conditions, the FDA will grant Orphan Drug Designation for that product for the orphan disease indication. Orphan Drug Designation must be requested before submitting an NDA. After the FDA grants Orphan Drug Designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA.

Orphan Drug Designation provides manufacturers with research grants, tax credits and eligibility for orphan drug exclusivity. If a product that has Orphan Drug Designation subsequently receives the first FDA approval of the active moiety for that disease or condition for which it has such designation, the product is entitled to orphan drug exclusivity, which for seven years prohibits the FDA from approving another product with the same active ingredient for the same indication, except in limited circumstances. If a drug designated as an orphan product receives marketing approval for an indication broader than the orphan indication for which it received the designation, it will not be entitled to orphan drug exclusivity. Orphan exclusivity will not bar approval of another product under certain circumstances, including if a subsequent product with the same active ingredient for the same indication is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand. Further, the FDA may approve more than one product for the same orphan indication or disease as long as the products contain different active ingredients. Moreover, competitors may receive approval of for the same product but for a different indication for which the orphan product has exclusivity. As a result, even if we obtain orphan exclusivity, we may still be subject to competition.

In the EU, the EMA's Committee for Orphan Medicinal Products, or COMP, grants Orphan Drug Designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the European Union and for which no satisfactory method of diagnosis, prevention, or treatment has been authorized (or the product would be a significant benefit to those affected). Additionally, designation is granted for products intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the EU would be sufficient to justify the necessary investment in developing the medicinal product. In the EU, Orphan Drug Designation entitles a party to financial incentives such as reduction of fees or fee waivers and 10 years of data exclusivity is granted following medicinal product approval.

This period may be reduced to six years if the Orphan Drug Designation criteria are no longer met after five years, including where it is shown that the product is sufficiently profitable not to justify maintenance of data exclusivity.

Orphan Drug Designation must be requested before submitting an application for marketing approval. Orphan Drug Designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

Pediatric Studies and Exclusivity

NDAs must contain data (or a proposal for post-marketing activity) to assess the safety and effectiveness of an investigational new drug product for the claimed indications in all relevant pediatric populations in order to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults or full or partial waivers if certain criteria are met. The requirements for pediatric data do not apply to any drug for an indication for which orphan designation has been granted.

Pediatric exclusivity is another type of non-patent exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the five-year and three-year non-patent and orphan exclusivity. This six-month exclusivity may be granted if an NDA or Biologic License Application sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical study is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of FDA-requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application relying on the NDA sponsor's data. We have applied for this additional six-month pediatric extension for PROCYSBI.

Hatch-Waxman Amendments and Exclusivity

As an alternative path to FDA approval for modifications to formulations or uses of products previously approved by the FDA, an applicant may submit an NDA under Section 505(b)(2) of the FDCA. Section 505(b)(2) was enacted as part of the Hatch-Waxman Amendments and permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by, or for, the applicant. If the 505(b)(2) applicant can establish that reliance on FDA's previous findings of safety and effectiveness is scientifically appropriate, it may eliminate the need to conduct certain preclinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements, including clinical trials, to support the change from the approved branded reference drug. The FDA may then approve the new product candidate for all, or some, of the label indications for which the branded reference drug has been approved, as well as for any new indication sought by the 505(b)(2) applicant.

In seeking approval for a drug through an NDA, including a 505(b)(2) NDA, applicants are required to list with the FDA certain patents whose claims cover the applicant's product. Upon approval of an NDA, each of the patents listed in the application for the drug is then published in the Orange Book. Any applicant who files an abbreviated new drug application, or ANDA, seeking approval of a generic equivalent version of a drug listed in the Orange Book or a 505(b)(2) NDA referencing a drug listed in the Orange Book must satisfy a number of conditions prior to FDA approval and marketing of the generic product. Initially, an ANDA filer must certify to the FDA that (1) no patent information on the drug product that is the subject of the application has been submitted to the FDA; (2) such patent has expired; (3) the date on which such patent expires; or (4) such patent is invalid or will not be infringed upon by the manufacture, use or sale of the drug product for which the application is submitted. This last certification is known as a paragraph IV certification. A notice of the paragraph IV certification must be provided to each owner of the patent that is the subject of the certification and to the holder of the approved NDA to which the ANDA or 505(b)(2) application refers. In certain limited circumstances in which the Orange Book only lists patents for methods of using the drug product, the applicant may instead choose to submit a "section viii" statement (instead of a paragraph IV certification) stating that its proposed label does not describe the patented method of use.

Following notice of a Paragraph IV certification, the NDA holder and patent owners can block FDA approval of the ANDA by filing a lawsuit against the ANDA filer asserting that the generic product infringes one or more of the Orange Book listed patents. As long as the patent infringement suit is filed within 45 days of the receipt of the paragraph IV certification notice, the FDA is automatically prohibited from approving the application for 30 months from the receipt of the paragraph IV certification unless (i) the patents expire, (ii) the ANDA filer receives a verdict in its favor, or (iii) the parties settle the lawsuit. Further, if the NDA holder's suit is successful, the FDA will be barred from approving the ANDA until all of the asserted patents have expired. The FDA also cannot approve an ANDA or 505(b)(2) application until all applicable non-patent exclusivities listed in the Orange Book for the branded reference drug have expired. For example, a pharmaceutical manufacturer may obtain five years of non-patent exclusivity upon NDA

approval of a new chemical entity, (NCE), which is a drug containing an active moiety that has not been approved by FDA in any other NDA. An “active moiety” is defined as the molecule responsible for the drug substance’s physiological or pharmacologic action. During that five-year exclusivity period, the FDA cannot accept for filing (and therefore cannot approve) any ANDA seeking approval of a generic version of that drug or any 505(b)(2) NDA that relies on the FDA's approval of the drug, provided that that the FDA may accept an ANDA four years into the NCE exclusivity period if the ANDA applicant also files a paragraph IV certification.

A drug, including one approved under Section 505(b)(2), may obtain a three-year period of exclusivity for a particular condition of approval, or change to a marketed product, such as a new formulation for a previously approved product, if one or more new clinical studies (other than bioavailability or bioequivalence studies) was essential to the approval of the application and was conducted/sponsored by the applicant. Should this occur, the FDA would be precluded from approving any ANDA or 505(b)(2) application for the protected modification until after that three-year exclusivity period has run. However, unlike NCE exclusivity, the FDA can accept an application and begin the review process during the exclusivity period.

Coverage and Reimbursement

The commercial success of PROCYSBI, QUINSAIR and our drug candidates and our ability to commercialize those products successfully will depend in part on the extent to which governmental payor programs , including Medicare and Medicaid in the United States with respect to PROCYSBI, provincial and federa1 governmental authorities in Canada and European regional and national governmental authorities throughout Europe, with respect to QUINSAIR, private health insurers and other third-party payors provide adequate coverage and reimbursement. These third-party payors generally develop their own policies as to which drugs they will pay for and the reimbursement levels for the drugs. For example, governmental programs in the United States often require manufacturers to pay certain rebates or otherwise provide discounts to secure coverage of drug products. To control healthcare expenditures generally, in the United States, the EU and other potentially significant markets for PROCYSBI, QUINSAIR and our drug candidates, government authorities and third party payors are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative products and therapies. The measures taken often have resulted in lower average selling prices. Further, the increased emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the EU places additional pressure on product pricing, reimbursement and usage, which may adversely affect our future product sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, as well as drug coverage and reimbursement policies and pricing in general.

Some of the additional requirements and restrictions on coverage and reimbursement levels imposed by third-party payors influence the purchase of healthcare services and products. For example, there may be limited coverage to specific drug products on an approved list, or formulary, which, in the United States, might not include all of the FDA-approved drug products for a particular indication. There may also be formulary placements that result in lower reimbursement levels and higher cost-sharing borne by patients. Further, third-party payors are increasingly examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain the FDA, EMA and Health Canada approvals. Our products may not be considered medically necessary or cost-effective. Even if a third-party payor determines to provide coverage for a drug product, adequate reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in drug development. In some countries in Europe, pricing and reimbursement are separate processes; thus, an authority may approve PROCYSBI or QUINSAIR but deny national reimbursement for it. In the EU and Canada, reimbursement rates may be determined by comparison to approved therapeutic competitors, review of pricing of the same product in other countries and, in some circumstances, through health technology assessments that seek to quantify how the expected benefits at a price may influence the cost and quality of patient care. Because we have just begun the process of providing guidance to the relevant pricing and reimbursement authorities for QUINSAIR in anticipation of our launch of that product in the EU and Canada, we cannot predict what cost containment measures such third party payors may seek to apply. Whereas the majority of health authorities in Europe have supported patient access to inhaled antibiotics, budget constraints may affect the pricing we are able to achieve, and because inhaled levofloxacin has not previously been marketed in Europe, the lack of external reference data contributes to the difficulty in predicting pricing and reimbursement outcomes.

Healthcare legislative proposals to reform healthcare or reduce costs under government insurance programs may also result in lower reimbursement for our drugs and drug candidates or exclusion of our drugs and drug candidates from coverage altogether. The cost containment measures that healthcare payors and providers are instituting and any healthcare reform could significantly reduce our revenues from the sale of PROCYSBI, QUINSAIR and any of our approved drug candidates. We cannot provide any assurances that we will be able to obtain and maintain third party coverage or adequate reimbursement for PROCYSBI, QUINSAIR or any of our approved drug candidates in whole or in part.

Healthcare Reform

With respect to legislative reform, in the United States, there have been and continue to be a number of significant legislative initiatives to contain healthcare costs. For example, in March 2010, the Affordable Care Act was passed, which substantially changes the way health care is financed by both governmental and private insurers, and significantly impacts the U.S. pharmaceutical industry. The Affordable Care Act, among other things, subjects biologic products to potential competition by lower-cost biosimilars, addresses a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, increases the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extends the rebate program to individuals enrolled in Medicaid managed care organizations, establishes annual fees and taxes on manufacturers of certain branded prescription drugs, and a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D.

In addition, other legislative changes have been proposed and adopted in the United States since the Health Care Reform Law was enacted. On August 2, 2011, the Budget Control Act of 2011 among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013, due to subsequent legislative amendments to the statute, and will remain in effect through 2025 unless additional Congressional action is taken.

We expect that additional state and federal healthcare reform measures could be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

Other Healthcare Laws

We are also subject to healthcare regulation and enforcement by the federal government and the states and foreign governments in which we conduct our business. These laws include, without limitation, state and federal anti-kickback, fraud and abuse, false claims, privacy and security and physician sunshine laws and regulations.

The federal Anti-Kickback Statute prohibits, among other things, any person from knowingly and willfully offering, soliciting, receiving or providing remuneration, directly or indirectly, to induce either the referral of an individual, for an item or service or the purchasing or ordering of a good or service, for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs. The Anti-Kickback Statute is subject to evolving interpretations. In the past, the government has enforced the Anti-Kickback Statute to reach large settlements with healthcare companies based on sham consulting and other financial arrangements with physicians. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act. The majority of states also have anti-kickback laws which establish similar prohibitions and in some cases may apply to items or services reimbursed by any third-party payor, including commercial insurers.

Additionally, the civil False Claims Act prohibits knowingly presenting or causing the presentation of a false, fictitious or fraudulent claim for payment to the United States government. Actions under the False Claims Act may be brought by the Attorney General or as a qui tam action by a private individual in the name of the government. Violations of the False Claims Act can result in very significant monetary penalties and treble damages. The federal government is using the False Claims Act, and the accompanying threat of significant liability, in its investigation and prosecution of pharmaceutical and biotechnology companies throughout the country, for example, in connection with the promotion of products for unapproved uses and other sales and marketing practices. The government has obtained multi-million and multi-billion dollar settlements under the False Claims Act in addition to individual criminal convictions under applicable criminal statutes. Given the significant size of actual and potential settlements, it is expected that the government will continue to devote substantial resources to investigating healthcare providers' and manufacturers' compliance with applicable fraud and abuse laws.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, also created new federal criminal statutes that prohibit among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payors, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense, and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or

payment for healthcare benefits, items or services. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

In addition, a person who offers or transfers to a Medicare or Medicaid beneficiary any remuneration, including waivers of co-payments and deductible amounts (or any part thereof), that the person knows or should know is likely to influence the beneficiary's selection of a particular provider, practitioner or supplier of Medicare or Medicaid payable items or services may be liable for civil monetary penalties of up to $10,000 for each wrongful act. Moreover, in certain cases, providers who routinely waive copayments and deductibles for Medicare and Medicaid beneficiaries can also be held liable under the Anti-kickback Statute and civil False Claims Act, which can impose additional penalties associated with the wrongful act. One of the statutory exceptions to the prohibition is non-routine, unadvertised waivers of copayments or deductible amounts based on individualized determinations of financial need or exhaustion of reasonable collection efforts. The Office of Inspector General of the Department of Health and Human Services emphasizes, however, that this exception should only be used occasionally to address special financial needs of a particular patient. Although this prohibition applies only to federal healthcare program beneficiaries, the routine waivers of copayments and deductibles offered to patients covered by commercial payers may implicate applicable state laws related to, among other things, unlawful schemes to defraud, excessive fees for services, tortious interference with patient contracts and statutory or common law fraud. To the extent our patient assistance programs are found to be inconsistent with applicable laws, we may be required to restructure or discontinue such programs, or be subject to other significant penalties.

There has also been a recent trend of increased federal and state regulation of payments made to physicians and other healthcare providers. The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, the Affordable Care Act, among other things, imposes new reporting requirements on drug manufacturers for payments made by them to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit required information may result in civil monetary penalties of up to an aggregate of $150,000 per year (or up to an aggregate of $1 million per year for "knowing failures"), for all payments, transfers of value or ownership or investment interests that are not timely, accurately and completely reported in an annual submission. Drug manufacturers were required to begin collecting data on August 1, 2013 and submit reports to the government by March 31, 2014 and June 30, 2014, and the 90th day of each subsequent calendar year. Certain states also mandate implementation of compliance programs, impose restrictions on drug manufacturer marketing practices and/or require the tracking and reporting of gifts, compensation and other remuneration to physicians.

We may also be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology and Clinical Health Act, or HITECH, and their respective implementing regulations, including the final omnibus rule published on January 25, 2013, imposes specified requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to "business associates," defined as independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways, thus complicating compliance efforts.

The shifting commercial compliance environment and the need to build and maintain robust and expandable systems to comply with different compliance and/or reporting requirements in multiple jurisdictions increase the possibility that a healthcare company may violate one or more of the requirements. If our operations are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs and imprisonment, any of which could adversely affect our ability to operate our business and our financial results.

Manufacturing

PROCYSBI drug product and the active pharmaceutical ingredient (API), cysteamine bitartrate, are manufactured on a contract basis by third parties. QUINSAIR drug product, and its API, levofloxacin, and the Zirela nebulizer device are all manufactured on a contract basis by third parties. We believe that our third party manufacturers all have sufficient manufacturing capacity to support our commercial and clinical demands for PROCYSBI for the foreseeable future as well as the clinical and commercial requirements for the initial launch of QUINSAIR.

In general we expect to continue to contract with outside providers for manufacturing services, including API and drug product manufacture, encapsulation, vialing and packaging. Third-party manufacturers' facilities are subject to periodic inspections to confirm compliance with applicable law and must be GMP certified. We are aware that the EMA plans to inspect the manufacturing facilities

of our PROCYSBI drug product manufacturer in the first half of 2016. Although we have never experienced a material disruption in supply from our contract manufacturers, we cannot assure that such a disruption will not occur in the future.

Research and Development

We have an active research and development effort. We plan to focus our research and development efforts in the discovery, research, preclinical and clinical development of our drug candidates in order to provide therapies that we believe will be safer, less intrusive and more effective than current approaches in treating a wide variety of disorders. During the years ended December 31, 2015, 2014, and 2013, we incurred approximately $58.6 million, $43.5 million, and $29.2 million, respectively, in research and development expenses.

Operating Segment and Geographic Information

Operating segments are components of an enterprise for which separate financial information is available and is evaluated regularly by a company in deciding how to allocate its resources and to assess its performance. We have reviewed how we allocate our resources and analyze performance worldwide and have determined that, because employees work on integrated programs in the United States and in Europe, encompassing all stages of product development and commercialization, we operate in one segment.

Compliance with Environmental Laws

We estimate the annual cost of compliance with environmental laws, comprised primarily of hazardous waste removal, will not be material.

Employees

As of December 31, 2015, we had 158 full time employees (126, 30, and 2 in the United States, EU and Canada, respectively). Of the 158 employees, 49 are sales and marketing, and 44 are general and administrative personnel, 6 are in manufacturing, 15 in quality control and assurance, and 44 are in research and development. Based on our current plan, over the next 12-month period we intend to expand our employee base across most functions in the Company. None of our employees are represented by a collective bargaining unit.

Facilities

Our primary offices are located at 7 Hamilton Landing, Suite 100, Novato, CA 94949. Our main phone number is (415) 408-6200 and our facsimile number is (415) 382-8002. Our European headquarters are located at Naritaweg 165, 1043 BW Amsterdam, Netherlands and we have administrative offices in Utrecht, Netherlands.

Website

Our corporate website is located at www.raptorpharma.com. Any information contained in, or that can be accessed through, our website is not incorporated by reference into this Annual Report on Form 10-K.

Available Information

Our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act may be accessed through the SEC's website at www.sec.gov and on our website at www.raptorpharma.com free of charge. Such filings are placed on our website as soon as reasonably practicable after they are filed with the SEC. Our code of business conduct and ethics, audit committee charter, corporate governance and nominating committee charter and compensation committee charter are also posted on our website.

ITEM 1A: RISK FACTORS

Investing in our common stock involves a high degree of risk. Before deciding whether to invest in our common stock, you should consider carefully the risk factors described below, together with the other information contained in this Annual Report on Form 10-K and other documents we file with the SEC, such as our quarterly reports on Form 10-Q, our current reports on Form 8-K and any public announcements we make from time to time. If any of these risks actually occur, it may materially harm our business, financial condition, operating results or cash flow. As a result, the market price of our common stock could decline, and you could lose all or part of your investment. Additional risks and uncertainties that are not yet identified or that we think are immaterial may also materially harm our business, operating results and financial condition and could result in a complete loss of your investment.

Risks Associated with Commercialization and Product Development

Our revenues currently depend on the success of our only current commercial drug, PROCYSBI, for the management of nephropathic cystinosis.

PROCYSBI is our only currently marketed product and as a result, our net revenue and operating results substantially depend on the continued commercial success of PROCYSBI. We commenced marketing for PROCYSBI in the United States in June 2013 and Europe in April 2014. In the United States, we are permitted to market PROCYSBI for the management of nephropathic cystinosis in adults and children two years and older. In September 2013, we received marketing authorization from the European Commission ("EC") to commercialize PROCYSBI for the treatment of proven nephropathic cystinosis in the European Economic Area ("EEA"). We commenced commercial sales of PROCYSBI in Germany in April 2014 and have launched commercial sales in select additional countries in Europe. We have no assurance of securing reimbursement or subsequently launching in additional countries in the EEA. We believe that our results of operations and, in particular, our net product sales of PROCYSBI will affect the trading price of our common stock substantially. If PROCYSBI sales do not meet market expectations, our stock price may significantly decrease.

Our ability to successfully commercialize our current and any other future drug products will depend on multiple factors, including:

- our ability to provide acceptable evidence of the safety and efficacy of our products;
- compliance with regulatory requirements, including fulfilling post-approval commitments;
- our ability to obtain approval by regulatory agencies in other countries, including appropriate product labeling;
- the effect of current and future healthcare laws;
- the manufacture and supply of adequate quantities of our products in compliance with current good manufacturing practices as needed to meet commercial demand;
- adequate coverage and reimbursement for our products from commercial health plans and government health programs, which we refer to collectively as "third-party payors";
- our ability to obtain acceptable prices in EEA countries and other select territories, including acceptable reimbursement at the country-specific price;
- limitations or warnings currently contained in or as may later be required in approved labeling and the breadth of product labeling or product insert requirements;
- our ability to enter into agreements with wholesalers, distributors and pharmacies on commercially reasonable terms; and
- the protection, development and maintenance of intellectual property and other commercial product protection for our products.

If we fail to grow sales of PROCYSBI in existing markets, to successfully sell PROCYSBI in other countries or to successfully commercialize QUINSAIR or any other future products within a reasonable time period, we will have reduced financial resources and will be unable to fully execute our business plans, and our results of operations and financial condition will be materially adversely affected.

Our ability to generate significant product sales from our products is dependent upon market acceptance among physicians, patients, patient families, third-party payors and the healthcare community.

Our current and any future drug products may not attain or maintain market acceptance among physicians, patients, patient families, third-party payors or the healthcare community compared to the current and evolving standards of care and to standards of care from new competitors. We believe that the degree of market acceptance and our ability to generate significant product sales of our current and any future drug products will depend on a number of factors, including:

- the efficacy, safety, availability and ease of administration of our products relative to alternative treatments;
- the price of our products, both in absolute terms and relative to the quality of therapeutic benefits and price of alternative treatments;
- the timing of market introductions of our products and product lines relative to competitive treatments;
- the nature of publicity related to our products relative to the publicity related to our competitors' products;
- the prevalence and severity of adverse side effects of our current and any future products relative to competitive products;

- good patient compliance to therapy;
- availability of coverage and adequate reimbursement from third-party payors;
- provision of affordable out-of-pocket costs to patients and/or other programs to ensure patient access to our products; and
- the identification of currently diagnosed and undiagnosed patients and continued growth of the cystinosis and cystic fibrosis markets and the markets for any other future products.

Our efforts to educate patients, physicians, parents, the medical community and third-party payors on the benefits of our products may require significant resources and may not be successful at the levels planned. If our products do not achieve and maintain significant market acceptance among physicians, patients, patient families, third-party payors and the healthcare community, our business, results of operations and financial condition will be materially adversely affected.

The amount of our product sales in the EEA is dependent in part upon the pricing and reimbursement decisions adopted in each of the EEA countries, which may not be at acceptable levels to us.

One or more EEA countries may not support pricing within our target pricing and reimbursement range for our products due to budgetary decisions made by regional, national and local health authorities and third-party payors in the EEA, which would negatively affect our revenues. The pricing and reimbursement process in EEA countries can be lengthy, involved and difficult to predict.. Failure to timely complete the pricing and reimbursement process in the EEA countries will delay our ability to market PROCYSBI, to bring QUINSAIR to market in the EEA and to derive revenues from those countries.

We may be subject to penalties and litigation and large incremental expenses if we fail to comply with regulatory requirements or experience problems with our products.

Even after we achieve regulatory approvals, we are subject to ongoing obligations and continued regulatory review with respect to many operational aspects including our manufacturing processes, labeling, packaging, distribution, storage, adverse event monitoring and reporting, dispensation, advertising, promotion and recordkeeping. These requirements include submissions of safety and other post-marketing information and reports, ongoing maintenance of product registration and continued compliance with good manufacturing practices, or GMPs, good clinical practices, or GCPs, good pharmacovigilance practice, or GVPs, good distribution practices, or GDPs, and good laboratory practices, or GLPs. We are in the process of implementing corrective and preventive actions that we expect will complete in the first quarter of 2016 related to our pharmacovigilance system to address findings issued in August 2015 following a routine inspection from a European regulatory authority in June 2015 and our own internal reviews of our internal processes.

If we, our products or product candidates, or the third-party manufacturing facilities for our products or product candidates fail to comply with applicable regulatory requirements, a regulatory agency may:

- impose injunctions or restrictions on the marketing, manufacturing or distribution of a product, suspend or withdraw product approvals, revoke necessary licenses or suspend product reimbursement;
- issue warning letters, show cause notices or untitled letters describing alleged violations, which may be publicly available;
- suspend any ongoing clinical trials or delay or prevent the initiation of clinical trials;
- delay or refuse to approve pending applications or supplements to approved applications we have filed;
- refuse to permit drugs or precursor or intermediary chemicals to be imported or exported to or from the United States;
- suspend or impose restrictions or additional requirements on operations, including costly new manufacturing quality or pharmacovigilance requirements;
- seize or detain products or require us to initiate a product recall; and/or
- commence criminal investigations and prosecutions.

Moreover, existing regulatory approvals and any future regulatory approvals that we obtain will be subject to limitations on the approved indicated uses and patient populations for which our products may be marketed, the conditions of approval, requirements for potentially costly, post-market testing and requirements for surveillance to monitor the safety and efficacy of the products. In the EEA, the advertising and promotion of pharmaceuticals is strictly regulated. The direct-to-consumer promotion of prescription pharmaceuticals is not permitted, and some countries in the EEA require the notification and/or prior authorization of promotional or advertising materials directed at healthcare professionals. The FDA, European Medicines Agency (“EMA”), EC and other authorities in the EEA countries strictly regulate the promotional claims that may be made about prescription products, and our product labeling,

advertising and promotion are subject to continuing regulatory review. Physicians nevertheless may prescribe our products to their patients in a manner that is inconsistent with the approved label or that is off-label. Positive clinical trial results in any of our product development programs increase the risk that approved pharmaceutical forms of the same active pharmaceutical ingredients may be used off-label in those indications. Our investigational product candidate RP103 is comprised of the same active pharmaceutical ingredient ("API") as PROCYSBI. If we are found to have improperly promoted off-label uses of approved products, we may be subject to significant sanctions, civil and criminal fines and injunctions prohibiting us from engaging in specified promotional conduct.

In addition, engaging in improper promotion of our products for off-label uses in the United States can subject us to false claims litigation under federal and state statutes. These false claims statutes in the United States include the federal False Claims Act, which allows any individual to bring a lawsuit against a pharmaceutical company on behalf of the federal government alleging submission of false or fraudulent claims or causing to present such false or fraudulent claims for payment by a federal program such as Medicare or Medicaid. Growth in false claims litigation has increased the risk that a pharmaceutical company will have to defend a false claim action, pay civil money penalties, settlement fines or restitution, agree to comply with burdensome reporting and compliance obligations and be excluded from Medicare, Medicaid and other federal and state healthcare programs.

The regulations, policies or guidance of regulatory agencies may change and new or additional statutes or government regulations may be enacted that could prevent or delay regulatory approval of our product candidates or further restrict or regulate post-approval activities. For example, the Food and Drug Administration Safety and Innovation Act ("FDASIA"), requires the FDA to issue new guidance describing its policy regarding internet and social media promotion of regulated medical products, and the FDA may soon specify new restrictions on this type of promotion. In January 2014, the FDA released draft guidance on how drug companies can fulfill their regulatory requirements for post-marketing submission of interactive promotional media, and though the guidance provided insight into how the FDA views a company's responsibility for certain types of social media promotion, there remains a substantial amount of uncertainty. We cannot predict the likelihood, nature or extent of adverse government regulation that may arise from pending or future legislation or administrative action, either in the United States or abroad. If we are unable to achieve and maintain regulatory compliance, we will not be permitted to market our drugs, which would materially adversely affect our business, results of operations and financial condition.

If we are unable to expand the use of RP103 or MP-376 pursuant to regulatory approval for additional clinical indications or geographic territories, or are unable to obtain regulatory approval for other product candidates, we may delay or terminate some of our product development activities. This would adversely affect the long term value of RP103, MP-376 or other product candidates as well as our growth prospects.

The research, testing, manufacturing, clinical development, labeling, approval, sale, marketing and distribution of drug products, among other things, are subject to extensive regulation by the FDA and other regulatory authorities in the United States and by similar foreign governmental regulatory entities. We are not permitted to market any of our drug product candidates unless we obtain and maintain appropriate marketing approvals from regulatory agencies in each of the markets in which we intend to market our products. Once approved, we may only market our products for the specific uses that are reflected in the product's approved labeling. A product's approved labeling may contain limitations or warnings or may be for different patient populations or for fewer or more limited indications than we request in our pre-market approval application, which could result in limiting reimbursement, access for intended use or the commercial profile of a drug. In the United States, we are permitted to market the active pharmaceutical ingredient of RP103 in the formulation of a final drug product and in the doses approved under the brand name PROCYSBI only for the management of nephropathic cystinosis in adults and children two years and older. We are permitted to market PROCYSBI in the EEA as an orphan medicinal product for the treatment of proven nephropathic cystinosis. MP-376 has been approved for marketing in Canada and the European Union ("EU") under the specific indication as a medicinal product for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adults 18 years and older with cystic fibrosis. Neither RP103 nor MP-376 has been approved in any other market or for any other disease indication. There can be no assurance that we will obtain regulatory approval for any other uses for our product candidates or that, even if we obtained additional approvals, we would be able to commercialize the product candidates successfully.

A new drug application ("NDA"), submitted to the FDA, or a marketing authorization application ("MAA"), submitted to the EMA, must be supported by extensive clinical and preclinical data, as well as extensive information regarding chemistry, manufacturing and controls. This information must demonstrate the safety and efficacy of the applicable product candidate for the management of each individual indication to the satisfaction of the applicable regulatory authority. Obtaining approval of an NDA, MAA or any other filing for marketing authorization in a foreign country for a drug product candidate is an extensive, expensive and uncertain process. The time required to obtain approval by the FDA and comparable foreign authorities is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. The FDA, EC, EMA or other regulatory authorities may delay, limit or deny approval of RP103, MP-376 or our future drug product candidates for many reasons, including:

- the results of clinical trials may not meet the level of statistical or clinical significance required by regulatory authorities for approval;
- regulatory authorities may disagree with the number, design, size, conduct or implementation of our clinical trials; they may change the requirements for approval even after having reviewed and commented on the design for our clinical trials;
- regulatory authorities may not find the data from preclinical studies and clinical trials sufficient to demonstrate that product candidates have adequate clinical and other benefits or adequate safety profiles, even if they achieve their specified endpoints in clinical trials; or they may disagree with our interpretation of data from preclinical studies or clinical trials and/or require that we conduct additional trials;
- regulatory authorities may not accept data generated at our clinical trial sites;
- if requested by us, regulatory authorities may not hold an advisory committee meeting in a timely manner or at all, or, if an advisory committee is convened it may recommend against approval of our application or may recommend that the regulatory agency require, as a condition of approval, additional preclinical studies or clinical trials; approval may also be contingent on a Risk Evaluation and Mitigation Strategy, which limits the labeling, distribution or promotion of a drug product;
- regulatory authorities may require additional preclinical or clinical studies or other data prior to granting approval, and we may not be able to generate the required data on a timely basis, if at all;
- regulatory authorities may identify deficiencies in the manufacturing processes or in the facilities of our third-party suppliers and/or contract manufacturers or may require us to manufacture additional validation batches or change our submitted regulatory documents, process, specifications or third-party suppliers or contract manufacturers; and
- we may not be able to validate manufacturing processes to the satisfaction of the regulatory authorities.

With respect to QUINSAIR, the FDA has indicated in previous written communications that it believes the data submitted in connection with EMA's subsequent approval of MP-376 for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adults with cystic fibrosis does not provide substantial evidence of efficacy and safety to support FDA approval of MP-376 for treatment of patients with cystic fibrosis. The FDA identified a number of limitations with the design of the pivotal trial upon which approval of QUINSAIR in the EU and Canada was based that, in the FDA's view, impacts its ability to be used as a pivotal efficacy study. The FDA also questioned whether patients in the study achieved any overall benefit, as the primary endpoint in the study was not met. We intend to discuss potential registration strategies with the FDA. We may not agree with the developmental pathway that the FDA recommends or be able to conduct the clinical trials that the FDA requests, which would limit our ability to seek regulatory approval for MP-376 in the United States.

If we fail to gain regulatory approval for RP103 or MP-376 for other indications, in additional geographic jurisdictions, or for our other future drug product candidates, we will have to delay or terminate some or all of our research product development programs, and our business, results of operations and financial condition will be materially adversely affected.

We do not have internal manufacturing capabilities. In the near term, we expect to continue to rely on a single source supplier for our API for PROCYSBI and a single third-party manufacturer for the conversion to finished commercial drug product. Similarly, we expect to utilize single source suppliers for the QUINSAIR API, drug product and delivery device, upon commercial launch. We also rely on third parties for the distribution and pharmaceutical services of PROCYSBI in the United States and the EEA. If we are unable to rely on these third parties, our revenue will be delayed or diminished and our business, results of operations and financial condition will be materially adversely affected.

We do not own or operate manufacturing facilities and currently lack the in-house capability to manufacture our current products or product candidates. As a result, we currently contract with external contract manufacturing organizations ("CMOs"), for commercial and clinical quantities of our products for the indications under development. We rely on a single source supplier for our cysteamine API. While we have procured additional manufacturing support with a second provider for clinical supply of PROCYSBI,

we will continue to rely on a single third-party manufacturer for supply of finished commercial product. Our ability to obtain sufficient quantities of PROCYSBI and RP103 is constrained by limited supplies of raw materials and the limited capacity and output of these third parties. Furthermore, any reduction, delay or interruption in our supply of APIs from the single source supplier or of our supply of finished goods from our CMOs could result in significant additional operating costs, interruptions in product supply, delays in sales of PROCYSBI, delays in the commercial launch of QUINSAIR, and delays in developing RP103 and MP-376 for additional indications. In addition, supply arrangements from alternative sources not currently under contract may not be available on acceptable economic terms, if at all.

The manufacture of pharmaceutical products requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Pharmaceutical products have stringent specifications for product quality including stability that must be maintained within product specifications. Manufacturers of pharmaceutical products often encounter difficulties in production, particularly in scaling up initial production volume to commercial requirements as more batches are produced and usually at greatly increased scale per batch. Assessing process capability takes time after launch of a pharmaceutical product as process experience grows with manufacturing experience and products are periodically evaluated for improvements or specification revisions. Moreover, cysteamine bitartrate is difficult to manufacture because the molecule is labile and can be sensitive to process and stability conditions. Difficulties may arise related to internal processes, production costs and yields, quality control, including stability of the product and quality control testing, sourcing scarcities, resource constraints, equipment problems, shortages of qualified personnel, labor disputes, severe weather events, unstable political environments or financial difficulties at foreign facilities, as well as compliance with strictly enforced federal, state and foreign regulations. Manufacturers may breach their agreements with us or may terminate or decline to renew their agreements with us, whether due to our breach of the relevant agreements or based on their own business priorities. In addition, due to our small patient population, the manufacture of our drug may be given lower priority on the production line if manufacturing priority is decided by scale. As a result of the above-discussed issues, contract manufacturers may decide that the business risk associated with products such as ours is not justified.

Manufacturers and suppliers are subject to regulatory requirements covering, among other things, manufacturing, process controls, testing, quality control and record keeping and are subject to ongoing inspections by regulatory agencies. We have no direct control over the ability of our contract manufacturing parties to maintain adequate quality control, quality assurance and qualified personnel, and while final outputs are reviewed by our own internal quality control, we depend on our third-party supplier and manufacturers for compliance with the FDA's current cGMP requirements and other FDA requirements, the Drug Enforcement Administration's regulations and other rules and regulations prescribed by applicable non-U.S. regulatory authorities. If our contract manufacturing partners cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or other regulatory authorities, they will not be able to supply manufactured product to us and they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities, and we may experience long delays and interruptions to our manufacturing supply and increased costs.

Pursuant to ongoing obligations from the NDA for PROCYSBI, we are required to collect and submit data to the FDA regularly regarding our currently observed clinical and commercial product profile and overall product safety assessment. Similarly, pursuant to obligations in the MAA for QUINSAIR, we will be required to conduct post-marketing clinical studies in cystic fibrosis patients and submit data to the EMA regularly regarding observed clinical product profile and safety assessment. In addition, we intend to continue to evaluate our product specification limits, and any changes to our product specifications may require additional review and approval by regulators in the United States and Europe. If there are material delays in any such review and approval process, or if regulators reject any proposals for changes in product specifications or require additional data to support the updated specifications, we may experience an inventory shortfall, which would have a material adverse effect on sales of our products.

If we or our third-party suppliers and manufacturers fail to comply with applicable regulatory requirements, we could experience significant delays or interruptions to our manufacturing supply that may result in the delay or suspension of our preclinical or clinical trials. In addition, a regulatory agency could issue warning letters or untitled letters, seek an injunction, impose civil or criminal penalties or monetary fines, suspend or withdraw regulatory approval, require specification changes, suspend any ongoing clinical trials, refuse to approve pending applications or supplements to applications, suspend or impose restrictions on operations, including costly new manufacturing requirements, seize or detain products or request or require that we initiate a product recall.

We also rely on a third-party logistics provider and specialty pharmacy to distribute PROCYSBI to patients in the United States and to pharmacies in the EEA and to collect from insurance companies and government agencies in the United States and from pharmacies in the EEA. We plan to employ a similar network of third-party services providers to distribute QUINSAIR in the EU and Canada. Our ability to collect from a particular logistics provider is not only subject to such provider's credit worthiness but is also dependent, in part, on its ability to arrange for full reimbursement from third-party payors. The outsourcing of our distribution function is complex, and we may experience difficulties that could reduce, delay or stop shipments of our products. If we encounter such distribution problems, and we are unable to quickly enter into a similar agreement with another specialty distributor on substantially similar terms, if at all, the distribution of our products could become disrupted, resulting in reduced revenues, healthcare

provider dissatisfaction and/or patient dissatisfaction, which may materially adversely affect our business, results of operations and financial condition.

If any of these events were to occur, our reputation would be harmed, revenues from sales of our products would be delayed or diminished and our business, results of operations and financial condition would be materially adversely affected.

If serious adverse side effects become associated with our current or future products, our business, results of operations and financial condition will be materially adversely affected.

The prescribing information for both PROCYSBI and QUINSAIR include several warnings relating to observed adverse reactions of the active pharmaceutical ingredient usage. The FDA may require products approved under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act (the "FDCA") to bear the same or similar warning statements as the reference product used in the approval. We expect to update adverse reactions listed in the prescribing information for our products based on continued commercial use and additional clinical trials. If additional adverse reactions emerge, or if there is a pattern of severe or persistent previously observed side effects in the relevant patient populations, the FDA, the EMA or other regulatory agencies could modify or revoke our marketing approvals, require us to modify our labels or require us to suspend production, require a product recall, or we may choose to withdraw a product from the market.

Regulatory authorities could also require us to change the way our products are administered or modify a product in some other way, or they could require us to conduct additional clinical trials or costly post-marketing testing and surveillance to monitor the safety or efficacy of our products. If this were to occur, we may be unable to maintain marketing approvals in our approved indications and/or obtain marketing approval in other indications. In addition, patients or their representatives may bring claims against us alleging serious adverse side effects or harm suffered as a result of use of our products. Any such side effects or related claims could have a material adverse effect on our business, results of operations and financial condition. See also the risk factor titled "*We may be subject to product liability claims.*"

If we fail to demonstrate safety or efficacy in our preclinical studies or clinical trials or to keep to the terms of a product development program, our future business prospects for our drug product candidates will be materially adversely affected.

Clinical trials are very expensive, time consuming and difficult to design and implement. The outcome of clinical trials is uncertain, and results of earlier studies and trials may not be predictive of future trial results. Delays in the commencement or completion of clinical or preclinical testing for RP103 or MP-376 or any of our other product candidates could significantly affect our product development costs and business plan.

Preclinical studies involve testing in multiple non-human disease models to demonstrate efficacy and safety. Regulatory agencies evaluate these data carefully as part of their determination whether to authorize clinical testing in humans. If certain preclinical data reveal potential safety issues or if the results are inconsistent with an expectation of the drug product candidate's efficacy in humans, the regulatory agencies may require additional testing before allowing human clinical trials. This additional testing will increase program expenses and extend timelines. There are many potential preclinical models to test for different disease states, and we could fail to choose the best or a predictive preclinical model to determine proof of concept, safety and efficacy of our drug product candidates. We may decide to suspend further testing on our drug product candidates or technologies if, in the judgment of our management and advisors, the preclinical test results do not support further development. Following successful preclinical testing, drug product candidates must be tested in a clinical development program to provide data on safety and efficacy in humans prior to becoming eligible for product approval and licensure by regulatory agencies. Success in preclinical testing and early clinical trials does not ensure that later clinical trials will be successful. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through preclinical studies and initial clinical trials.

Clinical trials may also be delayed or repeated as a result of ambiguous or negative interim results or unforeseen complications in testing. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials. The clinical trial process may fail to demonstrate with statistical significance that our drug product candidates are safe for humans and effective for indicated uses. This failure may cause us to abandon a drug product candidate and may delay development of other drug product candidates. For example, we announced in September 2015, based on information then available, that we would not advance our program for the treatment of pediatric non-alcoholic steatohepatitis (NASH) with RP103 after topline results from a Phase 2b trial which failed to show efficacy as measured by the trial's primary endpoints. Unless the full data set, which we expect to receive later this year, provides a compelling rationale for us to continue the NASH program, our decision will remain unchanged. Any delay in, or termination of, our preclinical testing or clinical trials will delay the filing of relevant marketing applications with regulatory agencies and, ultimately, our ability to commercialize our drug product candidates and generate revenues from related products.

The rate of completion of any clinical trials will be dependent upon, among other factors, the rate of patient enrollment. Patient enrollment is a function of many factors, including the size of the patient population, the nature of the trial, the nature of the disease or medical condition being studied, the availability of alternative therapies, drugs and competing clinical trials of potential alternative therapeutics, the proximity of patients to clinical sites and the eligibility criteria for the study. Delays in planned patient enrollment may result in increased costs and delays. In addition, because many of our clinical trials involve small patient populations, the results of these early clinical trials may not be indicative of future results. Further, the timing of regulatory approval of clinical trial applications by local regulatory agencies or ethics committees may also affect the initiation of trial sites and therefore the rate of patient enrollment.

Under the Prescription Drug User Fee Act, the FDA seeks to respond to NDAs within ten months of the filing date, but this timeframe is often extended. For example, a sponsor may seek FDA designation of a drug candidate as a "fast track product." Fast track products are those products intended for the treatment of a serious or life-threatening disease or condition and which demonstrate the potential to address unmet medical needs for such disease or condition. If fast track designation is obtained, the FDA may initiate review of sections of an NDA before the application is complete. This "rolling review" is available if the applicant provides and the FDA approves a schedule for the remaining information. In addition, FDASIA established a new category of drugs referred to as "breakthrough therapies," which are defined as drugs intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. In the future, we may request breakthrough designation or fast track designation from the FDA for our other drug product candidates, but there can be no assurance that we will obtain such designations. Moreover, even if we obtain breakthrough designation or fast track designation from the FDA, the designations do not guarantee that the FDA will approve our NDA, that the development program or review timeline will ultimately be shorter than if we had not obtained the designations or that the FDA will not request additional information, including additional clinical studies, during its review.

We do not know whether our investigational new drug, or IND, applications for future products or the protocols for any future clinical trials will be accepted by the FDA or EMA. We do not know if our clinical trials will begin or be completed on schedule or at all. Even if completed, we do not know if these trials will produce clinically meaningful results sufficient to support an application for marketing approval. The commencement and completion of our planned clinical trials could be substantially delayed or prevented by several factors, including:

- a limited number of, and competition for, suitable patients with particular types of disease for enrollment in clinical trials;
- delays or failures in obtaining regulatory clearance to commence a clinical trial;
- delays or failures in obtaining sufficient clinical materials;
- inability to design appropriate clinical trial protocols;
- delays or failures in reaching agreement on acceptable clinical trial agreement terms or clinical trial protocols with the Institutional Review Boards at prospective sites;
- inability of our clinical research organizations ("CROs"), or other third-party contractors to comply with all contractual requirements or to perform their services in a timely or acceptable manner;
- inability by us, our CROs or their employees to conduct the clinical trial in accordance with all applicable FDA, Drug Enforcement Administration or other regulatory requirements or our clinical protocols;
- lack of efficacy during, or other unfavorable results from, clinical trials or preclinical studies;
- discovery of serious or unexpected toxicities or side effects experienced by study participants or other unforeseen safety issues;
- failure of patients to complete the clinical trial, or inability or unwillingness of patients or medical investigators to follow our clinical trial protocols;
- inability to monitor patients adequately during or after treatment;
- regulatory action by the FDA or other regulatory authorities; and/or
- lack of adequate funding to continue the clinical trial, including the incurrence of any unforeseen costs.

In addition, changes in applicable regulatory requirements and guidance may occur, and we may need to amend clinical trial protocols to reflect these changes. Amendments may require us to resubmit our clinical trial protocols to Institutional Review Boards for reexamination, which may affect the costs, timing or successful completion of a clinical trial.

Sales of our products outside of the United States are also subject to foreign regulatory requirements governing clinical trials, manufacturing and marketing approvals. Even if the FDA and EC grant marketing approval for a product candidate, comparable regulatory authorities of foreign countries must also approve the manufacturing and marketing of our product candidates in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and greater than, those in the United States, including additional preclinical studies or clinical trials or manufacturing and control requirements. In many countries outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In many cases, the price that we propose to charge for our products is also subject to approval by individual countries before we can launch our product candidates in those countries. Obtaining foreign regulatory approvals, complying with foreign regulatory requirements and gaining approved pricing and reimbursement could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries. Further, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries. Regulatory approval in one country does not ensure approval in any other country, while a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory approval process in others.

Any delay in our preclinical or clinical programs or the failure to demonstrate safety or efficacy in our clinical trials would have a material adverse effect on our business, results of operations and financial condition.

If we fail to obtain or maintain orphan drug or other regulatory exclusivity for our products or to obtain and maintain exclusivity for our orphan drug product candidates relative to competitive products, our competitors may sell products to treat the same conditions, possibly at lower prices, and our revenues will be significantly reduced.

PROCYSBI received marketing approval from the FDA for the management of nephropathic cystinosis in adults and children two years and older and seven years of market exclusivity as an orphan drug in the United States through the year 2020 for the treatment of patients six years and older and separately received orphan designation with market exclusivity through the year 2022 for patients ages two to six years. PROCYSBI has also received approval as an orphan medicinal product for the management of proven nephropathic cystinosis and 10 years of market exclusivity in the EEA. QUINSAIR received marketing approval from the EMA in 2015 and has also received 10 years of market exclusivity for management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adults with cystic fibrosis. In the United States, the FDA has designated QUINSAIR as an orphan drug for treatment of pulmonary infections due to *Pseudomonas aeruginosa* and other bacteria in patients with cystic fibrosis. As part of our business strategy, we intend to develop RP103 and MP-376, and potentially other drugs, for additional therapeutic indications that may be eligible for FDA and EMA orphan drug designation.

Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug intended to treat a rare disease or condition, defined as a patient population of less than 200,000 in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. The company that first obtains FDA approval for a designated orphan drug for a given rare disease receives marketing exclusivity for use of that drug for the stated condition for a period of seven years, plus an additional six months if designated for a pediatric indication.

In the EU, the EMA's Committee for Orphan Medicinal Products grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the EU and for which no satisfactory method of diagnosis, prevention or treatment has been authorized (or if the product would be a significant benefit to those affected). In addition, designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition as well as when it is unlikely that sales of the drug in the EU would be sufficient to justify the necessary investment in developing the medicinal product without incentives. An EU orphan drug designation entitles a party to financial incentives such as reduced fees or fee waivers, and 10 years of market exclusivity is granted following medicinal product approval. This period may be reduced to six years if the orphan drug designation criteria are no longer met after five years, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. An applicant must request orphan drug designation before submitting an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. Even though we have been granted orphan drug designation in the United States and in the EU prior to the approval of RP103 for the treatment of Huntington's Disease ("HD"), and even if we obtain orphan drug designation for our future drug product candidates, we may not fulfill the criteria for exclusivity, or we may not be the first to obtain marketing approval for any orphan indication. Further, even if we obtain orphan drug exclusivity for a particular product, that exclusivity may not effectively protect the product from competition because different drugs can be approved for the same condition. Even after an orphan drug is approved, the FDA can subsequently approve a drug for the same condition if the FDA concludes that the later drug is safer, more effective or makes a major contribution to patient care. Orphan drug exclusive marketing rights may also be lost if the FDA later determines that the request for designation was materially defective, if a subsequent product is deemed clinically superior or if the manufacturer is unable to deliver sufficient quantities of the drug.

Because the extent and scope of patent protection for some of our drug products may be particularly limited, orphan drug designation is especially important for our eligible products and we plan to rely on the orphan or other regulatory exclusivity period to maintain a competitive position. However, if we do not obtain and/or maintain orphan drug exclusivity for our drug products, or if our drug products do not have strong patent protection, our competitors may sell the same drug to treat the same condition, possibly at lower prices, and our revenues will be reduced. Also, without strong patent protection, competitors may sell a generic version of our products upon the expiration of orphan exclusivity if our patent position is not upheld or physicians may prescribe a generic version of our product off-label when our orphan status or marketing exclusivity has expired with respect to one indication, but not others.

If our competitors succeed in developing products and technologies that are more effective than our own, or if scientific developments change our understanding of the potential scope and utility of our drug product candidates, then our technologies and future drug product candidates may be rendered less competitive.

We face significant competition from industry participants that are pursuing technologies similar to those that we are pursuing and are developing pharmaceutical products that are competitive with our products or our product candidates. Many of the pharmaceutical companies in areas competitive with us have greater capital resources, larger overall research and development staff and facilities and a longer history in drug discovery, development, regulatory approval, manufacturing and marketing than we do. With these additional resources and experience, our competitors may be able to respond to rapid and significant technological changes in the biotechnology and pharmaceutical industries faster than we can.

We expect that the technologies associated with biotechnology research and development will continue to develop rapidly. Our future success will depend in large part on our ability to maintain a competitive position with respect to these technologies. Rapid technological development, as well as new scientific developments, may result in our compounds, drug products, drug product candidates or processes becoming obsolete before we can recover any or all of the expenses incurred to develop them. For example, changes in our understanding of the appropriate population of patients who should be treated with a targeted therapy like those we are developing may limit the drug's market potential if it is subsequently demonstrated that only certain subsets of patients should be treated with the targeted therapy.

No clinical data have been generated for the use of MP-376 to treat non-cystic fibrosis bronchiectasis ("BE") or non-tuberculous mycobacteria infection ("NTM")..

We plan to pursue a Phase 2 clinical trial of MP-376 for use in the indication of BE not associated with cystic fibrosis in 2016 and also plan to do work in preparation to support its further clinical development in the treatment of pulmonary NTM, based on third-party data generated pertaining to the susceptibility of certain pathogens to treatment with levofloxacin and other fluoroquinolone molecules. No clinical data have been generated with MP-376 in patients with BE or with NTM infections, either by us or by other parties. This creates substantial uncertainty as the efficacy of MP-376 in these indications. Successful completion of well-controlled clinical trials of adequate size and design is a prerequisite to submitting an NDA to the FDA and, consequently, the ultimate approval and commercial marketing of MP-376 or any other potential product candidate in these indications. A failure of one or more clinical trials can occur at any stage of testing. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later preclinical testing or clinical trials, and interim results of a clinical trial do not necessarily predict final results. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval for their products from regulatory authorities.

The approval of any product or product candidate, including QUINSAIR, in any given market does not ensure approval in any other market.

In order to market any product candidate for a specific indication, we must establish and comply with numerous regulatory requirements on a country-by-country basis regarding safety and efficacy. Clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not guarantee regulatory approval in any other country. Approval processes vary among countries and can involve additional product testing and validation, and additional administrative review periods. As a result, international regulatory requirements could delay or prevent the introduction of our products and product candidates across different countries. For example, approval of QUINSAIR for use in CF patients with *Pseudomonas aeruginosa* in the EU and Canada does not ensure approval by the FDA or regulatory authorities in other countries or jurisdictions, nor does it ensure approval for the same conditions of use. Further, seeking U.S. regulatory approval for QUINSAIR for a specific indication could result in difficulties and costs for us and require additional preclinical studies or clinical trials which could be costly and time consuming. If we fail to comply with regulatory requirements in international markets or to obtain and maintain required approvals, or if regulatory approvals in international markets are delayed, our target market will be reduced and our ability to realize the full market potential of our products and product candidates will be unrealized.

We have obligations to Tripex to conduct certain regulatory and development activities with respect to QUINSAIR. Delays or other factors that prevent us from completing these regulatory and development activities may put us in breach of our obligations to Tripex.

The terms of our asset purchase agreement for the acquisition of QUINSAIR require us to pursue commercially reasonable efforts to initiate, and subsequently to complete, an additional clinical trial in a non-cystic-fibrosis patient population within a specified period of time. These terms also require us to progress toward filing an NDA for approval of QUINSAIR in the United States in all or part of the cystic fibrosis patient population within a specified period of time. These obligations are subject to certain exceptions due to, for example, manufacturing delays not under our control, or delays caused by the FDA. If we fail to properly exercise such efforts to initiate and complete an appropriate clinical trial, or fail to file an NDA for U.S. approval in the cystic fibrosis patient population, during the time periods specified in the asset purchase agreement, we may be subject to various claims by Tripex and parties affiliated with Tripex.

Because the target patient populations for our products and some of our drug product candidates are small, we must achieve significant market share and obtain sufficient per-patient prices for our products to achieve meaningful gross and operating profits.

PROCYSBI, QUINSAIR and clinical development of RP103 and MP-376 target rare diseases with small patient populations, including cystinosis, cystic fibrosis, mitochondrial disorders including Leigh's Disease, NTM, BE and HD. To successfully commercialize a drug product for these indications, we must identify patients and a targeted prescriber base for each drug product. Due to small patient populations, we believe that we would need to have significant market penetration to achieve meaningful revenues. In addition, the per-patient prices at which we sell our current products for these indications will need to be relatively high in order for us to generate meaningful gross and net operating profits because we must recoup our investment in our product development programs, which programs often require ongoing investment after a product's approval. Patients who discontinue therapy or do not fill prescriptions are not easily replaced by new patients because of the limited patient populations. There can be no assurance that we will successfully obtain or maintain sufficient market share or per-patient prices. Because our current potential target populations are very small, even if we obtain significant market share for our current or future products and product candidates, we may never achieve profitability despite obtaining such significant market share.

If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs in the United States, we could be subject to additional reimbursement requirements, penalties, sanctions and fines, which could have a material adverse effect on our business, results of operations and financial condition.

We participate in the Medicaid Drug Rebate Program, as administered by the Centers for Medicare & Medicaid Services ("CMS"), and other federal and state government pricing programs in the United States, and we may participate in additional government pricing programs in the future. These programs generally require us to pay rebates or otherwise provide discounts to government payors in connection with drugs, including PROCYSBI, that are dispensed to beneficiaries of these programs. In some cases, such as with the Medicaid Drug Rebate Program, the rebates are based on pricing and rebate calculations that we report on a monthly and quarterly basis to the government agencies that administer the programs. Pricing and rebate calculations are complex, vary among products and programs, and are often subject to interpretation by governmental or regulatory agencies and the courts. The terms, scope and complexity of these government pricing programs change frequently. Responding to current and future changes may increase our costs and the complexity of compliance will be time consuming.

In addition, the Office of Inspector General has recently increased its focus on the methodologies used by manufacturers to calculate average manufacturer price ("AMP"), and best price ("BP"), to assess manufacturer compliance with reporting requirements under the Medicaid Drug Rebate Program. We are liable for errors associated with our submission of pricing data and for any overcharging of government payors. For example, failure to submit monthly/quarterly AMP and BP data on a timely basis could result in a civil monetary penalty of $10,000 per day for each day the submission is late beyond the due date. Failure to make necessary disclosures and/or to identify overpayments could result in allegations against us under the Federal False Claims Act and other laws and regulations.

Any required refunds to the U.S. government or responding to a government investigation or enforcement action would be expensive and time consuming and could have a material adverse effect on our business, results of operations and financial condition. In the event that the CMS were to terminate our rebate agreement, no federal payments would be available under Medicaid or Medicare for our covered outpatient drugs.

Pricing and reimbursement policy changes from third-party payor coverage may impair our customers' ability to be reimbursed for our products and product candidates at adequate prices or on adequate terms, which may in turn materially adversely affect our business, results of operations and financial condition.

Market acceptance and sales of our products will depend in large part on third-party payor coverage and reimbursement policies and may be affected by future healthcare reform measures in the United States, the EEA and other key international markets. The continuing efforts of governmental and other third-party payors to contain, reduce or shift the costs of healthcare through various means, including expansion of compulsory drug rebate programs, an increased emphasis on managed care and attempts to limit or regulate the price of medicinal products and services, particularly for new and innovative products and therapies, is likely to result in downward pressure on pricing, reimbursement and utilization, which would adversely affect our product sales and results of operations. Moreover, because private health insurers and other third-party payors often follow the coverage and reimbursement policies of government payors, including the Medicare and Medicaid programs, cost-containment measures or pricing or reimbursement policy changes under these programs play a particularly significant role in the reimbursement landscape. The government programs relevant to our products include, without limitation, the following:

- the Medicaid Drug Rebate Program, under which manufacturers must report pricing information and pay rebates in order for their drug products to be covered under state Medicaid programs;
- the Public Health Service's 340B Drug Pricing Program, under which manufacturers must offer discounts to certain healthcare organizations that care for underserved populations;
- the Department of Veterans Affairs' Federal Supply Schedule pricing program, under which manufacturers agree to offer drugs to certain governmental providers at reduced rates;
- the TRICARE Retail Pharmacy Program, under which manufacturers must agree to honor certain discounted prices, specifically Federal Ceiling Prices under the Veterans Health Care Act, as a condition for placement in the Department of Defense uniform formulary; and
- the Medicare Part D program, under which manufacturers contract with plan sponsors to offer certain outpatient drugs to Medicare beneficiaries.

In addition, in the United States, third-party payors often develop cost containment measures using policies that specifically target specialty products and high-cost drugs. For example, formulary placements may be less favorable for brand and higher-costing drugs, which may result in, among other things, greater out-of-pocket costs to patients. PROCYSBI often is subject to such measures, and similar future policies addressing such cost-containment measures may also affect PROCYSBI.

Further, third-party payors also are increasingly considering new metrics as the basis for reimbursement rates, such as average sales price, AMP or actual acquisition cost, and for cost-benefit analyses with comparable drugs. Although the changes to reimbursement methodologies are generally intended to limit payment increases, it is difficult to project the impact of these and other alternative reimbursement methodologies on the willingness of payors to reimburse for our products and any product candidates that we may develop. To date, PROCYSBI generally has been covered and reimbursed commercially in the United States and the select countries in which we have sold PROCYSBI worldwide, but we do not know whether third-party payors will continue to cover and reimburse PROCYSBI in these markets or at the level PROCYSBI is currently covered, will reimburse PROCYSBI in other EEA countries or will reimburse our future products until we enter into payor negotiations. Further, we have recently filed for marketing approval for PROCYSBI in Canada. Even if such approval is obtained, we must negotiate pricing and reimbursement and cannot be assured of obtaining levels that are acceptable to us. If coverage and reimbursement are not available or limited, or reimbursement is available only at limited levels, our business, results of operations and financial condition will be materially adversely affected. In addition, we plan to launch sales of QUINSAIR in Europe and Canada in 2016 and are in ongoing negotiations with respect to pricing and reimbursement in those markets. There can be no guarantee that we will achieve our target pricing for QUINSAIR. See the Risk Factor titled "*The amount of our product sales in the EEA is dependent in part upon the pricing and reimbursement decisions adopted in each of the EEA countries, which may not be at acceptable levels to us.*"

Legislative changes may increase the difficulty and cost for us to commercialize our products or any other product candidate that we develop and affect the prices we may obtain.

In the United States, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that restrict or regulate post-approval activities. The changes may affect our ability to sell PROCYSBI or any other product candidate for which we obtain marketing approval at adequate prices.

In 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, which we refer to together as the "Affordable Care Act," was adopted. This law intends to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements

for healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. The Affordable Care Act, among other things:

- increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program;
- revised the definition of AMP for reporting purposes, which could further increase the amount of rebates paid by manufacturers under the Medicaid Drug Rebate Program;
- extended the Medicaid Drug Rebate Program to beneficiaries enrolled in Medicaid managed care organizations;
- addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected and for oral solid line extensions and reformulated drugs, which, depending on how the provision is interpreted and implemented, could increase our Medicaid rebate rate substantially;
- imposed a significant annual fee on companies that manufacture or import branded prescription drug products and established an annual non-deductible fee on entities that sell branded prescription drugs or biologics to specified government programs in the United States;
- expanded the 340B drug discount program (excluding orphan drugs), including the creation of new penalties for non-compliance; and
- included a 50% point-of-sale discount off negotiated prices on applicable brand-name drugs for Medicare Part D participants in the coverage gap, or "donut hole," as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D.

Other legislative and regulatory changes have also been proposed and adopted in the United States since the enactment of the Affordable Care Act. On August 2, 2011, the Budget Control Act of 2011 created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These automatic reductions included aggregate reductions of Medicare payments to providers of 2%. These reductions went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2024 unless additional Congressional action is taken.

In addition, legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. Increased scrutiny by the U.S. Congress of the FDA's approval process may subject us to more stringent product labeling and post-marketing testing and other requirements, and delays in feedback from the FDA may affect our ability to update or adjust our label in a timely manner in the interest of patient adherence and tolerability. We cannot predict whether other legislative changes will be adopted or how such changes would affect the pharmaceutical industry generally and the commercialization of PROCYSBI or any future product candidate specifically.

We are subject, directly and indirectly, to federal and state healthcare fraud and abuse laws, false claims laws, physician payment transparency laws, corrupt practices and bribery laws and health information privacy and security laws. Failure to comply with these laws may subject us to substantial penalties.

We do not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid or other third-party payors. However, federal and state healthcare laws and regulations pertaining to fraud and abuse, physician payment transparency, privacy and security laws and regulations may apply to us depending on programs we operate and have been asserted by the government and others to apply to companies like us, and our arrangements with healthcare providers, customers and other entities, including our marketing practices, educational programs and pricing policies. These laws include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in exchange for or to induce either the referral of an individual for, or the purchase, order or recommendation of, any good or service for which payment may be made under federal healthcare programs, such as the Medicare and Medicaid programs. The Affordable Care Act amended the federal Anti-Kickback Statute to provide that a person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act;
- federal false claims laws, including, without limitation, the False Claims Act, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid or other federal third-party payors that are false or fraudulent, such as engaging in improper promotion of products or submitting inaccurate price reports to the Medicaid Drug Rebate program;

- the federal Civil Monetary Penalties law, which prohibits, among other things, offering or transferring remuneration to a federal healthcare beneficiary that a person knows or should know is likely to influence the beneficiary's decision to order or receive items or services reimbursable by the government from a particular provider or supplier;
- federal criminal laws that prohibit executing a scheme to defraud any federal healthcare benefit program or making false statements relating to healthcare matters; Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it to have committed a violation;
- the federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, which governs the conduct of certain electronic healthcare transactions and protects the security and privacy of protected health information held by certain covered entities and their business associates;
- the federal Physician Payment Sunshine Act, which requires manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually to CMS information related to payments or other "transfers of value" made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, and requires applicable manufacturers and group purchasing organizations to report annually to CMS ownership and investment interests held by the physicians described above and their immediate family members and payments or other "transfers of value" to such physician owners (manufacturers are required to submit reports to CMS by the 90th day of each calendar year);
- in the EEA, in various member states including France, the United Kingdom, the Netherlands, Italy and Spain, rules adopted by the legislature or self-regulatory industry bodies requiring the notification and/or publication of certain transfers of value from pharmaceutical companies to healthcare professionals (for example, France has recently adopted legislation (Law No. 2011-2012, or the "French Sunshine Act," and Decree no. 2013-414 which implements it) requiring pharmaceutical companies to disclose and publish agreements with or transfers of value to healthcare professionals);
- anti-bribery and anti-corruption laws, such as the U.S. Foreign Corrupt Practices Act (the "FCPA"), which prohibits corporations and individuals from corruptly paying, offering or promising to pay, or authorizing the payment of anything of value, directly or indirectly, to any foreign government official, political party or party official, or political candidate in an attempt to improperly influence a person working in an official capacity or secure an improper advantage, and which also requires companies to keep accurate books and records and maintain an adequate system of internal accounting controls; the UK Bribery Act, which prohibits both domestic and international bribery, as well as bribery across both public and private sectors; bribery provisions contained in the German Criminal Code, which, pursuant to draft legislation being prepared by the German government, may make the corruption and corruptibility of physicians in private practice and other healthcare professionals a criminal offense; and
- analogous state and foreign law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payor, including commercial insurers; state laws that require pharmaceutical companies to comply with the industry's voluntary compliance guidelines and the applicable compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

The risk of our being found in violation of these laws is increased by the fact that many of them have not been fully interpreted by the regulatory authorities or the courts, and their provisions are open to a variety of interpretations. In addition, as we expand our development and commercialization activities outside of the United States, we will need to establish and expand business relationships with various third parties, such as independent contractors, distributors, vendors, consultant, advocacy groups and physicians, and we will interact more frequently with foreign officials, including regulatory authorities and physicians employed by state-run healthcare institutions who may be deemed to be foreign officials under the FCPA, the UK Bribery Act or similar laws of other countries that may govern our activities. Any interactions with any such parties or individuals where compensation or anything of value is provided that are found to be in violation of such laws could result in significant civil and criminal penalties.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available under such laws, it is possible that some of our business activities, including our relationships with physicians and other healthcare providers, some of whom recommend, purchase and/or prescribe our products, and the manner in which we promote our products, could be subject to challenge under one or more of such laws. We are also exposed to the risk that our employees, independent contractors, principal investigators, consultants, vendors, distributors and CROs may engage in fraudulent or other illegal activity. While we have policies and procedures in place prohibiting such activity, misconduct by these parties could include, among other infractions or violations,

intentional, reckless and/or negligent conduct or unauthorized activity that violates FDA requirements, including those laws that require the reporting of true, complete and accurate information to the FDA, manufacturing standards, federal and state healthcare fraud and abuse laws and regulations, laws that require the true, complete and accurate reporting of financial information or data or other commercial or regulatory laws or requirements. It is not always possible to identify and deter misconduct by our employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If our operations are found to violate any of the laws described above or any other laws and regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, disgorgement, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs and imprisonment of officers involved, any of which could adversely affect our ability to market our current and any future products, once approved, and materially adversely affect our business, results of operations and financial condition. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. See also the risk factor titled "*If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs in the United States, we could be subject to additional reimbursement requirements, penalties, sanctions and fines, which could have a material adverse effect on our business, results of operations and financial condition.*"

Our reliance on third parties may result in delays in completing, or a failure to complete, preclinical testing, clinical trials or regulatory marketing submissions.

In the course of product development, we engage and collaborate with a variety of external organizations to perform services essential to drug product development. The organizations which perform services may include, but are not limited to: governmental agencies and university laboratories; other biotechnology and pharmaceutical companies; CMOs; CROs; distribution and supply (logistics) service organizations; contract testing organizations; consultants or consulting organizations with specialized knowledge based expertise; and intellectual property law firms.

As a result of our engagement of these types of organizations to help us with our product development programs, many important aspects of our business are and will be out of our direct control. Nevertheless, we are responsible for ensuring that each of our product development programs complies with applicable regulatory requirements, and our reliance on these organizations does not relieve us of our regulatory responsibilities. If any such organizations we engage in the future fail to perform their obligations under our agreements with them or fail to perform in a satisfactory manner in compliance with applicable regulatory requirements, we may face delays in completing our development and commercialization processes for any of our drug product candidates and could be required to repeat testing or clinical trials, which would delay the regulatory approval process. Furthermore, any loss or delay in obtaining contracts with such entities may also delay the completion of our clinical trials, regulatory filings and the potential market approval of our drug product candidates.

Specifically, we have and will continue to rely on third parties, such as CROs and/or co-operative groups, to assist us in overseeing and monitoring clinical trials as well as to process the clinical results. Any failure of such third parties to perform or to meet the applicable standards will result in delays in or failures to complete trials. A failure by such third parties to observe the terms of a product development program for any particular product candidate or to complete the clinical trials for a product candidate in the anticipated time frame could materially adversely affect our business, results of operations and financial condition.

In addition, our dependence on collaborative arrangements with third parties subjects us to a number of risks that could harm our ability to develop and commercialize products:

- collaborative arrangements might not be available on terms which are reasonably favorable to us, or at all;
- disagreements with partners may result in delays in the development and marketing of products, termination of collaboration agreements or time consuming and expensive legal action;
- agreement terms may be difficult or costly to enforce;
- partners may not allocate sufficient funds or resources to the development, promotion or marketing of our product candidates, or may not perform their obligations as expected;
- partners may choose to develop, independently or with other companies, alternative products or treatments, including products or treatments which compete with ours;
- agreements with partners may expire or be terminated without renewal, or partners may breach agreements with us;

- business combinations or significant changes in a partner's business strategy or financial resources might adversely affect that partner's willingness or ability to fulfill its obligations to us; and
- the terms and conditions of the relevant agreements may no longer be suitable.

We cannot guarantee that we will be able to negotiate acceptable future collaboration agreements or that those currently in existence will make it possible for us to fulfill our objectives.

We depend on the support of key scientific and medical collaborators.

We must establish and maintain relationships with key opinion leaders, leading scientists and research institutions. We believe that such relationships are critical to research and development and developing products that may become standard of care for their approved indications. Although we have various medical and scientific advisors and research collaborations, there is no assurance that our advisors and our research collaborators will continue to work with us or that we will be able to attract additional advisors or collaborators. If we are not able to maintain existing or establish new clinical and scientific relationships to assist in our research and development and commercialization efforts, we may not be able to establish our products as the standard of care or successfully develop our drug product candidates.

If we fail to maintain an effective system of internal controls, we may not be able to accurately report our financial results and prevent fraud.

The Sarbanes-Oxley Act of 2002 (the "Sarbanes-Oxley Act") requires, among other things, that we maintain effective internal control over financial reporting and disclosure controls and procedures. In particular, we must perform system and process evaluation and testing of our internal control over financial reporting to allow management to report on the effectiveness of our internal control over financial reporting, as required by Section 404 of the Sarbanes-Oxley Act. During its evaluation of the effectiveness of internal control over financial reporting as of December 31, 2014, management identified a material weakness related to our inventory costing and overhead allocations for our commercial product PROCYSBI and determined that our review of our inventory costing and overhead allocations were not performed at a sufficiently detailed level to detect errors in our inventory and related accounts. With the oversight of management and our Audit Committee, we have initiated actions to address the root causes of the material weakness identified in 2014. Based on the results of management's internal controls assessment during 2015, it considers the material weakness to be remediated (in the fourth quarter of 2015) once testing of these controls were operational long enough to enable management to conclude they were operating effectively. There can be no assurance that additional material weaknesses or other control or significant deficiencies will not be identified in the future. If we fail to maintain improved controls, such circumstances could cause us to fail to meet our periodic reporting obligations or result in material misstatements in our financial statements or adversely affect the results of periodic management evaluations and annual auditor attestation reports. We could be required to restate our financial results. Each of the foregoing results could cause stockholders to lose confidence in our reported financial information and lead to a decline in our stock price or to stockholder litigation.

We may be subject to product liability claims.

The nature of our business exposes us to potential liability risks inherent in the testing (including through human trials), manufacturing and marketing of drugs. Our products and our drug product candidates could potentially harm people, and we may be subject to costly and damaging product liability claims regardless of actual harm. Many of the participants in our clinical trials, cystinosis patients and cystic fibrosis patients are already critically ill or suffering from chronic debilitating diseases. The waivers we obtain from participants in clinical trials may not be enforceable and may not protect us from liability or the costs of product liability litigation.

The active ingredient in QUINSAIR, levofloxacin, is currently subject to several pending product liability claims. We may have to defend against liability claims related to QUINSAIR or any other of our products in the future. Although we currently carry product liability insurance, it may not be sufficient to cover all or a significant amount of any claims. We may be unable to maintain product liability insurance in the future at satisfactory rates or in adequate amounts. Regardless of the merits or eventual outcome, product liability claims may result in decreased demand for our product candidates, injury to our reputation, withdrawal of clinical trial participants and inability to continue clinical trials, costs to defend the related litigation, diversion of management's time, substantial monetary awards to trial participants, or patients, regulatory investigations, product recalls or withdrawals, labeling, marketing or promotional restrictions and loss of revenue, any of which may materially adversely affect our business, results or operations and financial condition.

Our success depends on our ability to manage our projected growth.

Our business strategy, including continued commercial sales of PROCYSBI in the United States and certain countries in the EEA, the launch of QUINSAIR in Canada and Europe, expansion of our commercial operations into other markets, the continuation of our clinical-stage programs and the in-license and acquisition of additional clinical-stage product candidates, will require us to retain existing and add required new qualified and experienced personnel in multiple functional areas over the next several years.

Our management may need to divert a substantial disproportionate amount of its attention away from our critical other activities to devote the necessary amount of time to managing these growth activities. We may not be able to manage the expansion of our operations effectively, which may result in weaknesses in our infrastructure, operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could require significant capital expenditures, which we may not be able to fund or otherwise finance on reasonable terms or at all and may divert financial resources from other projects, including additional product candidates.

In connection with the commercial launch of PROCYSBI in new territories in the EEA and the planned launch of QUINSAIR in Europe, we expect to continue to expand our operations and add personnel in Europe. We may encounter difficulties successfully managing remotely a substantially larger and internationally diverse organization and may encounter delays in commercialization if we are not successful in integrating our international operations. Challenges related to managing international operations may arise from staffing and managing foreign operations, reduced or varied protection for intellectual property rights in some countries, potential strain on our financial and managerial controls and reporting systems and procedures, diverse individual country regulatory and statutory laws, the costs of maintaining EEA presence, in-country legal entities and related tax structures, fluctuations in currency exchanges and political and economic instability, including wars, terrorism and political unrest, boycotts, curtailment of trade and other business restrictions.

If our management is unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate revenue could be reduced and we will not be able to fully implement our business strategy.

Our dependence on key executives and scientists could impact the development and management of our business.

We are highly dependent upon our ability to attract and retain qualified scientific, technical and managerial personnel. There is intense competition for qualified personnel in the pharmaceutical and biotechnology industries, and we cannot be sure that we will be able to continue to attract and retain the qualified personnel necessary, particularly as business prospects change, for the development and management of our business. Although we do not believe the loss of one individual would materially harm our business, our business might be harmed by the loss of the services of multiple existing personnel, as well as the failure to recruit additional key scientific, technical and managerial personnel in a timely manner. Much of the know-how we have developed resides in our scientific and technical personnel and is not readily transferable to other personnel.

Credit risks from customers outside the United States may materially adversely affect our business, results of operations and financial condition.

Sales of our products to government supported customers outside of the United States are likely to be subject to significant payment delays due to government funding and reimbursement practices, which will result in an increase in the length of time that we may have accounts receivable outstanding. In addition, many governments in Europe are facing significant liquidity crises. If government reimbursement for sales of our products in EEA countries is delayed or becomes unavailable, we may not be able to collect on amounts payable to us in reasonable time frames from such customers, which would cause our capital requirements to increase and would materially adversely affect our business, results of operations and financial condition.

Macroeconomic conditions could materially adversely affect our business, results of operations and financial condition.

Various macroeconomic factors, such as changes in inflation, interest rates, foreign currency exchange rates and overall business and economic conditions and uncertainties, including those resulting from conditions in the global financial markets or changes in political and/or public policy climate, could adversely affect our business, results of operations and financial condition. For example, if inflation or other factors were to significantly increase our business costs, it may not be feasible to increase the price of our current or any future products due to reimbursement procedures and other pricing pressures.

In the recent past, the global financial crisis caused financing to be unavailable in many cases or caused the cost of financing to significantly increase. More recent, disruptions in the financial markets related to concerns of slowing economic growth in and trade with China, slow GDP growth in the United States and even lower rates in Europe, drops in commodity prices, especially the drop in crude oil prices, among other factors, and any similar future disruptions may increase uncertainty and decrease risk tolerance in the

debt and equity markets, which may adversely affect our ability to access financing on favorable terms in the future. In addition, our suppliers, manufacturers and other third parties important to our business also may be negatively affected by such potential market dislocations and disruptions, and their businesses may be disrupted, which could materially adversely affect our business, results of operations and financial condition.

Our product sales in the United States could be reduced by imports from countries where our products are available at lower prices.

Our recognized product sales in the United States may be reduced if PROCYSBI is imported into the United States from lower-priced markets, whether legally or illegally. In the United States, prices for pharmaceuticals are generally higher than in the bordering nations of Canada and Mexico. There have been proposals to legalize the import of pharmaceuticals from outside the United States. If such legislation were enacted, our revenues could be reduced, and our business, results of operations and financial condition could be materially adversely affected.

Our international sales and operating expenses are subject to fluctuations in currency exchange rates.

A portion of our business is conducted in currencies other than our reporting currency, the U.S. dollar. We recognize foreign currency gains or losses arising from our operations in the period in which we incur those gains or losses. As a result, currency fluctuations between the U.S. dollar and the currencies in which we do business cause foreign currency translation gains and losses. Because of the number of currencies that may be involved as we enter new markets, the variability of currency exposures and the potential volatility of currency exchange rates, we may suffer significant foreign currency translation and transaction losses due to the effect of exchange rate fluctuations. We have not entered into derivative instruments to offset the impact of foreign exchange fluctuations. Given the volatility of exchange rates, there is no assurance that we will be able to effectively manage currency transaction and/or conversion risks.

We may engage in strategic transactions, in addition to the QUINSAIR acquisition, that could affect our liquidity, increase our expenses and present significant challenges in focus and energy to our management or prove not to be successful.

From time to time, we may consider additional strategic transactions, such as acquisitions of companies, other asset purchases and out-licensing or in-licensing of intellectual property, products or technologies. Pursuant to the asset purchase agreement for the QUINSAIR acquisition, we paid $35,370,000 in cash consideration upon closing of the transaction (subject to certain deductions), and issued 3,448,001 in shares of our common stock at our election. The transaction consideration also includes contingent payments of up to $350.0 million associated with development, regulatory and commercial milestones, up to $50.0 million of which is payable in our common stock at our election, and a single digit royalty on future global net sales. In the event of a change of control of our company under certain circumstances, a portion of these contingent payments must be prepaid by the acquirer in cash. In addition, we will have single-digit contingent royalty obligations to two additional parties involved in QUINSAIR's development. Additional potential transactions that we may consider include a variety of business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and investments. The QUINSAIR acquisition and any future transactions could result in potentially dilutive issuances of our equity securities, including our common stock, or the incurrence of debt, contingent liabilities, amortization expenses or acquired in-process research and development expenses, any of which could harm our business, financial condition and results of operations. Future acquisitions may also require us to obtain additional financing, which may not be available on favorable terms or at all. Our ability as an organization to integrate acquisitions is relatively unproven. The QUINSAIR acquisition did not involve the acquisition of a workforce, as no employees were involved in the transaction. The QUINSAIR acquisition and any future transactions may entail numerous operational and financial risks, including exposure to unknown liabilities; disruption of our business and diversion of our management's time and attention in order to develop acquired products or technologies or to conduct business in new markets; use of existing cash reserves, dilutive issuances of equity securities to replenish cash requirements or to directly pay for transactions, or incurrence of substantial debt to pay for acquisitions; higher-than-expected acquisition and integration costs; increases in near- and long-term expenditures; unexpected difficulties or shortcomings in the development or commercialization of QUINSAIR and any other acquired assets, products or businesses; write-downs of assets or goodwill or impairment charges; increased amortization expenses; difficulty and cost in combining the operations and personnel of any future acquired businesses with our operations and personnel; impairment of relationships with key suppliers or customers of any acquired businesses due to changes in management and ownership; and inability to retain key employees of any acquired businesses. We may not realize the anticipated benefits of the QUINSAIR acquisition or any future transactions.

Accordingly, although we cannot assure you that we will undertake or successfully complete any transactions of the nature described above, the QUINSAIR acquisition and any other future transactions that we do complete may be subject to the foregoing or other risks and could have a material adverse effect on our business, results of operations and financial condition.

Our business involves the use of hazardous materials, and we and our third-party manufacturers and suppliers must comply with environmental laws and regulations, which can be expensive and restrict how we do business.

Our research and development activities and those of our third-party manufacturers and suppliers involve the controlled storage, use and disposal of hazardous materials, including components of our product and product candidates and other hazardous compounds. We and our manufacturers and suppliers are subject to laws and regulations governing the use, manufacture, storage, handling and disposal of these hazardous materials. In some cases, these hazardous materials and various wastes resulting from their use are stored at our and our manufacturers' facilities pending their use and disposal. We cannot eliminate the risk of contamination, which could cause an interruption of our commercialization efforts, research and development efforts and business operations, environmental damage resulting in costly clean-up and liabilities under applicable laws and regulations governing the use, storage, handling and disposal of these materials and specified waste products. Although we believe that the safety procedures utilized by our third-party manufacturers for handling and disposing of these materials generally comply with the standards prescribed by these laws and regulations, we cannot guarantee that this is the case or eliminate the risk of accidental contamination or injury from these materials. In such an event, we may be held liable for any resulting damages and such liability could exceed our resources and state or federal or other applicable authorities may curtail our use of certain materials and/or interrupt our business operations. We do not currently carry biological or hazardous waste insurance coverage. Furthermore, environmental laws and regulations are complex, change frequently and have tended to become more stringent. We cannot predict the impact of such changes and cannot be certain of our future compliance.

Significant disruptions of information technology systems or breaches of data security could materially adversely affect our business, results of operations and financial condition.

We are increasingly dependent on information technology systems and infrastructure to operate our business. In the ordinary course of our business, we collect, store and transmit large amounts of confidential information, including intellectual property, proprietary business information and personal information. It is critical that we do so in a secure manner to maintain the confidentiality and integrity of such confidential information. We have also outsourced elements of our information technology infrastructure, and as a result a number of third-party vendors may or could have access to our confidential information. The size and complexity of our information technology systems, and those of third-party vendors with whom we contract, make such systems potentially vulnerable to breakdown, malicious intrusion, security breaches and other cyber-attacks. In addition, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information, trade secrets or other intellectual property. The costs to us to eliminate or alleviate network security problems, bugs, viruses, worms, malicious software programs and security vulnerabilities could be significant, and while we have implemented security measures to protect our data security and information technology systems, our efforts to address these problems may not be successful, and these problems could result in unexpected interruptions, delays, cessation of service and other harm to our business. Despite the extensive measures we may take to secure data and our information technology systems, a determined hacker or other bad actor may still breach these security measures and our information technology systems. Moreover, if a computer security breach affects our systems or results in the unauthorized release of personally identifiable information, our reputation could be materially damaged. In addition, such a breach may require notification to governmental agencies, the media or individuals pursuant to various federal and state privacy and security laws, if applicable, including the Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Clinical Health Act of 2009, and its implementing rules and regulations, as well as regulations promulgated by the Federal Trade Commission and state breach notification laws. We would also be exposed to a risk of loss or litigation and potential liability, which could materially adversely affect our business, results of operations and financial condition.

Business disruptions from the occurrence of a catastrophic disaster could cause damage to our facilities and equipment or that of our third-party manufacturers or suppliers.

Our executive offices and laboratory facility are located in the San Francisco Bay Area near known earthquake fault zones and are vulnerable to significant damage from earthquakes. We and our contract manufacturers and source suppliers of raw materials and critical services are also vulnerable to damage from other types of disasters, including fires, storms and other extreme weather conditions, floods, water shortages, power losses, telecommunications failures, outbreaks of disease and similar events. If such a disaster were to occur, our ability to continue our operations, including commercial sales and product development programs, could be seriously, or potentially completely, impaired. The insurance we maintain may not be adequate to cover our losses resulting from disasters or other business interruptions, and we may not be able to maintain insurance in the future at satisfactory rates or in adequate amounts.

Risks Related to Intellectual Property and Competition

If we are unable to protect adequately our proprietary technology, we may not be able to compete as effectively, and our business, results of operations and financial condition will be materially adversely affected.

Our success depends significantly on our ability to protect our proprietary technology from unauthorized use by third parties. We will be able to obtain such protection only to the extent our products are covered by valid and enforceable patents or trade secrets. Any non-confidential disclosure to or misappropriation by third parties of our confidential or proprietary information could enable competitors to erode our competitive position in the market. Where we elect to pursue patent protection on our proprietary technology, we file, prosecute and maintain patent applications covering certain aspects of our technology. Patent protection may not be available, however, for some of the drug product candidates we are developing. We are required to spend significant time and money obtaining, maintaining and enforcing our patent rights, designing around patents held by others and obtaining licenses to third-party patents or other proprietary rights that cover aspects of our product candidates. The patent application process, also known as patent prosecution, is expensive and time consuming. It is possible that we or our current licensors, or any future licensors or licensees, may not be able to prepare, file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner or identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection on them. If our current licensors, or any future licensors or licensees, are not fully cooperative or disagree with us regarding any aspect of the prosecution, maintenance or enforcement of the patent rights covering our product candidates where they have decision-making rights on such matters, our preferred approach may not be followed and the scope, strength, duration or other aspects of such patent rights could be compromised.

In addition, our patents and applications or those of our licensors may not be prosecuted and enforced in a manner consistent with the best interests of our business. Defects in form in the preparation or filing of our patents or patent applications or those of our licensors may adversely affect proper priority claims, inventorship, claim scope or patent term adjustments. As a result, the patent rights we depend upon to protect our technology may be held invalid or unenforceable or may be limited in scope. Moreover, we cannot assure you that all of the patent applications that we own or license will issue as patents or that, if issued, the claims of such patents will be held valid or enforceable or will have a scope that will be advantageous to us.

The rights granted to us under the issued patents, as well as those that may be granted on pending patent applications that we own or license, may not be of sufficient scope or strength to provide us with any meaningful protection or commercial advantage. In such case, competitors may be able to design around our patents or develop products that provide outcomes comparable to ours without infringing on our intellectual property rights. In addition, we may in the future be subject to claims by our former employees or consultants asserting an ownership right in our patents or patent applications as a result of the work they performed on our behalf. Although we generally require all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to assign or grant similar rights to us under their inventions arising while working for us, we cannot be certain that we have executed such agreements with all who may have contributed to our inventions and intellectual property, nor can we be certain that our agreements with such parties will not be breached.

If any of our patents or those of our licensors are challenged, invalidated or legally circumvented by third parties, and if we do not own other enforceable patents or otherwise have regulatory exclusivity protecting our products, competitors could market products and use processes that are substantially similar to, or superior to, ours, and our business will suffer. Any of these outcomes could impair our ability to succeed against competition from third parties and materially adversely affect our business, results of operations and financial condition.

Our patents, even if issued, may not afford us the degree of protection we require to maintain a competitive advantage.

We own or license issued U.S. and foreign patents and pending U.S. and foreign patent applications related to certain of our drug product candidates and our other technologies. Evaluating the strength of patents covering our products candidates and other technologies in the biopharmaceutical field involves complex legal and scientific questions and can be highly uncertain. While we also rely on orphan drug exclusivity for PROCYSBI for commercial protection, the degree of patent protection we require may be unavailable or severely limited in some cases and may not adequately protect our products or permit us to gain or keep any competitive advantage. For example, the patent applications that we own or license may fail to result in issued patents in the United States or in other countries. Even if patents do issue on such patent applications, third parties may challenge the validity, enforceability or scope thereof, which may result in such patents being narrowed, invalidated or held unenforceable. For example, U.S. patents can be challenged by any person before the U.S. Patent and Trademark Office ("USPTO") Patent Trial and Appeal Board ("PTAB"). Patents granted by the European Patent Office may be similarly opposed by any person within nine months from the publication of the grant. Similar proceedings are available in other jurisdictions, and in the United States, Europe and other jurisdictions, third parties can raise questions of validity with a patent office even before a patent has granted. See also the risk factor titled "*Changes to the patent law in the United States and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products.*"

While we currently have five patents identified in the FDA Orange Book for PROCYSBI, in 2015 we requested that the FDA remove one of our patents from the FDA Orange Book. If a third party such as a generic drug company decided to file an abbreviated new drug application ("ANDA") for a generic version of PROCYSBI, that third party would not be required to provide a statement that the specific patent we requested be removed from the FDA Orange Book is invalid or would not be infringed upon by the manufacture, use or sale of the drug product for which the ANDA is submitted (a "paragraph IV certification") with respect to that specific patent. However, the third party would be obligated to submit an appropriate certification against the five other patents currently listed in the Orange Book for PROCYSBI as well as any additional patents that, if issued, may be listed in the future. While PROCYSBI has received exclusive marketing rights as an orphan drug for the treatment of nephropathic cystinosis in the United States into 2020 for adults and into 2022 for pediatric patients two to six years of age and therefore has commercial protection on that basis, the FDA can subsequently approve a drug for the same conditions as PROCYSBI under certain circumstances See also the risk factor titled "*If we fail to maintain orphan drug or other regulatory exclusivity for our products or to obtain and maintain exclusivity for our orphan drug product candidates, our competitors may sell products to treat the same conditions, possibly at lower prices, and our revenues will be significantly reduced.*"

Even if they are unchallenged, our patents and patent applications, if granted, may not adequately protect our product candidates or technology or prevent others from designing around our patent claims. For example, a third party may develop a competitive product that provides therapeutic benefits similar to one or more of our product candidates but that falls outside the scope of our patent protection. If the breadth or strength of protection provided by the patents and patent applications we own or license covering our product candidates is successfully challenged, then our ability to commercialize such product candidates could be adversely affected, and we may face unexpected competition that may materially adversely affect our business, results of operations and financial condition.

In addition, competitors may interfere with our success in obtaining and maintaining patent protection for our product candidates and technologies in a variety of ways. Competitors may claim that they invented the claimed invention prior to us or our licensors or may file patent applications before we or our licensors do. For example, because patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we or our licensors were the first to file any patent application related to a product candidate. Furthermore, if third parties have filed such patent applications, for patent applications filed before March 2013 in the United States an interference proceeding in the United States can be initiated by a third party to determine who was the first to invent any of the subject matter covered by the patent claims of our applications.

Competitors may also claim that we are infringing on their patents and that we therefore cannot develop or commercialize our product candidates or practice our technology. Competitors may also challenge our patents, if issued, by showing the USPTO or a court that the invention claimed was not novel, was obvious or is not valid for a number of other reasons. If the USPTO or a court agrees, we could lose some or all of our rights to the challenged patents. Competitors may also initiate validity challenges to our patents at the USPTO PTAB. See also the risk factor titled "*Changes to the patent law in the United States and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products.*"

Furthermore, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after it is filed. Various extensions may be available; however, the life of a patent, and the protection it affords, is limited. Thus, if we encounter delays in regulatory approvals, the period of time during which we could market a product candidate under patent protection could be reduced. Without adequate and continuing patent protection for our product candidates and technologies, we may be open to competition from generic versions of such products and competitive versions of our technologies.

If we do not obtain, or if we lose, adequate patent protection for our product candidates, and if we do not have other regulatory exclusivity for such product candidates, others may develop and commercialize products that are the same as, or similar to, our product candidates, which would adversely affect our business, results of operations and financial condition.

We may in the future become involved in lawsuits to defend against third-party allegations of infringement or to protect or enforce our intellectual property, which could be expensive, time consuming and unsuccessful and have a material adverse effect on our business, results of operations and financial condition.

The drug product and biopharmaceutical industry has been characterized by frequent and extensive intellectual property litigation. Our competitors or other third-party patent holders may assert that our products are covered by their patents. Although we believe we have adequate defenses available if faced with any allegations that we infringe third-party patents, we cannot be certain that we do not infringe on those patents or that we will not infringe on patents granted in the future. Furthermore, because patent applications can take many years to issue and may be confidential for 18 months or more after filing, and because pending patent claims can be revised before issuance, there may be applications now pending which may later result in issued patents that may be infringed by the manufacture, use or sale of our products. If a patent holder believes our drug product infringes on its patent, the patent holder may sue us even if we have received patent protection for our technology. Moreover, we may face patent infringement claims

from non-practicing entities that have no relevant product revenue and against whom our own patent portfolio may thus have no deterrent effect. If our products are found to infringe, we could be prevented from manufacturing or marketing those products.

In addition, competitors may infringe our patents or misappropriate or otherwise violate our intellectual property rights. To stop any such infringement or unauthorized use, litigation may be necessary. If we or one of our licensors were to initiate legal proceedings against a third party to enforce a patent, the defendant could seek to have the patent's validity reviewed through PTAB proceedings or counterclaim that our patent is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements for patent issuance, including lack of novelty, obviousness or enablement. Patents may be unenforceable if someone connected with prosecution of the patent withheld relevant information from the USPTO or made a misleading statement during prosecution. The outcomes of proceedings involving assertions of invalidity and unenforceability are unpredictable. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability of our patents covering one of our product candidates or technologies, we would lose at least part, and perhaps all, of the patent protection on such product candidates or technologies. Such a loss of patent protection would materially adversely affect our business, results of operations and financial condition, particularly if we do not have other regulatory protection. Moreover, our competitors could counterclaim in any suit to enforce our patents that we infringe their intellectual property.

Third parties may initiate legal proceedings against us to challenge the validity or scope of our intellectual property rights or may allege an ownership right in our patents resulting from their past employment or consultancy with us. Many of our current and potential competitors have the ability to dedicate substantially greater resources to defend their intellectual property rights than we can. Accordingly, despite our efforts, we may not be able to prevent third parties from claiming an ownership interest in or infringing upon or misappropriating our intellectual property. Competing products may also be sold in other countries in which our patent coverage might not exist or be as strong. If we lose a foreign patent lawsuit alleging our infringement of a competitor's patents, we could be prevented from marketing our product candidates in one or more foreign countries.

Litigation related to infringement or misappropriation of a third parties' intellectual property rights, with or without merit, is unpredictable, is generally expensive and time consuming and can divert management's attention from our core business. If we do not prevail in any litigation in which we are alleged to have infringed or misappropriated intellectual property rights, a court could require us to pay substantial damages, treble damages and attorneys' fees and could prohibit us from using technologies essential to our product candidates, any of which would have a material adverse effect on our business, results of operations and financial condition. If patents asserted against us are upheld as valid and enforceable and we are found to infringe them, we could be prevented from selling our product candidates or technologies unless we can obtain licenses to use the technology or ideas covered by such patents. We do not know whether any necessary licenses would be available to us on satisfactory terms, if at all. If we cannot obtain such licenses, we could be forced to design around the infringed patents at additional cost or to abandon the infringing product candidate or technology altogether. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the market price of our common stock. As a result, our ability to grow our business and compete in the market may be harmed.

We may also support and collaborate in research conducted by government organizations, hospitals, universities or other educational institutions. These research partners may be unwilling to grant us any exclusive rights to technology or product candidates derived from these collaborations. If we do not obtain required licenses or rights, we could encounter delays in our product development efforts while we attempt to design around other patents or even be prohibited from developing, manufacturing or selling drug product candidates requiring these licenses. There is also a risk that disputes may arise as to the rights to technology or drug product candidates developed in collaboration with other parties. Any such disputes may cause our competitive position to be adversely affected and may materially adversely affect our business, results of operations and financial condition.

Obtaining and maintaining patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. In addition, periodic maintenance fees on issued patents often must be paid to the USPTO and foreign patent agencies over the lifetime of the patent. While an unintentional lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we or our licensors fail to maintain the patents and patent applications

covering our product candidates or technologies, we may not be able to prevent a competitor from marketing products that are the same as or similar to our products, which would have a material adverse effect on our business, results of operations and financial condition, particularly if we do not have other regulatory protection for our products.

We may not be able to effectively enforce our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on our product candidates and technologies in all countries throughout the world would be prohibitively expensive. The requirements for patentability may differ in certain countries, particularly in developing countries. Moreover, our ability to protect and enforce our intellectual property rights may be adversely affected by unforeseen changes in foreign intellectual property laws. In addition, laws of some countries outside of the United States do not afford intellectual property protection to the same extent as the laws of the United States. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property rights. This could make it difficult for us to stop the infringement of our patents or the misappropriation of our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States. In addition, competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection, if our ability to enforce our patents to stop infringing activities is inadequate. These products may compete with our products, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing. See also the risk factor titled "*Our success depends on our ability to manage our projected growth.*"

Proceedings to enforce our patent rights in foreign jurisdictions, whether or not successful, could result in substantial costs and divert our efforts and resources from other aspects of our business. Furthermore, while we intend to protect our intellectual property rights in major markets for our products, there can be no assurance that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our products. In addition, our efforts to protect our intellectual property rights in such countries may be inadequate.

Changes to the patent law in the United States and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biopharmaceutical companies, our success is heavily dependent on our having valid and enforceable intellectual property rights, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involve both technological and legal complexity and is therefore costly, time consuming and inherently uncertain. Recent patent reform legislation in the United States and other countries, including the Leahy-Smith America Invents Act (the "America Invents Act"), which became effective on September 16, 2012, could increase those uncertainties and costs. The America Invents Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications are prosecuted, redefine prior art and provide more efficient and cost-effective avenues for competitors to challenge the validity of patents. For example, the America Invents Act enacted proceedings involving post-issuance patent review procedures conducted before the PTAB, including inter parties review ("IPR"). The IPR process permits third parties to challenge the validity of a patent on the grounds that it was anticipated or made obvious by prior art, and generic drug manufactures and entities associated with hedge funds have recently begun challenging biopharmaceutical patents with increased frequency based on prior art through the IPR process. Prior art could render our patents or those of our licensors invalid, and the availability of the IPR process as a lower-cost alternative to litigation and faster method for challenging patents could therefore increase the likelihood that our patents or those of our licensors will be challenged and potentially rendered invalid. Moreover, if such challenges occur with respect to our University of California, San Diego ("UCSD") licensed patents, UCSD has the right to control the defense of such proceedings.

In addition, the America Invents Act has transformed the U.S. patent system into a "first to file" system. The first-to-file provisions, however, only became effective on March 16, 2013. Accordingly, it is not yet clear what, if any, impact the America Invents Act will have on the operation of our business. However, the America Invents Act and its implementation could make it more difficult to obtain patent protection for our inventions and increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could materially adversely affect our business, financial condition and results of operations.

The U.S. Supreme Court has ruled on several patent cases in recent years, narrowing the scope of patent protection available in certain circumstances and weakening the rights of patent owners in certain situations. In addition, there have been recent proposals for additional changes to the patent laws of the United States and other countries that, if adopted, could affect our ability to obtain patent protection for our proprietary technology or our ability to enforce our proprietary technology. Depending on future actions by the U.S. Congress, the U.S. courts, the USPTO and the relevant law-making bodies in other countries, the laws and regulations governing

patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

If we are limited in our ability to utilize acquired or licensed technologies, or if we lose our rights to critical in-licensed technology, we may be unable to successfully develop, out-license, market and sell our products, which could prevent or delay new product introductions.

We have acquired and licensed certain proprietary technologies and plan to further license and acquire various patents and proprietary technologies owned by other parties. The agreements in place are critical to our product development programs. For example, most of our patent portfolio pertaining to PROCYSBI and RP103 for cystinosis and other therapeutic indications has been licensed from academic institutions. Our license agreements with these institutions include termination clauses that permit the licensor to terminate our license under certain circumstances, including if we materially breach our obligations under the applicable agreement. We are currently behind in our developmental diligence obligations under our license agreement with UCSD with respect to the development of RP103 for the treatment of NASH and HD. If one or more of our licenses is terminated, we would have no further right to use or exploit the patents, know-how and other intellectual property rights licensed to us under the agreement, which could adversely affect our ability to market PROCYSBI or continue our development programs of RP103 in other clinical indications.

In connection with the QUINSAIR acquisition, we entered into a license to certain patent rights held by PARI Pharma GmbH pertaining to customized PARI nebulizer devices for the administration of QUINSAIR. We will be dependent on PARI to maintain these patents and to prosecute any third-party infringement of them. PARI may limit or terminate our rights under this license in the event that we do not fulfill certain diligence obligations. Our business strategy depends on the successful development of licensed and acquired technologies into commercial products. Therefore, any limitations on our ability to utilize these technologies may impair our ability to develop, out-license or market and sell our product candidates, could delay new product introductions and could adversely affect our reputation, any of which could have a material adverse effect on our business, results of operations and financial condition.

If we are unable to protect the confidentiality of our trade secrets, our competitive position may be harmed, and our business, results of operations and financial condition will be materially adversely affected.

In addition to patent protection, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. Our trade secrets may not be adequately protected, however. We have taken steps to protect our trade secrets and proprietary information, including entering into confidentiality agreements and intellectual property assignment agreements with our employees, consultants, advisors and corporate and educational institution partners. Nevertheless, such agreements may not be enforceable or may not provide meaningful protection for our trade secrets or other proprietary information in the event of unauthorized use or disclosure, whether willful or unintentional, or other breaches of the agreements, and we may not be able to prevent such unauthorized disclosure. Monitoring unauthorized disclosure is difficult, and we do not know whether the steps we have taken to prevent such disclosure are, or will be, adequate. In addition, we may not be able to obtain adequate remedies for any such breaches. Enforcing a claim that someone illegally obtained and is using our trade secrets, like patent litigation, is expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the United States may be less willing to protect trade secrets. Our competitors may independently develop equivalent knowledge, methods and know-how. Competitors could purchase our products and attempt to replicate some or all of the competitive advantages we derive from our development efforts, willfully infringe or misappropriate our intellectual property rights, design around our protected technology or develop their own competitive technologies that fall outside of our intellectual property rights. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us.

We may be subject to damages resulting from claims that we or our employees have wrongfully used or disclosed alleged trade secrets of our competitors or are in breach of non-competition or non-solicitation agreements with our competitors.

We could in the future be subject to claims that we or our employees have inadvertently or otherwise used or disclosed alleged trade secrets or other proprietary information of former employers or competitors. Although we try to ensure that our employees and consultants do not use the intellectual property, proprietary information, know-how or trade secrets of others in their work for us, we may in the future be subject to claims that we caused an employee to breach the terms of his or her non-competition or non-solicitation agreement or that we or these individuals have, inadvertently or otherwise, used or disclosed the alleged trade secrets or other proprietary information of a former employer or competitor in breach of their obligations to that employer or competitor. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and could be a distraction to management. If our defenses to these claims fail, in addition to requiring us to pay monetary damages, a court could prohibit us from using technologies or features that are essential to our products, if such technologies or features are found to incorporate or be derived from the trade secrets or other proprietary information of the former employers. An inability to incorporate such technologies or features would have a material adverse effect on our business, and may prevent us from successfully commercializing our products. In addition, we may lose the right to practice valuable intellectual property rights or

personnel as a result of such claims. Moreover, any such litigation or the threat thereof may adversely affect our ability to hire employees or contract with independent sales representatives. A loss of key personnel or their work product could hamper or prevent our ability to commercialize our products. Any of these events, or a combination thereof, could have a material adverse effect on our business, results of operations and financial condition.

Risks Related to Our Financial Position and Capital Requirements

Our commercial operations and clinical development programs will require substantial future funding which will affect our business, results of operations and financial condition.

Our commercial sales program for PROCYSBI, potential commercial program for QUINSAIR and any future approved products and our product development programs will require substantial additional capital, arising from costs incurred to:

- conduct research, preclinical testing and human studies and clinical trials;
- develop and submit regulatory submissions for marketing approvals;
- establish or contract for pilot scale and commercial scale manufacturing processes and facilities;
- obtain adequate reimbursement for our products;
- market and distribute our products; and
- establish, develop and maintain quality control, manufacturing, regulatory, medical, distribution, marketing, sales, finance and administrative capabilities to support these programs.

We base our outlook regarding the need for funds on many uncertain variables. Such uncertainties include the success of our commercial sales of PROCYSBI in the United States, the EEA and any additional markets; the success of our efforts to commercialize QUINSAIR in Europe and Canada and any future approved products; the scope and results of our research initiatives, preclinical testing and human clinical trials; regulatory approvals; the timing of events outside our direct control, such as competing technological and market developments, negotiations with third-party payors and potential strategic partners; and other factors. In addition, certain product programs may require collaborative agreements with corporate partners with greater financial and organizational resources than we have. Such agreements may require substantial time to complete and may not be available in the time frame desired or with acceptable financial terms, if at all. Any of these factors may significantly change the timing and amount of our cash requirements as they determine such one-time events as the receipt or payment of milestone-based and other payments.

If we fail to raise additional financing when needed, we may have to delay or terminate some or all of our research and development programs, scale back our operations and/or reduce our commercial finance and administrative expenses to sustainable levels, which would have a material adverse effect on our business, results of operating and financial condition.

While we believe that, based on current operating plan assumptions, our cash and cash equivalents will be sufficient to fund operations into the first half of 2018, we may need to sell equity or debt securities to raise additional funds to support, among other things, our development and commercialization programs. The sale of additional equity securities or convertible debt securities will result in additional dilution to our stockholders, and newly issued securities may have rights, preferences and privileges senior to those of holders of our common stock. Additional financing may not be available on a timely basis, in amounts or on terms satisfactory to us, or at all. We may be unable to raise additional capital due to a variety of factors, including our financial condition, the status of our research and development programs, the status of regulatory reviews for marketing approvals, the status of our commercialization activities for QUINSAIR and any future approved products, sales of PROCYSBI in existing and additional markets and the general condition of the financial markets and other factors beyond our control, including, but not limited to macro-economic conditions and investors' tolerance for risks related to investments in biotechnology and biopharmaceutical companies that have not achieved cash self-sufficiency or profitability. If we fail to raise additional financing when needed, we may have to delay, partner, or terminate some or all of our research and development programs, scale back our operations and/or reduce our commercial expenses. If such actions are required, our business, results of operations and financial condition will be adversely affected, and the market value of our common stock will likely significantly decline.

Our loan agreement with HC Royalty and outstanding convertible senior notes contain a number of restrictive covenants and other provisions, which, if violated, could result in the acceleration of the payment terms of our outstanding indebtedness, which in turn could have a material adverse effect on our business, results of operations and financial condition.

In December 2012, we entered into the Royalty Loan Agreement. Under the HC Royalty Loan Agreement, we agreed to borrow $50.0 million in two $25.0 million tranches. We drew down the first tranche in the amount of $25.0 million in December 2012 and the second tranche of $25.0 million in May 2013 when we achieved the milestone of U.S. approval of PROCYSBI. In July 2014, we

entered into an amendment and restatement of the original HC Royalty Loan Agreement and borrowed from HC Royalty a third, $10.0 million tranche under the loan facility. Also in July 2014, we issued $60.0 million aggregate principal amount of 8.0% convertible senior notes due 2019 to HC Royalty and other purchasers.

The HC Royalty Loan Agreement includes a number of affirmative and negative covenants, including requirements to use commercially reasonable efforts to exploit PROCYSBI and RP103 in specific markets and to comply with applicable laws, and additional restrictions on mergers, sales of assets, the incurrence of liens, the incurrence of additional indebtedness and transactions with our affiliates, among other requirements. The convertible senior notes also include a number of affirmative and negative covenants, including our obligation to offer to repurchase the notes upon a change of control of our company, limitations on the incurrence of additional indebtedness, registration rights for the holders of the notes and other requirements.

The performance of our obligations under the HC Royalty Loan Agreement is secured by our grant of a security interest to HC Royalty in substantially all of our assets and the assets of our domestic subsidiaries and a pledge of stock of certain of our domestic subsidiaries. Our failure to comply with the terms of the HC Royalty Loan Agreement, the convertible senior notes and related documents could result in an event of default. A change of control of our company, an uncured material adverse effect on our company and certain other specified events could also constitute an event of default under the agreements. In the event of an event of default that is not cured or waived, the payment of all of our indebtedness to HC Royalty and interest thereon and the repayment of the convertible senior notes could accelerate. Under the terms of the security agreement, an event of default could also enable the lender to take possession of, foreclose on, sell, assign or grant a license to use our pledged collateral and to assign and transfer the pledged stock of certain of our subsidiaries. An event of default, a material adverse effect or a change of control would also trigger a prepayment penalty under the HC Royalty Loan Agreement, which would require us to pay a substantially higher amount due than the current balance of our loan.

Any of the events described above, or a combination thereof, could have a material adverse effect on our financial condition and results of operations.

Our cash flows and capital resources may be insufficient to make required payments on our indebtedness.

The required payments of principal and interest on our indebtedness under the HC Royalty Loan Agreement and convertible senior notes may require a substantial portion, or all, of our available cash to be dedicated to the service of these debt obligations. Both the HC Royalty Loan Agreement and the convertible senior notes bear interest at an annual fixed rate of 8.0%. The HC Royalty Loan Agreement also bears a synthetic royalty based on our net revenues from PROCYSBI and other future-approved products in each calendar year. This royalty and the interest under the HC Royalty Loan Agreement and the convertible senior notes are payable quarterly. Principal payments under the HC Royalty Loan Agreement became due beginning in June 2015, and we made our first quarterly principal payment of $3.0 million to HC Royalty in June 2015. The convertible senior notes will mature on August 1, 2019, unless earlier converted, redeemed or repurchased.

There can be no assurance that our business will generate sufficient cash flow or that we will have capital resources in an amount sufficient to enable us to pay our indebtedness to HC Royalty or the holders of the convertible senior notes. Our debt obligations may also limit our flexibility to plan for or react to changes in our business and industry and place us at a competitive disadvantage compared to competitors with superior financial resources including less debt. If our cash flows and capital resources are insufficient to fund these debt service obligations, we may be forced to reduce or delay product development, sales and marketing and capital and other expenditures. We may also be forced to restructure our indebtedness or raise additional capital through the issuance of equity or debt instruments, and there can be no assurance that we will be able to refinance any of our indebtedness or raise additional capital on a timely basis, in sufficient amounts, on satisfactory terms or at all. The terms of the HC Royalty Loan Agreement and convertible senior notes may also limit our ability to pursue any of these financing alternatives, and these alternatives nonetheless may not enable us to meet our scheduled debt service obligations.

Failure to meet our debt service obligations may result in an event of default under the HC Royalty Loan Agreement, which would permit the lender to accelerate the payment of all of our indebtedness to HC Royalty and interest thereon. An event of default could also enable the lender to take possession of, foreclose on, sell, assign or grant a license to use our pledged collateral and to assign and transfer the pledged stock of certain of our subsidiaries. An event of default, a material adverse effect or a change of control would also trigger a prepayment penalty under the HC Royalty Loan Agreement, which would require us to pay a substantially higher amount than the current balance of our loan.

Failure to meet our debt service obligations may also result in an event of default under the convertible senior notes, which would permit the holders to accelerate the payment of the outstanding principal amount of the notes and interest thereon and require us to pay a repayment premium and higher interest. A change of control would also trigger an obligation to repurchase the convertible senior notes.

Any of the events described above, or a combination thereof, could have a material adverse effect on our business, financial condition and results of operations.

Our ability to use our net operating losses to offset future taxable income may be subject to certain limitations.

In general, under Section 382 of the Internal Revenue Code of 1986, as amended, a corporation that undergoes an "ownership change" is subject to limitations on its ability to utilize its pre-change net operating loss carryforwards to offset future taxable income. Our existing net operating loss carryforwards may be subject to limitations arising from previous ownership changes, and if we undergo an ownership change in the future, our ability to utilize our net operating loss carryforwards could be further limited by Section 382. Future changes in our stock ownership, some of which are outside of our control, could result in an ownership change. Furthermore, we may be unable to use a substantial part of our net operating loss carryforwards if we do not attain profitability in an amount sufficient to utilize such losses.

Risks Related to Our Common Stock

Our stock price has been volatile and may continue to be volatile in the future, and our stockholders may not be able to resell shares of our common stock at or above the prices that they paid. The trading volume in our common stock may be relatively low.

Our common stock is quoted on The NASDAQ Global Select Market. The trading price of our common stock has been and may continue to be volatile. During the 52-week period ended December 31, 2015, our average daily trading volume was approximately 1,268,470 shares and the closing sales price per share of our common stock on The NASDAQ Global Select Market ranged from $16.13 to $4.53. Our operating performance, both financial and in the development of approved products, significantly affects the market price of our common stock. A number of factors may affect the market price of our common stock, including:

- the success of our early development work and clinical trials compared to those of others with products similar or related to our products;
- announcements regarding regulatory approvals or approved label indications and patient populations or changes or delays in the regulatory review process;
- unexpected difficulties in commercialization or lower than expected sales;
- lower than expected pricing and reimbursement levels, or no reimbursement at all, for our current and any future products in various markets;
- actions taken by regulatory agencies with respect to our clinical trials, manufacturing supply chain, quality system or sales and marketing activities;
- changes in our relationships with manufacturers, suppliers or collaborators, or our inability to supply enough product to meet demand;
- announcements of new products or innovations by us or our competitors and announcements concerning our competitors or our industry in general;
- our ability to obtain additional funding;
- changes or developments in applicable laws or regulations;
- any intellectual property infringement actions in which we may become involved;
- sales and profitability;
- announcements of significant acquisitions, strategic partnerships, joint ventures, or capital commitments by us, our strategic collaboration partners or our competitors;
- our ability to manage our projected growth;
- actual or anticipated fluctuations in our results of operations;
- changes in financial estimates or recommendations by securities analysts or their ceasing to publish research or reports about our business;
- the trading volume of our common stock;
- general economic and market conditions and overall fluctuations in the U.S. equity markets;

- the appeal and current level of investor interest in the biotechnology/biopharmaceutical capital market sector and in companies in general with business, research strategies and product development pipelines which are similar to us; and
- the loss of any of our key scientific or management personnel.

For planning purposes, we estimate the timing of the accomplishment of various scientific, clinical, regulatory, market launch and commercialization goals, which we sometimes refer to as milestones. These milestones include the completion of reimbursement and pricing negotiations and commercial launches in additional territories, commencement or completion of scientific studies and clinical trials and the submission of regulatory filings. We also prepare estimates of future financial results for planning and budget purposes. From time to time, we may publicly announce the estimated timing of some of these milestones and provide guidance regarding financial results and other metrics. All of these projections will be based on a variety of assumptions. The actual timing of these milestones and actual financial results can vary dramatically compared to our estimates for a number of reasons, including those set forth above, in many cases for reasons beyond our control. If we do not meet the milestones, financial guidance or other expectations as publicly announced or as projected by various security analysts who follow our company, our stockholders or potential stockholders may lose confidence in our ability to meet overall objectives and our financial planning capabilities, and as a result, the market price of our common stock may decline.

In addition, The NASDAQ Global Select Market has, from time to time, experienced extreme price and trading volume fluctuations. The market prices of securities of pharmaceutical, biotechnology and other life sciences companies in a comparable stage to ours historically have been particularly volatile, and trading volume in such securities and our common stock has often been relatively low. Moreover, the stock markets in general have experienced substantial volatility that has often been unrelated or disproportionate to the operating performance of individual companies. During certain periods, the favor of certain industry segments, such as the biotechnology segment, may also be volatile. These changes may affect in particular the market price of our common stock and the stock prices of companies such as ours that do not have conventional measures of financial and business health such as sales, earnings, profitability and related measures. These broad market fluctuations, during which our industry and companies at our stage may experience a stronger degree of market sensitivity, will adversely affect the market price of our common stock. In the past, following periods of volatility in the market resulting in substantial declines in the market price of a company's securities, stockholders have often instituted class action securities litigation against those companies. Such litigation can result in substantial costs and diversion of management attention and resources, which could significantly harm our and reputation and materially adversely affect our business, financial condition and results of operations.

A substantial number of shares of our common stock are eligible for future sale in the public market, and the issuance or sale of equity, convertible or exchangeable securities in the market, including shares issuable upon conversion of our convertible senior notes and shares issuable at our election in satisfaction of payments related to the QUINSAIR acquisition, or the perception of such future sales or issuances, could lead to a decline in the trading price of our common stock.

Any issuance of shares of our common stock or other securities, including for the purposes of raising capital to fund our operations, financing acquisitions and the expansion of our business, will have a dilutive effect on our existing stockholders. In addition, the perceived market risk associated with the possible issuance of a large number of shares of our common stock, including pursuant to the exercise of our currently outstanding stock options, or issuances of securities convertible or exchangeable into a large number of shares of our common stock could cause some of our stockholders to sell their common stock, thus causing the trading price of our common stock to decline. Subsequent sales of our common stock in the open market, exercises of our currently outstanding stock options and the subsequent sale of the shares acquired thereunder or the sale by us of shares of our common stock or securities convertible or exchangeable into our common stock for capital raising purposes could also have an adverse effect on the trading price of our common stock. If our common stock price declines, it will be more difficult for us to raise additional capital or we may be unable to raise additional capital at all.

In July 2014, we issued $60.0 million aggregate principal amount of 8.0% convertible senior notes due 2019. The convertible senior notes are convertible at the option of the holder at an initial conversion rate of approximately 57.14 shares of common stock per $1,000 principal amount of convertible senior notes, which is equivalent to an initial conversion price of $17.50, and is subject to adjustment upon certain events and conditions. In addition, we may redeem for cash or require holders to convert the convertible senior notes into shares of common stock if the price of the common stock is at or above 175% of the applicable conversion price over a period of 30 consecutive trading days. The note purchase agreement governing the convertible senior notes provides the holders with registration rights for the shares issued upon conversion of their convertible senior notes subject to certain conditions, and we filed a registration statement to register the resale of the shares of common stock issuable upon conversion of the convertible senior notes. We may be required to pay increased interest on the convertible senior notes if we do not comply with the registration rights provisions of the note purchase agreement. A substantial number of shares of our common stock are reserved for issuance upon conversion of the convertible senior notes. The issuance of shares of our common stock upon conversion of the convertible senior notes would dilute the ownership interest of our common stockholders and may materially adversely affect the market price of our common stock and impair our ability to raise capital through the sale of additional equity securities.

We issued 3,448,001 shares of our common stock as partial consideration at the closing of the QUINSAIR acquisition. The transaction consideration also includes contingent payments associated with development, regulatory and commercial milestones, up to $350.0 million of which up to $50.0 million is payable in our common stock at our election. In connection with the QUINSAIR acquisition, we entered into a registration rights agreement with respect to the shares of common stock issued at the closing of the acquisition and the additional shares that may be issued as contingent consideration pursuant to the QUINSAIR asset purchase agreement. In October 2015, we filed a registration statement to register the resale of the shares of our common stock issued at the closing of the QUINSAIR acquisition.

In September 2015, we entered into a Sales Agreement with Cowen and Company, LLC ("Cowen") to sell shares of our common stock, with aggregate gross sales proceeds of up to $75.0 million, from time to time, through an "at the market" equity offering program under which Cowen will act as sales agent. No shares have been sold under the Sales Agreement and $75.0 million in shares of common stock remain available for issuance under this program.

In connection with other collaborations, joint ventures, license agreements or future financings that we may enter into in the future, we may issue additional shares of common stock or other equity securities, and the value of the securities issued may be substantial and create additional dilution to our existing and future common stockholders.

Because we do not intend to pay any cash dividends on our common stock, investors will benefit from an investment in our common stock only if it appreciates in value. Investors seeking dividend income should not purchase shares of our common stock.

We have not declared or paid any cash dividends on our common stock since our inception. We anticipate that we will retain our earnings to support our operations and to finance the growth and development of our business and do not expect to pay cash dividends in the foreseeable future. As a result, the success of an investment in our common stock will depend upon any future appreciation in the value of our common stock. There is no guarantee that our common stock will appreciate in value or even maintain its current price. Investors seeking dividend income should not invest in our common stock.

Anti-takeover provisions under Delaware law and in our Certificate of Incorporation and Bylaws, as amended, may prevent or complicate attempts by stockholders to change the Board of Directors or current management and could make a third-party acquisition of us difficult.

Our Certificate of Incorporation and Bylaws, as amended, contain provisions that could significantly reduce the value of our shares to a potential acquiror or delay or prevent changes in control or changes in our management without the consent of our Board of Directors. The provisions in our charter documents include the following:

- the right of our Board of Directors to elect a director to fill a vacancy created by the expansion of the Board of Directors or the resignation, death or removal of a director, which prevents stockholders from being able to fill vacancies on our Board of Directors;
- the required approval of at least 66 2⁄3% of the shares entitled to vote to remove a director without cause;
- the ability of our Board of Directors to authorize the issuance of shares of preferred stock and to determine the price and other terms of those shares, including preferences, dividend rights and voting rights, which may be superior to those of the common stock, without stockholder approval, which could be used to significantly dilute the ownership of a hostile acquiror;
- the ability of our Board of Directors to alter our bylaws without obtaining stockholder approval;
- the required approval of at least 66 2⁄3% of the shares entitled to vote at an election of directors to adopt, amend or repeal our bylaws;
- a prohibition on stockholder action by written consent, which forces stockholder action to be taken at an annual or special meeting of our stockholders;
- the requirement that a special meeting of stockholders may be called only by the Chairman of the Board of Directors, the chief executive officer or the Board of Directors, which may delay the ability of our stockholders to force consideration of a proposal or to take action, including the removal of directors; and
- advance notice procedures that stockholders must comply with in order to nominate candidates to our Board of Directors or to propose matters to be acted upon at a stockholders' meeting, which may discourage or deter a potential acquiror from conducting a solicitation of proxies to elect the acquiror's own slate of directors or otherwise attempting to obtain control of us.

We are also subject to the anti-takeover provisions contained in Section 203 of the Delaware General Corporation Law. Under Section 203, a corporation may not, in general, engage in a business combination with any holder of 15% or more of its capital stock unless the holder has held the stock for three years or, among other exceptions, the Board of Directors has approved the transaction.

Our Board of Directors may use the provisions described above to prevent changes in the management and control of our company. These provisions could limit the price that investors might be willing to pay in the future for shares of our common stock. These provisions would apply even if we were to receive an offer that some stockholders may consider beneficial. Also, under applicable Delaware law, our Board of Directors may adopt additional anti-takeover measures in the future.

Provisions of the note purchase agreement governing our convertible senior notes and the asset purchase agreement for the acquisition of QUINSAIR may discourage a takeover, which could cause the market price of our common stock to decline.

The repurchase rights and related repurchase premium provided in our convertible senior notes and the accelerated contingent payment provisions of the asset purchase agreement for the acquisition of QUINSAIR triggered by the occurrence of a change of control may discourage, delay or prevent a third party from acquiring us, even if doing so would benefit our stockholders. In turn, this could cause the market price of our common stock to decline.

ITEM 1B: UNRESOLVED STAFF COMMENTS

None.

ITEM 2: PROPERTIES

We lease 52,319 square feet of office and laboratory space as our headquarters in Novato, California. This space is situated in two adjacent facilities. We expect to require more space as we expand our operations.

In addition, we lease small office spaces in Paris, France and Frankfurt, Germany; and in Utrecht, Netherlands as our European sales, marketing and administrative headquarters.

ITEM 3: LEGAL PROCEEDINGS

From time to time we are involved in litigation arising out of claims in the normal course of business. We are not aware of any material pending legal proceedings against us, nor are we involved as a plaintiff in any material pending legal proceedings.

ITEM 4: MINE SAFETY DISCLOSURES

Not applicable.

PART II

ITEM 5: MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

Our common stock trades on the NASDAQ Global Select Market under the symbol "RPTP." As of February 22, 2016, there were 85,243,864 shares of our common stock outstanding. The closing price for our common stock on February 22, 2016 was $4.26 per share.

The following table sets forth the range of high and low sales prices of our common stock for the quarterly periods indicated, as reported by NASDAQ.

	High	Low
Fiscal Year Ended December 31, 2015:		
First Quarter (January 1 – March 31, 2015)	$ 12.16	$ 8.52
Second Quarter (April 1 – June 30, 2015)	16.28	9.42
Third Quarter (July 1 – September 30, 2015)	16.28	5.45
Fourth Quarter (October 1 – December 31, 2015)	7.95	4.27
Fiscal Year Ended December 31, 2014:		
First Quarter (January 1 – March 31, 2014)	17.72	9.38
Second Quarter (April 1 – June 30, 2014)	12.19	7.12
Third Quarter (July 1 – September 30, 2014)	12.20	8.00
Fourth Quarter (October 1 – December 31, 2014)	11.10	7.85

Holders of Record

As of February 22, 2016 there were approximately 92 holders of record of our common stock.

Dividends

We have not declared or paid any cash dividends on our common stock since our inception. We anticipate that we will retain our earnings to support our operations and to finance the growth and development of our business and do not expect to pay cash dividends in the foreseeable future. In addition, our loan agreement with HC Royalty prohibits us from paying cash dividends.

Securities Authorized for Issuance under Equity Compensation Plans

Information regarding securities authorized for issuance under equity compensation plans is incorporated by reference into the information in Part III, Item 12 of this Annual Report on Form 10-K.

Recent Sales of Unregistered Securities

On October 2, 2015, we issued 3,448,001 unregistered shares of our common stock to Tripex Pharmaceuticals LLC ("Tripex") and certain of its stockholders who were accredited investors in connection with our acquisition of QUINSAIR. The shares were issued pursuant to an exemption from registration under Sections 4(a)(1) and 4(a)(2) under the Securities Act of 1933, as amended. Pursuant to the terms of a registration rights agreement among us and the Tripex stockholders, we filed an automatically effective shelf registration statement on Form S-3 with the Securities and Exchange Commission on October 9, 2015 covering the holders' re-sale of such shares.

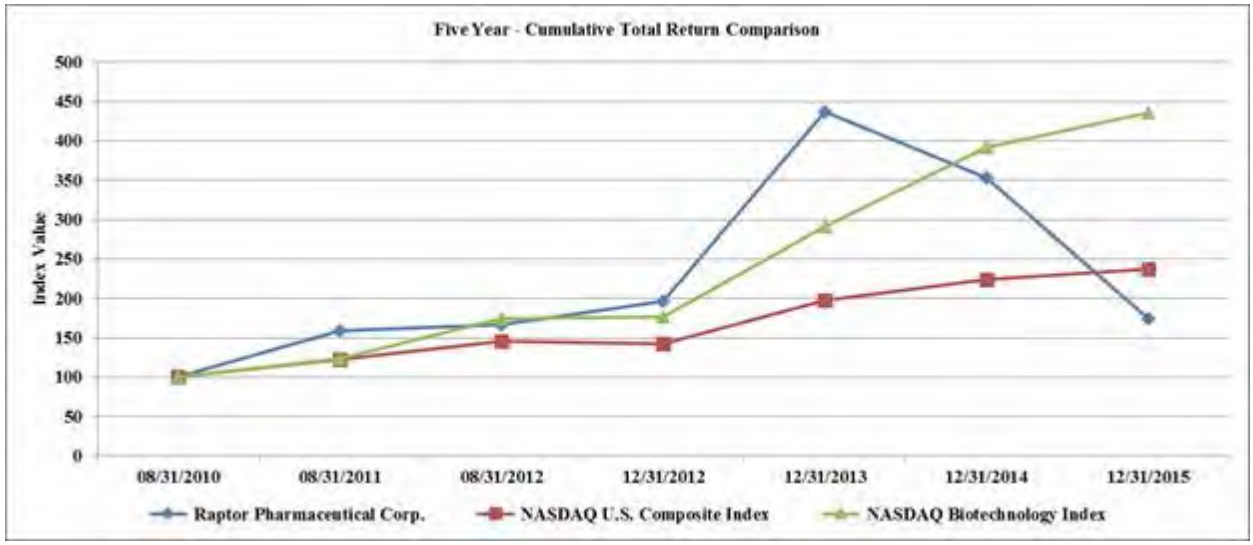
Purchase of Equity Securities and Affiliated Purchasers

We did not repurchase any shares of our common stock during the three months ended December 31, 2015.

Performance Graph

The following is not deemed "filed" with the Securities and Exchange Commission and is not to be incorporated by reference into any filing we make under the Securities Act of 1933, as amended, whether made before or after the date hereof and irrespective of any general incorporation by reference language in such filing.

The following graph shows the value of an investment of $100 on August 31, 2010 in our common stock, the NASDAQ Composite Index (U.S.), and the NASDAQ Biotechnology Index. All values assume reinvestment of the pretax value of dividends paid by companies included in these indices and are calculated as of August 31, 2011 and 2012, for the four months ended December 31, 2012 and as of the years ended December 31, 2013, 2014 and 2015. The comparisons shown in the graph are based upon historical data and we caution that the stock price performance shown in the graph is not indicative of, nor intended to forecast, the potential future performance of our stock.



	August 31,			Four Months Ended December 31,	December 31,		
	2010	2011	2012	2012	2013	2014	2015
Raptor Pharmaceutical Corp.	100.00	158.72	166.78	196.31	436.91	353.02	174.50
NASDAQ U.S. Composite Index	100.00	122.02	145.08	142.83	197.57	224.03	236.87
NASDAQ Biotechnology Index	100.00	123.16	174.53	176.18	291.77	391.26	435.95

ITEM 6: SELECTED FINANCIAL DATA

The following table shows selected historical consolidated financial and operating information for, and as of the end of, each of the periods indicated and should be read in conjunction with the information in the sections titled, “Management’s Discussion and Analysis of Financial Condition and Results of Operation” and “Business” and our consolidated financial statements and the corresponding notes to those consolidated financial statements included elsewhere in this Annual Report on Form 10-K.

The consolidated statements of income data for each of the years ended December 31, 2015, 2014, and 2013 and the select consolidated balance sheets data as of December 31, 2015 and 2014 are derived from our audited consolidated financial statements included in this Annual Report on Form 10-K. The consolidated statements of income data for the four months ended December 31, 2012 and the fiscal years ended August 31, 2012 and 2011 and the select consolidated balance sheet data as of December 31, 2013, 2012, and August 31, 2012 and 2011 are derived from our audited consolidated financial statements, except as otherwise noted, that are not included in this Annual Report on Form 10-K.

	For the Year Ended December 31,			For the Four Months Ended December 31,	For the Year Ended August 31,	
(In millions, except per share data) (1)	**2015**	**2014**	**2013**	**2012**	**2012**	**2011**
Consolidated statements of operations and net loss:						
Revenues	$ 94.2	$ 69.5	$ 16.9	$ —	$ —	$ —
Cost of sales	12.6	9.4	1.7	—	—	—
Gross profit	81.6	60.1	15.2	—	—	—
Operating expenses:						
Research and development	58.6	43.5	29.2	8.9	21.4	14.8
Selling, general and administrative	71.4	56.7	37.9	9.0	14.7	6.2
Total operating expenses	130.1	100.1	67.1	17.9	36.1	21.0
Loss from operations	(48.5)	(40.1)	(51.9)	(17.9)	(36.1)	(21.0)
Interest income	0.3	0.1	0.1	0.2	0.3	0.1
Interest expense	(15.8)	(14.0)	(6.8)	(0.1)	—	—
Foreign currency transaction gain (loss)	(0.3)	0.3	—	0.1	0.2	—
(Loss) gain on short-term investments	—	—	(0.1)	(0.1)	0.2	—
Adjustment to fair value of common stock warrants	(0.5)	(1.1)	(10.7)	(1.5)	(3.2)	(16.3)
Other income	—	2.3	—	—	—	—
Net loss before provision for income taxes	(64.8)	(52.5)	(69.4)	(19.3)	(38.6)	(37.2)
Provision for income taxes	0.4	0.1	—	—	—	—
Net Loss	$ (65.2)	$ (52.5)	$ (69.4)	$ (19.3)	$ (38.6)	$ (37.2)
Net loss per share:						
Basic and diluted	$ (0.83)	$ (0.83)	$ (1.20)	$ (0.37)	$ (0.80)	$ (1.15)
Weighted-average shares outstanding	78.9	63.2	57.9	51.7	48.1	32.3

(In millions)	December 31,				August 31,	
Balance Sheet:	**2015**	**2014**	**2013**	**2012**	**2012**	**2011**
Cash, cash equivalents and short-term investments	$ 157.4	$ 149.6	$ 83.1	$ 58.4	$ 38.9	$ 15.2
Working capital (deficit)	141.3	142.5	66.2	37.0	(20.6)	(11.0)
Total assets	423.3	189.1	108.7	68.1	48.3	22.6
Common stock warrant liability	—	0.7	7.1	16.4	17.3	23.6
Note payable	51.0	60.0	50.0	25.0	—	—
Convertible notes	60.0	60.0	—	—	—	—
Total liabilities	306.2	140.1	80.2	48.2	21.6	26.7
Accumulated deficit	(323.1)	(257.9)	(205.4)	(135.9)	(116.6)	(78.0)
Total stockholders' equity (deficit)	117.2	48.9	28.6	19.9	26.7	(4.1)

(1) Certain totals may not sum due to rounding

ITEM 7: MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion in conjunction with our consolidated financial statements as of December 31, 2015, and the notes to such consolidated financial statements included elsewhere in this Annual Report on Form 10-K. The "Management's Discussion and Analysis of Financial Condition and Results of Operations" section contains forward-looking statements. Please see "Forward-Looking Statements" for a discussion of the uncertainties, risks and assumptions associated with these statements. Our actual results and the timing of certain events could differ materially from those anticipated in these forward-looking statements as a result of certain factors, including those discussed below and elsewhere in this Annual Report on Form 10-K, particularly under the heading "Risk Factors," and in other documents we file with the SEC.

Overview

We are a biopharmaceutical company focused on developing and commercializing transformative treatments for people affected by rare diseases.

Our first commercial product, PROCYSBI, received marketing approval in the U.S. from the Food and Drug Administration (the "FDA") in April 2013 for the management of nephropathic cystinosis in adults and children six years and older. In August 2015 the Company received FDA approval for the expanded use of PROCYSBI to treat children two to six years of age with nephropathic cystinosis. In Europe, PROCYSBI gastro-resistant hard capsules of cysteamine (as mercaptamine bitartrate), received a marketing authorization in September 2013 from the European Commission (the "EC") as an orphan medicinal product for the management of proven nephropathic cystinosis in the European Union (the "EU"). The EU marketing authorization has been expanded to allow us to commercialize PROCYSBI in the 28 Member States of the EU plus Norway, Liechtenstein and Iceland (which are not EU Member States but are part of the European Economic Area, or "EEA"). PROCYSBI received seven and ten years of market exclusivity due to its designation as an orphan drug in the United States and the EU, respectively. We achieved first commercial sales of PROCYSBI in the United States in June 2013 and in the EU, specifically in Germany, in April 2014.

In October 2015, we acquired various assets and rights related to a levofloxacin solution for inhalation, a pharmaceutical product also known as "MP-376" and commercially as "QUINSAIR," from Tripex Pharmaceuticals, LLC ("Tripex"). QUINSAIR received marketing authorization by the EC for treating long-term lung infection caused by the bacteria *Pseudomonas aeruginosa* in adults who have cystic fibrosis in March 2015 and Health Canada in June 2015 for the management of cystic fibrosis in patients aged 18 years or older with chronic pulmonary *Pseudomonas aeruginosa* infections. QUINSAIR is the first inhaled fluoroquinolone approved for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis 18 years old and older. We plan to launch QUINSAIR in Europe in the first half of 2016 and Canada later in 2016. We plan to discuss the path to potential approval for the same indication in the United States with the FDA in 2016. We also plan to pursue clinical programs for the development of MP-376 in non-cystic fibrosis related bronchiectasis and to do work to support further clinical development of MP-376 in nontuberculous mycobacteria infections in 2016. QUINSAIR is not approved in the United States, and we may not market or commercialize QUINSAIR in the United States for any indication unless we receive FDA approval, which we may not be able to obtain.

Clinical Development Programs

Our two active clinical development programs utilize RP103, which contains the same active pharmaceutical ingredient as PROCYSBI, cysteamine bitartrate. RP103 and PROCYSBI both utilize our proprietary capsule formulation containing delayed-release enteric coated microbeads of cysteamine bitartrate. Cysteamine bitartrate was approved in the United States in 1994 and the EU in 1997 as an orally available immediate-release powder in a capsule for the management of cystinosis. We have an exclusive worldwide license from the University of California, San Diego ("UCSD"), to delayed-release cysteamine bitartrate, which is the basis for our proprietary formulation of cysteamine. We currently have product candidates in clinical development designed to potentially treat Huntington's disease ("HD") and mitochondrial disorders including Leigh syndrome. We announced in September 2015, based on information then available, that we would not advance our program for the treatment of pediatric non-alcoholic steatohepatitis (NASH) with RP103 after topline results from a Phase 2b trial which failed to show efficacy as measured by the trial's primary endpoints. Unless the full data set, which we expect to receive later this year, provides a compelling rationale for us to continue the NASH program, our decision will remain unchanged.

Preclinical Product Candidates

Our preclinical programs, for which we may seek development partners in the future, include RP105 and RP 106 being developed for a variety of rare diseases.

Future Activities

Over the next fiscal year, our efforts will be focused on increasing sales of PROCYSBI in the United States and Europe and continuing to provide comprehensive reimbursement and adherence support to commercial cystinosis patients in the United States; launching or providing access to PROCYSBI in other countries in the EEA and other select countries around the world; conducting a clinical trial to evaluate PROCYSBI in cysteamine-naïve cystinosis patients, as well as other supporting trials in underdeveloped markets; screening for undiagnosed and unidentified adult nephropathic cystinosis patients; regulatory pathways and/or clinical trials of RP103 for the potential treatment of HD while exploring potential partnership opportunities; preparing to launch QUINSAIR in Europe in the first half of 2016 and Canada later in 2016 and preparing to pursue clinical programs in non-cystic fibrosis related bronchiectasis and to do work in preparation to support further clinical development of MP-376 in nontuberculous mycobacteria; preparing for potential clinical studies of RP103 in new therapeutic indications; supporting our novel preclinical programs; seeking additional business development partners for one or more of our product candidates; and developing new preclinical, clinical and or commercial opportunities, including novel proprietary product candidates, technologies or products identified and acquired through business development activities.

Application of Critical Accounting Policies

Our consolidated financial statements and accompanying notes are prepared in accordance with generally accepted accounting principles used in the United States. Preparing financial statements requires management to make estimates and assumptions that affect the reported values of assets, liabilities, revenue and expenses. These estimates and assumptions are affected by management's application of accounting policies. We believe that understanding the basis and nature of the estimates and assumptions involved with the following aspects of our consolidated financial statements is critical to an understanding of our consolidated financial position and results of operations.

We believe the following policies to be the most critical to an understanding of our financial condition and results of operations because they require us to make estimates, assumptions and judgements about matters that are inherently uncertain.

Revenue Recognition and Accounts Receivable

We recognize revenue in accordance with the Financial Accounting Standards Board ("FASB") Accounting Standards Codification ("ASC") 605, Revenue Recognition, when the following criteria have been met: persuasive evidence of an arrangement exists; delivery has occurred and risk of loss has passed; the seller's price to the buyer is fixed or determinable and collectability is reasonably assured. We determine that persuasive evidence of an arrangement exists based on written contracts that define the terms of the arrangements. Pursuant to the contract terms, we determine when title to products and associated risk of loss has passed onto the customer. We assess whether the fee is fixed or determinable based on the payment terms associated with the transaction and whether the sales price is subject to refund or adjustment. We assess collectability based primarily on the customer's payment history and creditworthiness, and record a reserve for product returns based upon the timing and history of our product or of similar product sales and returns in the pharmaceutical industry. As of December 31, 2015, no products had been returned.

PROCYSBI is currently distributed in the U.S. by a specialty pharmacy distributor, the Accredo Health Group, Inc. ("Accredo") which is currently the Company's only U.S. customer and which subsequently ships directly to patients. The Company's distributor in the EU and other territories outside the U.S. is the Almac Group, Ltd., which ships directly to pharmacies after a prescription for PROCYSBI has been received. PROCYSBI is not available in U.S. retail pharmacies. Authorization of coverage by patients' commercial insurance plans, Raptor's patient assistance program ("PAP") or government payors is a prerequisite to the shipment of PROCYSBI to U.S. patients. Prior to the third quarter of 2014, revenue from the sale of PROCYSBI in the U.S. was recognized based on the amount of product sold through to the patients. Beginning July 2014, we were able to reasonably estimate and determine sales allowances in the U.S.; therefore we began recognizing PROCYSBI revenue in the U.S. at the point of sale to the specialty pharmacy, which resulted in the one-time non-recurring recognition of an additional $4.4 million in net revenues during the three months ended September 30, 2014. Revenue is currently recognized in the EU once confirmed orders from pharmacies have been shipped and invoiced for payment by the distributor on the Company's behalf.

We record revenue net of expected discounts, distributor fees, and rebates, including government rebates such as Medicare and Medicaid in the United States. Allowances are recorded as a reduction of revenue at the time product sales are recognized. Allowances for government rebates and discounts are established based on the actual payor and payor mix information, which is known in the United States at the time of shipment to the distributor and in Germany at the time of shipment to the pharmacy, and the government-mandated discount rates applicable to government-funded programs. The allowances are adjusted to reflect known changes in the factors that may impact such allowances in the quarter the changes are known.

For a roll-forward of estimated rebates, discounts and product returns, see Note 8 in the accompanying notes to the consolidated financial statements in this Annual Report on Form 10-K.

Trade accounts receivable are recorded net of product sales allowances for prompt-payment discounts and chargebacks. Estimates for chargebacks and prompt-payment discounts are based on contractual terms and our expectations regarding the utilization rates based largely on historical behavior. The Company estimates its allowance for doubtful accounts based upon an assessment of various factors, including historical experience, the age of the accounts receivable balances, credit quality of customers, current economic conditions, and other factors that may affect customers' ability to pay. Historically, the Company has not experienced any material losses with respect to the collection of accounts receivable.

Inventories and Cost of Sales

Inventories are stated at the lower of cost or market price, with cost determined on a first-in, first-out basis. We adjust our inventory value for estimated amounts of excess, obsolete, or unmarketable items. Such assumptions involve projections of future customer demand, as driven by economic and market conditions, and the product's shelf life. If actual demand, or economic or market conditions are less favorable than those projected by us, incremental inventory write-downs may be required and could be significant. Prior to the approval of PROCYSBI by the FDA on April 30, 2013 and in Europe, prior to EC approval on September 6, 2013, we recorded the purchase of raw materials and the manufacturing costs relating to PROCYSBI as research and development expense. Subsequent to FDA and EC approval, we began capitalizing these costs and manufacturing overhead as commercial inventory. Upon launching PROCYSBI in mid-June 2013 in the United States and in April 2014 in the EU, we began recognizing cost of sales. Cost of sales includes the cost of inventory sold or reserved; manufacturing, manufacturing overhead and supply chain costs; inventory variance amortization; product shipping, warehousing and handling costs; and amortization of licensing approval milestone payments and licensing royalties payable to UCSD.

We capitalize inventory produced in preparation for product launches and expanded access programs when positive results have been obtained for the clinical trials that we believe are necessary to support regulatory approval and we have determined it is probable that these capitalized costs will provide some future economic benefit in excess of capitalized costs. For these inventories, we also consider the expected approval date in assessing realizability. To the extent that inventory is expected to expire prior to being sold, we generally write down the value of inventory. If actual results differ from those estimates, additional inventory write-offs may be required.

Impairment of Goodwill and Intangible Assets

Goodwill represents the excess of the purchase price over the fair value of tangible and identified intangible net assets of businesses acquired. Goodwill is not amortized, but is evaluated for impairment on an annual basis or more often when impairment indicators are present. We have one reporting unit. Therefore, our consolidated net assets, including existing goodwill and other intangible assets, are considered to be the carrying value of the reporting unit. If the carrying value of the reporting unit is in excess of its fair value, an impairment may exist, and we must perform the second step of the analysis, in which the implied fair value of the goodwill is compared to its carrying value to determine the impairment charge, if any. If the estimated fair value of the reporting unit exceeds the carrying value of the reporting unit, goodwill is not impaired and no further analysis is required. We performed our goodwill impairment test as of December 31, 2015 and noted no impairment.

We make judgments about the recoverability of purchased intangible assets with finite lives whenever events or changes in circumstances indicate that impairment may exist. Recoverability of purchased intangible assets with finite lives is measured by comparing the carrying amount of the asset to the future undiscounted cash flows the asset is expected to generate. Impairment, if any, is measured as the amount by which the carrying value exceeds the fair value of the impaired asset.

Assumptions and estimates about future values and remaining useful lives of our purchased intangible assets are complex and subjective. They can be affected by a variety of factors, including external factors such as industry and economic trends and internal factors such as changes in our business strategy and our internal forecasts.

Common Stock Warrant Liabilities

Common stock warrants we issued in connection with certain fiscal year 2009 and 2010 equity financings contained conditional obligations that may have required us to transfer cash to settle the warrants upon the occurrence of certain fundamental transactions. Therefore, we classified the warrants as liabilities. We re-measured the liability at the end of every reporting period with the change in value reported in our consolidated statements of operations. At the exercise date, the fair values of these warrants were re-measured and reclassified to equity.

We used the Black-Scholes option pricing model as our method of valuation for warrants that were subject to warrant liability accounting. The determination of the fair value as of the reporting date was affected by our stock price as well as assumptions regarding a number of highly complex and subjective variables. These variables included, but were not limited to, expected stock price volatility over the term of the security and risk-free interest rate. In addition, the Black-Scholes option pricing model requires the input

of an expected life for the securities, which is based on the contractual terms of the underlying agreement. The fair value of the warrant liability was revalued as of each balance sheet date utilizing Black-Scholes valuation model computations with the decrease or increase in fair value being reported in the statement of operations as other income or expense, respectively. The primary factors affecting the fair value of the warrant liability are our stock price and volatility. At December 31, 2015, all common stock warrants subject to liability classification had been exercised or expired.

Contingent Consideration Liability

Contingent consideration payable from the October 5, 2015 QUINSAIR acquisition is payable upon the achievement of specified development, regulatory approval, sales-based milestone events or financial results. As of December 31, 2015, the fair value of the contingent consideration liability remained unchanged at $166.8 million due to the limited passage of time from the acquisition date and as there were no changes to the significant estimates and assumptions used in measuring the acquisition date fair value.

Changes in fair value of the contingent consideration liabilities can result from updates to assumptions such as the expected timing or probability of achieving the specified milestones, changes in projected revenues or changes in discount rates. Significant judgment is employed in determining these assumptions as of the acquisition or consolidation date and for each subsequent period. Updates to assumptions could have a significant impact on our results of operations in any given period. Actual results may differ from estimates.

Stock-Based Compensation

We estimate the fair value of stock options and Employee Stock Purchase Plan (ESPP) shares using the Black-Scholes valuation model. The Black-Scholes model requires the input of highly subjective assumptions. The most significant assumptions are our estimates of the expected volatility and the expected term of the award.

Risk-Free Interest Rate. The risk-free interest rate is based on the implied yield available on U.S. Treasury zero-coupon issues with a remaining term equal to the expected term of the option.

Expected Volatility. The volatility is based on a combination of the actual annualized volatility of our common stock price as quoted on NASDAQ since the closing of our 2009 Merger on September 30, 2009 and of annualized volatility of peer companies.

Expected Life of Options. We use historical option exercise data to estimate the expected life of the options.

Expected Dividend Yield. We have never paid any dividends and do not intend to in the near future.

As required, we review our valuation assumptions at each grant date and, as a result, we are likely to change our valuation assumptions used to value employee stock-based awards granted in future periods. Employee and director stock-based compensation costs are to be recognized over the vesting period of the award, which is generally on a straight-line basis over the period during which the employee or director is required to perform service in exchange for the award. Forfeitures are to be estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates. We estimate forfeitures based on historical experience.

Income Taxes

Income taxes are recorded under the liability method, under which deferred tax assets and liabilities are determined based on the difference between the financial statement and tax bases of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to affect taxable income. Valuation allowances are established when necessary to reduce deferred tax assets to the amount expected to be realized. Based on the weight of available evidence, including cumulative losses since inception and expected future losses, we have determined that it is more likely than not that the deferred tax asset amount will not be realized and therefore a full valuation allowance has been provided on our net deferred tax assets. We intend to maintain the valuation allowance until sufficient positive evidence exists to support the reversal of the valuation allowance. Any decision to reverse part or all of the valuation allowance would be based on our estimate of future profitability.

We identify uncertain tax positions and record or disclose any resulting potential tax liability based upon whether the position is more likely than not sustainable upon examination. We consider proposed assessments by tax authorities, changes in facts and circumstances, issuance of new regulations or new case law and negotiations between tax authorities of different countries concerning our transfer prices or intellectual property transfers. As of December 31, 2015, we had identified no uncertain tax positions.

We file U.S. federal, California, various other state and other income tax returns and various foreign country income tax returns. We are currently not subject to any income tax examinations. Due to our net operating losses, all tax years generally remain open in each jurisdiction.

Results of Operations

For the Years Ended December 31, 2015, 2014, and 2013

	For the Year Ended December 31,		
(In millions) (1)	**2015**	**2014**	**2013**
Revenues	$ 94.2	$ 69.5	$ 16.9
Cost of sales	12.6	9.4	1.7
Gross profit	81.6	60.1	15.2
Operating expenses:			
Research and development	58.6	43.5	29.2
Selling, general, and administrative	71.4	56.7	37.9
Total operating expenses	130.1	100.1	67.1
Loss from operations	(48.5)	(40.1)	(51.9)
Interest income	0.3	0.1	0.2
Interest expense	(15.8)	(14.0)	(6.8)
Foreign currency transaction gain (loss)	(0.3)	0.3	0.0
Gain on short-term investments	-	-	(0.1)
Adjustment to the fair value of common stock warrants	(0.5)	(1.1)	(10.7)
Other income	-	2.3	-
Net loss before provision for income taxes	$ (64.8)	$ (52.5)	$ (69.4)
Provision for income taxes	0.4	0.1	-
Net Loss	$ (65.2)	$ (52.5)	$ (69.4)

(1) Certain totals may not sum due to rounding

Revenue

Net PROCYSBI product sales for the years ended December 31, 2015, 2014, and 2013 totaled $94.2 million, $69.5 million, and $16.9 million, respectively. The increase in revenue was driven by continued market penetration in both the United States and Europe. PROCYSBI became commercially available in the U.S. in June 2013 and in Europe in April 2014.

Cost of Sales

Prior to the approval of PROCYSBI by the FDA on April 30, 2013 and in Europe, prior to EMA approval on September 6, 2013, we recorded manufacturing costs relating to PROCYSBI as research and development expense. Subsequent to approval, we began capitalizing these costs as commercial inventory. As a result, our cost of sales for 2013 and 2014 reflects a lower average per unit cost of goods than will be recorded in the future. Cost of sales primarily includes: raw materials and manufacturing costs for our commercial product PROCYSBI, amortization of licensing milestone payments, royalty fees due to UCSD on our net product sales, other indirect costs such as distribution, warehousing, labeling, shipping and supplies, and provision for inventory expiration. Costs capitalized as inventory are expensed as cost of sales as product is sold.

During the year ended December 31, 2015, we recorded cost of sales of $12.6 million, primarily due to a $5.1 million royalty expense, $3.8 million provision for inventory expiration, and allocated manufacturing costs. During the year ended December 31, 2014, we recorded cost of sales of $9.4 million, primarily due to a $3.2 million provision for inventory expiration, $3.8 million for royalties, and allocated manufacturing costs. During the year ended December 31, 2013, we recorded cost of sales of $1.7 million, including a $0.4 million reserve representing commercial inventory that was capitalized subsequent to FDA approval but written off due to an unanticipated minor change in the finished product presentation.

Research and Development

Research and development expenses include medical, clinical, regulatory, quality (excluding manufacturing quality control expenses), pharmacovigilance and research salaries and benefits; expenses associated with the manufacturing and testing of PROCYSBI inventory for our commercial launch in the United States and in Europe which were expensed prior to drug approvals;

preclinical studies; clinical trials; regulatory and clinical consultants; research supplies and materials; amortization of intangible assets; and allocated human resources and facilities expenses.

For the years ended December 31, 2015, 2014, and 2013, our research and development expenses were $58.6 million, $43.5 million, and $29.2 million, respectively. The increase in research and development expenses relates primarily to increased clinical product manufacture of RP103 for the potential treatment of HD, NASH, cystinosis extension, and other supporting study expenses and related employee compensation, partially offset by a reduction in Phase 3 cystinosis clinical trial expenses.

The following table shows major program expenses recorded as research and development expenses. In 2015, we began allocating internal compensation and overhead to individual program expense.

Major Program Expenses Recorded as Research and Development

	For the Year Ended December 31,				
(In millions)	2015	Change from 2014, %	2014	Change from 2013, %	2013
RP103:					
Cystinosis (pre-commercial and extension)	$ 26.0	102%	$ 12.9	-13%	$ 14.8
HD (clinical)	3.7	85%	2.0	150%	0.8
NASH (clinical)	3.7	95%	1.9	-5%	2.0
Mitochondrial	4.0				
Cystic fibrosis	5.6				
Discovery	5.3	165%	2.0	82%	1.1
Other programs	1.3	-41%	2.2	175%	0.8
R&D personnel and other costs not allocated to programs	9.0	-60%	22.5	132%	9.7
Total Research and Development Expenses	$ 58.6	35%	$ 43.5	49%	$ 29.2

Selling, General and Administrative Expenses

Selling, general and administrative expenses primarily include commercial expenses related to marketing and sales operations in the U.S. and EU, including marketing and pricing studies, advertising, sales force commissions and other expenses, and market access support activities; commercial launch expenses for PROCYSBI, including patient support activities such as reimbursement assistance and establishing a customer relationship management system for our PROCYSBI sales team, and salaries and benefits for our commercial operations; intellectual property, legal and audit fees, finance and executive expenses; and other administrative and facilities costs.

Selling, general and administrative expenses for the year ended December 31, 2015 were $71.4 million as compared to $56.7 million for the year ended December 31, 2014 or an increase of $14.7 million. This increase was primarily attributable to an increase in compensation related expenses of $6.5 million and professional fees including legal fees of approximately $7.0 million.

Selling, general and administrative expenses for the year ended December 31, 2014 were $56.7 million as compared to $37.9 million for the year ended December 31, 2013 or an increase of $18.8 million. This increase was primarily attributable to an increase in compensation related expenses of $12.5 million, marketing expenses of approximately $2.0 million and professional fees including legal fees of approximately $1.6 million.

Interest Expense

Interest expense for the years ended December 31, 2015, 2014, and 2013 was $15.8 million, $14.0 million, and $6.8 million, respectively. The increase in interest expense from 2013 to 2014 was due primarily to an increase in royalty fees pursuant to the HC Royalty loan agreement based on net sales for the period. Also contributing to the increase was the issuance of $60.0 million of convertible notes in July 2014 and an amendment to the $50.0 million loan agreement that we entered into with HealthCare Royalty Partners II, L.P., or HC Royalty, in December 2012, which was amended in July 2014 to provide for an additional $10.0 million in term loan funding. The increase in interest expense from 2014 to 2015 was primarily driven by greater fixed interest as a result of a greater level of outstanding principal debt from our HC Royalty loan agreement and outstanding convertible notes partially offset by a reduction in the rate of fixed interest on our HC Royalty loan.

Adjustment to the Fair Value of Common Stock Warrants

Adjustment to the fair value of common stock warrants were losses of $0.5 million, $1.1 million, and $10.7 million for the years ended December 31, 2015, 2014, and 2013, respectively. The decrease in fair value adjustment was due primarily to the decrease in the number of warrants outstanding. As of December 31, 2015, there were no common stock warrants outstanding.

Other Income

In 2014, we received a cash payment in the amount of $2.3 million from a stockholder in disgorgement of alleged short-swing profits under Section 16(b) of the Securities Exchange Act of 1934. This amount is recorded as *Other Income* on our consolidated financial statements.

Liquidity and Capital Resources

Capital Resources

As of December 31, 2015, we had $157.4 million in cash and cash equivalents, of which $6.9 million is held by our foreign subsidiaries, $40.1 million in current liabilities and $141.3 million of net working capital. During the year ended December 31, 2015, we completed a public offering of 10.925 million shares of our common stock for net proceeds of $92.0 million, raised $0.3 million net proceeds from warrant exercises and $7.5 million net proceeds from stock option exercises and our employee stock purchase plan. During the year ended December 31, 2014, we raised $66.0 million of net proceeds from modification of our loan agreement with HC Royalty Partners and the issuance of convertible notes, $44.8 million in proceeds after commissions under our at-the-market ("ATM") common stock sales agreement, $1.8 million net proceeds from warrant exercises and $6.8 million net proceeds from stock option exercises and our employee stock purchase plan. We believe that our cash balance will be sufficient to meet our projected operational requirements and obligations into the first half of 2018.

	December 31,	
	2015	2014
	(in thousands, except financial metrics data)	
Cash and cash equivalents	$ 157,352	$ 149,613
Restricted cash	$ 1,055	$ 1,562
Accounts receivable, net	$ 13,267	$ 7,455
Total current assets	$ 181,399	$ 171,605
Total current liabilities	$ 40,053	$ 29,120
Working capital surplus (a)	$ 141,346	$ 142,485
Days sales outstanding ("DSO") (b)	50	40
Current ratio (c)	4.5	5.9

(a) Total current assets at period end *minus* total current liabilities at period end.
(b) Net accounts receivable at period end *divided by* revenue, net for the fourth quarter *multiplied* by 92 days.
(c) Total current assets at period end *divided by* total current liabilities at period end.

Net Cash Used In Operating Activities

Cash used in operating activities was $44.2 million in 2015 consisting mainly of a net loss of $65.2 million adjusted for non-cash items such as stock-based compensation expense of $12.8 million and depreciation and amortization of $2.8 million and $4.6 million of net cash inflow related to changes in operating assets and liabilities.

Net Cash Used By Investing Activities

Net cash used in investing activities was $ 37.8 million in 2015 consisting mainly of a $35.4 million cash payment for QUINSAIR and $2.9 million for the purchase of property and equipment. Net cash used in investing activities was $ 6.1 million in 2014 consisting mainly of $5.1 million for the purchase of property and equipment.

Net Cash Provided By Financing Activities

Net cash provided by financing activities was $90.9 million in 2015 as compared to $119.4 million in 2014. Net cash provided by financing activities in 2015 consisted of $92.0 million of proceeds from the follow on public offering, $6.6 million from the issuance of common stock as a result of the exercise of employee stock options, and $0.9 million of proceeds from the issuance of

common stock as a result of employee stock purchases under our employee stock purchase plan. These amounts were partially offset by principal debt payments of $9.0 million. The net cash provided by financing activities in 2014 consisted primarily of $44.5 million of proceeds from the sale of common stock under ATM agreement, $70.0 million of proceeds from the issuance of debt offset by debt issuance costs of $3.5 million.

Note Payable and Convertible Debt

Under the terms of the HC Royalty loan agreement executed on December 20, 2012, we received $23.4 million in net proceeds from the first tranche of the loan at closing in December 2012. We received an additional $23.7 million in net proceeds in May 2013 from the second tranche upon FDA approval of RP103 for the management of cystinosis. In July 2014, we modified our original December 2012 loan agreement to provide for an additional $10.0 million in term loan funding. The loan matures on March 31, 2020, bears interest at an annual fixed rate of 8.0% (after the July 2014 modification) and has a synthetic royalty, tiered down, based on a percentage of net product sales. We paid the first quarterly principal payment of $3.0 million in June 2015. In July 2014, we also sold $60.0 million of convertible senior notes, which bear a fixed interest rate of 8.0% until maturity in August 2019 unless converted earlier. The proceeds from the loans are being used primarily to fund the further commercialization of PROCYSBI for the management of cystinosis, commercial launch of QUINSAIR advancement of our development programs and for general corporate purposes.

Common Stock Issuance under At-The-Market ("ATM") Agreement

On April 30, 2012, we entered into a Sales Agreement with Cowen and Company, or Cowen, to sell shares of our common stock, with aggregate gross sales proceeds of up to $40.0 million, from time to time through an "at the market" equity offering program under which Cowen acted as sales agent. We paid a 3% commission to Cowen on all sales pursuant to this Sales Agreement.

On July 3, 2013, we amended and restated the Sales Agreement to increase the aggregate gross sales proceeds that may be raised to $100.0 million. Cumulatively through December 31, 2014, we sold 12,569,914 shares under the ATM offerings at a weighted-average selling price of $7.96 per share for net proceeds of approximately $97.0 million.

On September 4, 2015, we entered into an ATM sales agreement, with Cowen, under which we may, at our discretion, sell our common stock with a sales value of up to a maximum of $75.0 million through ATM offerings on the NASDAQ Stock Market (the "2015 Sales Agreement"). Cowen is the sole sales agent for any sales made under the 2015 Sales Agreement, and we will pay Cowen a commission, or allow a discount, for its services in acting as agent in the sale of our common stock of up to 3.0% of the gross sales price per share of all shares sold through it as agent under the 2015 Sales Agreement. The common stock will be sold at prevailing market prices at the time of sale, and, as a result, prices will vary. During the year ended December 31, 2015, there were no shares sold under the 2015 Sales Agreement and $75.0 million was available for issuance under the 2015 Sales Agreement as of December 31, 2015.

2015 Follow-on Public Offering

On April 8, 2015, we closed an underwritten public offering of shares of our common stock at a price to the public of $9.00 per share. The offering resulted in net proceeds to us of approximately $92.0 million after deduction of underwriting discounts of 6% and other offering expenses paid by us.

Future Funding Requirements

We will need to raise additional capital either through the sale of equity or debt to fund our operations in the longer term and to, among other activities, continue to commercialize PROCYSBI, to launch QUINSAIR, and to develop RP103 and MP-376 for the potential treatment of other indications. Our future capital requirements may be substantial, and will depend on many factors, including:

- The continuing sales of PROCYSBI in the United States, Europe and other international markets;
- The success of the launch of QUINSAIR in Europe and Canada;
- The ongoing costs of establishing and maintaining sales and marketing capabilities in the United States, Europe and other international markets for PROCYSBI and QUINSAIR;
- Our ability to negotiate reimbursement and pricing of PROCYSBI and QUINSAIR in various countries outside of the United States, and of QUINSAIR in Europe and Canada;
- The cost of our manufacturing-related activities in support of PROCYSBI, QUINSAIR, MP-376, and RP103;

- The cost of activities and outcomes related to the regulatory submission of cysteamine bitartrate delayed-release capsules in Canada;
- The cost of additional clinical trials in order to obtain regulatory approvals for PROCYSBI in non-U.S. and non-European countries, and for QUINSAIR in the United States;
- The timing and cost of our ongoing clinical programs for RP103, including: evaluating PROCYSBI in treatment-naïve cystinosis patients, and other supportive studies; evaluating RP103 as a potential treatment for HD; evaluating RP103 as a potential treatment for Leigh syndrome and other mitochondrial disorders;
- The cost of regulatory submissions, as well as the preparation, initiation and execution of clinical trials of MP-376 in non-CF related bronchiectasis and NTM infections;
- The cost of evaluating and potentially acquiring or in-licensing and developing and commercializing new drug compounds;
- The cost of filing, continuing surveillance, prosecuting, defending and enforcing existing or new patent claims;

  and

- The determination of whether we will strategically partner or out-license one or more of our product candidates and depending on the decision pursuing and completing a strategic partnership or license.

There can be no assurance that we will be successful in raising sufficient funds when needed. Additional financing may not be available in amounts or on terms satisfactory to us or at all.

Research and Development Activities

We plan to conduct further research and development, to support several clinical trials for RP103, improve upon our internal discovery molecules and in-licensed technology and continue business development efforts for our preclinical and other clinical-stage product candidates in the next 12 months. We plan to conduct research and development activities by our own laboratory staff and also by engaging contract research organizations, clinical research organizations and contract manufacturing organizations. We also plan to incur costs for the production of our clinical study drug candidate RP103 for the potential treatment of HD; for production of RP103 for additional clinical trials in cystinosis; clinical and medical advisors; and consulting and collaboration fees. We anticipate that our research and development costs will increase during the next 12 months primarily due to the addition of new studies in support of cystinosis, HD, non-CF related bronchiectasis, and NTM. We may seek strategic partnerships in the development of one or more of our product candidates.

Selling, General and Administrative Activities

Selling, general and administrative costs in the next 12 months is expected to consist primarily of sales activities surrounding the sale of PROCYSBI in the United States and Europe and the commercial launch of PROCYSBI in additional countries in Europe, as well as the commercial launch of QUINSAIR in Canada and Europe. We anticipate that selling, general and administrative expenses will continue to increase in support of PROCYSBI sales growth, as well as an increase in facilities and administrative expenses to support our anticipated growth.

Capital Expenditures

In the next 12 months, we expect to increase our capital expenditures on laboratory and office equipment and computer software and hardware as we continue to increase our staff in 2016.

Contractual Obligations

Contractual Obligations with UCSD Relating to the Acquisition of the DR Cysteamine (RP103) License

Pursuant to our license agreement with UCSD, we are obligated to pay milestone payments (ranging in size for orphan and non-orphan indications) upon the occurrence of certain events during the life of the license agreement. These include a royalty on commercial net sales from products developed pursuant to the agreement, a percentage of sublicense fees, a percentage of sublicense royalties, and a minimum annual royalty. Under the license agreement, we are obligated to fulfill predetermined milestones within a specified number of years from the effective date of the agreement, depending on the indication. In 2013, we began paying UCSD royalties based upon our net sales of PROCYSBI. Other future milestones will be payable based on other regulatory approvals and clinical trial milestones.

Other Contractual Obligations

We have contractual obligations under our capital and operating leases and other obligations related to research and development activities, purchase commitments and licenses. Information about these obligations as of December 31, 2015 is presented in the table below.

(In thousands)	< 1 year	1 - 3 Years	3 - 5 Years	> 5 Years	Total
Debt principal	$ 12,000	$ 24,000	$ 15,000	$ —	$ 51,000
Convertible notes	—	—	60,000	—	60,000
Operating lease obligations	2,286	5,076	4,311	3,329	15,002
Purchase commitments and research and development/clinical	2,962	1,654	880	2,450	7,946
Total	$ 17,248	$ 30,730	$ 80,191	$ 5,779	$ 133,948

We maintain several contracts with contract manufacturers, clinical organizations and clinical sites, drug labelers and distributors and research organizations, primarily to assist with clinical research and clinical manufacturing for our cystinosis and HD programs. The future commitments pursuant to these agreements, some of which include estimates of amounts or timing of payments, are included in the table above as research and development and purchase commitments.

We are also subject to contingent payments related to various development activities totaling approximately $399.0 million, which are primarily due upon the achievement of certain development and commercial milestones. Of these contingent payments, $350.0 million relate to the purchase of QUINSAIR. These contingent payments are not included in the table above as we cannot reliably predict their timing or occurrence.

In conjunction with our HC Royalty loan agreement, we have contractual interest payments that began in December 2012 at a fixed rate of 10.75% plus a percentage of product revenue. In July 2014, these fixed interest payments were amended to 8.00%. We also issued senior convertible notes which bear fixed interest of 8.0%. The fixed interest amount that remains committed through the term of the amended loan agreement and convertible senior notes is approximately $26.8 million. We also began paying quarterly payments of $3.0 million on principal under the HC Royalty loan in June 2015.

Off-Balance Sheet Arrangements

We do not have any outstanding derivative financial instruments, off-balance sheet guarantees, interest rate swap transactions or foreign currency contracts. We do not engage in trading activities involving non-exchange traded contracts.

Recent Accounting Pronouncements

The information required by this item is included in Note 2 Summary of Significant Accounting Policies in our Consolidated Financial Statements included in this Annual Report on Form 10-K.

ITEM 7A: QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

Market risk represents the risk of changes in the value of market risk sensitive instruments caused by fluctuations in interest rates, foreign exchange rates and commodity prices. We are exposed to various market risks that may arise from adverse changes in market rates and prices, such as foreign exchange rate and interest rate fluctuations. We do not enter into derivatives or other financial instruments for trading or speculative purposes.

Foreign Exchange Risk

A majority of our assets and liabilities are maintained in the United States in U.S. dollars and a majority of our expenditures are transacted in U.S. dollars. We are subject to foreign exchange risk for the operations of Raptor Pharmaceuticals Europe B.V., Raptor Pharmaceuticals France SAS, and Raptor Pharmaceuticals Germany GmbH, which use the Euro as their functional currency. We do not believe that a hypothetical one percentage point fluctuation in the U.S. dollar exchange rate would materially affect our consolidated financial position, results from operations or cash flows as of December 31, 2015. We do not currently hedge our foreign currency transactions.

Interest Rate Risk

As of December 31, 2015, we had approximately $146.5 million in cash equivalent money market accounts, yielding approximately 0.32% per year. A hypothetical one percentage point decline in interest rates would not have materially affected our consolidated financial position, results of operations or cash flows as of December 31, 2015.

ITEM 8: FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

The information required to be filed in this item appears on pages [71 to 106] of this Annual Report on Form 10-K.

Documents filed as part of this Annual Report on Form 10-K:

Financial Statements

PART II – FINANCIAL INFORMATION

ITEM 9: CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

ITEM 9A: CONTROLS AND PROCEDURES

Our Chief Executive Officer and Chief Financial Officer have provided certifications filed as *Exhibits 31.1* and *32.1*, and *31.2*, respectively. Such certifications should be read in conjunction with the information contained in this *Item 9A* for a more complete understanding of the matters covered by those certifications.

(a) Management's Annual Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as defined in Rule 13a-15(f) of the Securities Exchange Act of 1934 (the "Exchange Act"). Our internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of the financial reporting and the preparation of financial statements for external purposes in accordance with U.S. generally accepted accounting principles. This process includes those policies and procedures (i) that pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of our assets; (ii) that receipts and expenditures are being made only in accordance with authorizations of our management and directors; (iii) that provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of our assets that could have a material effect on our financial statements; and (iv) that provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with U.S. generally accepted accounting principles.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of the internal control over financial reporting to future periods are subject to risk that the internal control may become inadequate because of changes in conditions, or that the degree of compliance with policies or procedures may deteriorate.

Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2015. In making this assessment, our management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in the 2013 *Internal Control-Integrated Framework* ("2013 COSO").

Based on our management's assessment, we have concluded that as of December 31, 2015, our internal control over financial reporting was effective, as evaluated under the 2013 COSO criteria. Our independent registered public accounting firm, Grant Thornton LLP, has issued a report on the effectiveness of our internal control over financial reporting. This report is referenced in the index appearing under Item 8 of this Annual Report on Form 10-K.

(b) Disclosure Controls and Procedures

We carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of the effectiveness of our disclosure controls and procedures as of December 31, 2015, pursuant to Rules 13a-15(e) and 15d-15(e) under the Exchange Act. Based on that evaluation, our Chief Executive Officer and Chief Financial Officer have concluded that our disclosure controls and procedures, as of such date, were effective.

(c) Changes in Internal Control over Financial Reporting

Remediation of material weakness identified as of December 31, 2014:

As disclosed in *Item 9A* of our 2014 Annual Report on Form 10-K, and in our Quarterly Reports on Form 10-Q filed during the 2015 fiscal year, we identified a material weakness in our internal control over financial reporting as of December 31, 2014. This internal control failure related to certain management review controls, including those designed to provide oversight over our inventory costing and tracking systems that were not effective. Our findings related to both the design and operating effectiveness of these controls.

Notwithstanding our material weakness as of December 31, 2014, we have concluded that the financial statements and other financial information included in this Annual Report on Form 10-K fairly present in all material respects our financial condition, results of operations and cash flows as of, and for, the periods presented.

During 2015, we executed our remediation plan for this material weakness. Our 2015 remediation activities involved numerous enhancements to our financial accounting processes, including the implementation of additional automated controls related to our standard costing overhead model, adding additional requirements to our tolerances, and adding additional and more precise general and management review controls to ensure that all available information is properly considered and reconciled. We also added personnel as needed to support our inventory supply chain process. We tested such newly established policies, procedures, and control activities designed to address the above-described material weakness. As a result, we believe that this material weakness was remediated as of December 31, 2015.

There have been no changes in our internal control over financial reporting during the fiscal fourth quarter of the year ended December 31, 2015 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting, other than completion of the actions taken to remediate the material weakness which existed as of December 31, 2014, as described above.

ITEM 9B: OTHER INFORMATION

None.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by Item 10 is incorporated herein by reference to the definitive Proxy Statement to be filed with the SEC pursuant to Regulation 14A within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

ITEM 11. EXECUTIVE COMPENSATION

The information required by Item 11 is incorporated herein by reference to the definitive Proxy Statement to be filed with the SEC pursuant to Regulation 14A within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The information required by Item 12 is incorporated herein by reference to the definitive Proxy Statement to be filed with the SEC pursuant to Regulation 14A within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

The information required by Item 13 is incorporated herein by reference to the definitive Proxy Statement to be filed with the SEC pursuant to Regulation 14A within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

ITEM 14. PRINCIPAL ACCOUNTING FEES AND SERVICES

The information required by Item 14 is incorporated herein by reference to the definitive Proxy Statement to be filed with the SEC pursuant to Regulation 14A within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

PART IV

ITEM 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES

EXHIBITS, FINANCIAL STATEMENT SCHEDULES

The information required to be filed in this item appears on pages 71 to 106 of this Annual Report on Form 10-K.

(a) Documents filed as part of this Annual Report on Form 10-K:

(1) Index list to Consolidated Financial Statements:

(2) Schedule II is included on page 106 of this report. All other schedules are omitted because they are not required or the required information is included in the financial statements or notes thereto.

Exhibits

The following exhibits are filed as part of, or incorporated by reference into this Annual Report on Form 10-K:

Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Here with
		Form	Date	Exhibit Number	
2.1++	Asset Purchase Agreement, dated as of August 20, 2015, between Raptor Pharmaceutical Corp. and Tripex Pharmaceuticals, LLC	8-K	9/8/2015	2.1	
2.2	Amended and Restated Asset Purchase Agreement, dated as of October 2, 2015, by and among Raptor Pharmaceuticals Inc., Raptor Pharmaceutical Corp. and Tripex Pharmaceuticals, LLC	8-K	10/5/2015	2.1	
3.1	Certificate of Incorporation of Raptor Pharmaceutical Corp.	8-K	10/10/2006	3.1	
3.2	Certificate of Amendment to Certificate of Incorporation changing name to Raptor Pharmaceutical Corp.	8-K	10/5/2009	3.1	
3.3	Amended and Restated Bylaws of Raptor Pharmaceutical Corp.	8-K	5/18/2015	3.2	
4.1	Specimen common stock certificate of Raptor Pharmaceutical Corp.	8-K/A	10/7/2009	4.7	
4.2	Form of 8.0% Convertible Senior Notes due 2019 issued on July 23, 2014.	8-K	7/3/2014	10.1	
4.3	Registration Rights Agreement, dated as of August 20, 2015, by and among Raptor Pharmaceutical Corp., Tripex Pharmaceuticals, LLC and certain members of Tripex Pharmaceuticals, LLC	8-K	9/8/2015	4.1	
10.1++	Pharmaceutical Development Services Agreement, dated January 7, 2008, between Raptor Therapeutics Inc. and Patheon Pharmaceuticals Inc.	10QSB/A**	4/15/2008	10.2	
10.2	Form Indemnity Agreement	8-K	12/15/2009	10.1	
10.3++	Manufacturing Services Agreement, dated November 15, 2010, between Patheon Pharmaceuticals Inc. and Raptor Therapeutics, Inc.	POS AM	11/23/2010	10.53	
10.4++	API Supply Agreement, dated November 15, 2010, between Cambrex Profarmaco Milano and Raptor Therapeutics Inc.	POS AM	11/23/2010	10.54	
10.5++	Cooperative Research and Development Agreement for Extramural-PHS Clinical Research, dated December 15, 2011, between the U.S. Department of Health and Human Services, as represented by the National Institute of Diabetes and Digestive and Kidney Diseases, an institute or center of the National Institutes of Health, and Raptor Therapeutics Inc.	10-Q	4/9/2012	10.1	
10.6++	Second Amendment to License Agreement, effective October 30, 2012, between The Regents of the University of California and Raptor Therapeutics, Inc.	10-KT	3/14/2013	10.37	
10.7++	Wholesale Product Purchase Agreement, dated April 3, 2013, between Accredo Health Group, Inc. and Raptor Pharmaceuticals Inc.	10-Q	8/9/2013	10.1	
10.8++	Pharmacy Services Agreement, dated April 3, 2013, between Accredo Health Group, Inc. and Raptor Pharmaceuticals Inc.	10-Q	8/9/2013	10.2	
10.9	Office Lease, dated April 18, 2013, between Hamilton Marin, LLC and Raptor Pharmaceutical Corp.	10-Q	8/9/2013	10.3	
10.10	First Amendment to Office Lease, dated June 10, 2013, between Hamilton Marin, LLC and Raptor Pharmaceutical Corp.	10-Q	8/9/2013	10.4	
10.11++	Amendment to Manufacturing Services Agreement, dated April 5, 2012, between Patheon Pharmaceuticals Inc. and Raptor Therapeutics, Inc.	10-Q	8/9/2013	10.5	

Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Here with
		Form	Date	Exhibit Number	
10.12++	Second Amendment to Manufacturing Services Agreement, dated June 21, 2013, between Patheon Pharmaceuticals Inc. and Raptor Therapeutics, Inc.	10-Q	8/9/2013	10.6	
10.13	Convertible Note Purchase Agreement, dated as of July 1, 2014, among Registrant, as Issuer, HealthCare Royalty Partners II, L.P., HCRP Overflow Fund, L.P. and MOLAG Healthcare Royalty, LLC, each as Holder, and the Guarantors party thereto	8-K	7/2/2014	10.1	
10.14	Amended and Restated Loan Agreement, dated as of July 1, 2014, by and among Healthcare Royalty Partners II, L.P., Registrant and the Guarantors party thereto	8-K	8/21/2014	10.1	
10.15	Third Amendment to License Agreement, dated as of March 1, 2013, between The Regents of the University of California and Raptor Pharmaceuticals, Inc.	10-K	3/2/2015	10.49	
10.16	Fourth Amendment to License Agreement, dated as of December 16, 2013, between The Regents of the University of California and Raptor Pharmaceuticals, Inc.	10-K	3/2/2015	10.50	
10.17++	Development and License Agreement, dated as of February 11, 2006, between PARI Pharma GmbH successor in interest to PARI GmbH, and Mpex Pharmaceuticals, Inc.	8-K	9/8/2015	10.1	
10.18++	Commercial Supply Agreement, dated as of August 20, 2015, between Raptor Pharmaceutical Corp. and PARI Pharma GmbH	8-K	9/8/2015	10.2	
10.19++	Letter Agreement, dated as of August 20, 2015, between Raptor Pharmaceutical Corp. and PARI Pharma GmbH	8-K	9/8/2015	10.3	
10.20++	Form of Amendment No. 1 to Development and License Agreement, to be entered into by and between Raptor Pharmaceutical Corp. and PARI Pharma GmbH	8-K	9/8/2015	10.4	
10.21	Sales Agreement, dated as of September 4, 2015, between Raptor Pharmaceutical Corp. and Cowen and Company, LLC	8-K	9/8/2015	10.1	
10.22#	TorreyPines Therapeutics, Inc. 2006 Equity Incentive Plan	8-K	10/4/2006	10.1	
10.23#	Form of Stock Option Agreement under TorreyPines Therapeutics, Inc. 2006 Equity Incentive Plan	8-K	10/4/2006	10.2	
10.24#	2006 Equity Incentive Plan of Raptor Pharmaceutical Corp., as amended	S-8**	2/28/2007	4.3	
10.25#	Amendment to 2006 Equity Incentive Plan of Raptor Pharmaceutical Corp.	10-K/A**	12/23/2008	10.5	
10.26#	Raptor Pharmaceutical Corp. 2010 Stock Incentive Plan	DEF14A	2/5/2010	Appendix A	
10.27#	2011 Amendment to the Raptor Pharmaceutical Corp. 2010 Stock Incentive Plan	S-8	4/26/2011	4.15	
10.28#	Form of Option Award Agreement under the Raptor Pharmaceutical Corp. 2010 Stock Incentive Plan	8-K	9/28/2011	10.1	
10.29#	Form of Restricted Share Unit Award Agreement under the Raptor Pharmaceutical Corp. 2010 Stock Incentive Plan				X
10.30#	2013 Amendment to the Raptor Pharmaceutical Corp. 2010 Stock Incentive Plan	8-K	7/25/2013	10.1	
10.31#	2015 Plan Amendment to the Raptor Pharmaceutical Corp. 2010 Stock Incentive Plan	DEF 14A	3/26/2015	Appendix A	
10.32#	Raptor Pharmaceutical Corp. 2013 Employee Stock Purchase Plan	DEF 14A	06/17/2014	Appendix A	

Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Here with
		Form	Date	Exhibit Number	
10.33#	Raptor Pharmaceutical Corp. 2014 Employment Commencement Stock Incentive Plan	10-K	3/2/2015	10.45	
10.34#	Form of Stock Option Agreement under Raptor Pharmaceutical Corp. 2014 Employment Commencement Stock Incentive Plan	10-K	3/2/2015	10.46	
10.35#	Amended and Restated Employment Agreement, dated as of July 7, 2014, by and between Julie Anne Smith and Raptor Pharmaceutical Corp	8-K	7/8/2014	10.1	
10.36#	Executive Employment Agreement, dated as of October 21, 2014, by and between David Happel and Raptor Pharmaceutical Corp.	10-K	3/2/2015	10.47	
10.37#	Executive Employment Agreement, dated as of January 2, 2015, by and between Michael Smith and Raptor Pharmaceutical Corp	8-K	1/7/2015	10.1	
10.38#	Executive Employment Agreement, dated as of January 2, 2015, by and between Krishna Polu, M.D. and Raptor Pharmaceutical Corp.	10-K	3/2/2015	10.48	
10.39#	Transition and Separation Agreement, dated as of July 15, 2015, by and between Thomas E. Daley and Raptor Pharmaceutical Corp.	8-K	7/17/2015	10.1	
10.40#	Executive Employment Agreement, dated as of July 15, 2015, by and between Ashley Gould and Raptor Pharmaceutical Corp.	10-Q	11/5/2015	10.1	
10.41#	Form of Executive Change in Control Severance Agreement	8-K	2/9/2016	10.1	
21.1	Subsidiaries of Raptor Pharmaceutical Corp.				X
23.1	Consent of Independent Registered Public Accounting Firm				X
24.1	Power of Attorney (included in the signature page hereto)				X
31.1	Certification of Julie Anne Smith, Chief Executive Officer and Director				X
31.2	Certification of Michael P. Smith, Chief Financial Officer and Treasurer				X
32.1	Certification of Julie Anne Smith, Chief Executive Officer and Director, and of Michael P. Smith, Chief Financial Officer and Treasurer				X
101.INS	XBRL Instance Document				
101.SCH	XBRL Taxonomy Extension Schema				
101.CAL	XBRL Taxonomy Extension Calculation Linkbase				
101.DEF	XBRL Taxonomy Extension Definition Linkbase				
101.LAB	XBRL Taxonomy Extension Label Linkbase				
101.PRE	XBRL Taxonomy Extension Presentation Linkbase				

** Incorporated by reference from the indicated filing of Raptor Pharmaceutical Corp. rather than that of the Registrant.
# Indicates a management contract or compensatory plan or arrangement.
++ Certain information omitted pursuant to a request for confidential treatment filed separately with and granted by the SEC.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

RAPTOR PHARMACEUTICAL CORP.

Dated: February 26, 2016

By: /s/ MICHAEL SMITH
Michael Smith
Chief Financial Officer and Treasurer
(Principal Financial Officer)

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Julie A. Smith and Michael Smith, his or her attorney-in-fact, with the power of substitution, for him or her in any and all capacities, to sign any amendments to this Annual Report on Form 10-K and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, hereby ratifying and confirming all that each of said attorneys-in-fact, or his or her substitute or substitutes, may do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated:

Signatures	Title	Date
/s/ Julie A. Smith Julie A. Smith	Chief Executive Officer and Director (Principal Executive Officer)	February 26, 2016
/s/ Michael Smith Michael Smith	Chief Financial Officer and Treasurer (Principal Financial Officer and Principal Accounting Officer)	February 26, 2016
/s/ Gregg Lapointe Gregg Lapointe	Chairman of the Board and Director	February 26, 2016
/s/ Raymond W. Anderson Raymond W. Anderson	Director	February 26, 2016
/s/ Suzanne L. Bruhn Suzanne L. Bruhn, Ph.D.	Director	February 26, 2016
/s/ Richard L. Franklin Richard L Franklin, M.D., Ph.D.	Director	February 26, 2016
/s/ Georges Gemayel Georges Gemayel, Ph.D.	Director	February 26, 2016
/s/ Llew Keltner Llew Keltner, M.D., Ph.D.	Director	February 26, 2016
/s/ Christopher M. Starr Christopher M. Starr, Ph.D.	Director	February 26, 2016

RAPTOR PHARMACEUTICAL CORP.

CONSOLIDATED FINANCIAL STATEMENTS,

REPORTS OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

For Inclusion in Annual Report on Form 10-K Filed With

Securities and Exchange Commission

December 31, 2015

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

RAPTOR PHARMACEUTICAL CORP.

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

Board of Directors and Stockholders
Raptor Pharmaceutical Corp.

We have audited the accompanying consolidated balance sheets of Raptor Pharmaceutical Corp. (a Delaware corporation) and subsidiaries (the "Company") as of December 31, 2015 and 2014, and the related consolidated statements of operations and comprehensive loss, stockholders' equity (deficit), and cash flows for each of the three years in the period ended December 31, 2015. Our audits of the basic consolidated financial statements included the financial statement schedule listed in the index appearing under Item 15(a)(2). These financial statements and financial statement schedule are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements and financial statement schedule based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of Raptor Pharmaceutical Corp. and subsidiaries as of December 31, 2015 and 2014, and the results of their operations and their cash flows for each of the three years in the period ended December 31, 2015 in conformity with accounting principles generally accepted in the United States of America. Also in our opinion, the related financial statement schedule, when considered in relation to the basic consolidated financial statements taken as a whole, presents fairly, in all material respects, the information set forth therein.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the Company's internal control over financial reporting as of December 31, 2015, based on criteria established in the 2013 Internal Control —Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO), and our report dated February 26, 2016 expressed an unqualified opinion thereon.

/s/ GRANT THORNTON LLP
San Francisco, California
February 26, 2016

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

Board of Directors and Stockholders
Raptor Pharmaceutical Corp.

We have audited the internal control over financial reporting of Raptor Pharmaceutical Corp. (a Delaware corporation) and subsidiaries (the "Company") as of December 31, 2015, based on criteria established in the 2013 Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting, included in the accompanying Management's Annual Report on Internal Control over Financial Reporting ("Management's Report"). Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit.

We conducted our audit in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

In our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2015, based on criteria established in the 2013 Internal Control—Integrated Framework issued by COSO.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the consolidated financial statements of the Company as of and for the year ended December 31, 2015, and our report dated February 26, 2016 expressed an unqualified opinion on those financial statements.

/s/ GRANT THORNTON LLP
San Francisco, California
February 26, 2016

RAPTOR PHARMACEUTICAL CORP.
CONSOLIDATED BALANCE SHEETS
(In thousands, except shares and per share data)

	December 31, 2015	December 31, 2014
ASSETS		
Current assets:		
Cash and cash equivalents	$ 157,352	$ 149,613
Restricted cash	1,055	1,562
Accounts receivable	13,267	7,455
Inventories	6,424	9,134
Prepaid expenses and other assets	3,301	3,841
Total current assets	181,399	171,605
Noncurrent assets:		
Property and equipment, net	7,644	5,880
Goodwill	12,223	3,275
Intangible assets, net	216,463	2,974
Other assets	5,619	5,332
Total Assets	$ 423,348	$ 189,066
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 5,423	$ 2,550
Accrued liabilities	22,630	16,859
Common stock warrant liability	—	711
Note payable, current portion	12,000	9,000
Total current liabilities	40,053	29,120
Noncurrent liabilities:		
Contingent consideration liability	166,800	—
Deferred tax liability	303	—
Note payable, net of current portion	39,000	51,000
Convertible notes	60,000	60,000
Total liabilities	306,156	140,120
Stockholders' equity:		
Preferred stock, $0.001 par value per share, 15,000,000 shares authorized, zero shares issued and outstanding	—	—
Common stock, $0.001 par value per share, 150,000,000 shares authorized, 85,235,591 and 68,861,366 shares issued and outstanding at December 31, 2015 and 2014, respectively	85	69
Additional paid-in capital	441,601	306,832
Accumulated other comprehensive loss	(1,377)	(60)
Accumulated deficit	(323,117)	(257,895)
Total stockholders' equity	117,192	48,946
Total Liabilities and Stockholders' Equity	$ 423,348	$ 189,066

The accompanying notes are an integral part of these consolidated financial statements.

RAPTOR PHARMACEUTICAL CORP.
CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(In thousands, except shares and per share data)

	For the Year Ended December 31,		
	2015	**2014**	**2013**
Product revenue	$ 94,190	$ 69,497	$ 16,872
Collaborative revenue	50	—	—
Total revenue	94,240	69,497	16,872
Cost of sales	12,621	9,416	1,653
Gross profit	81,619	60,081	15,219
Operating expenses:			
Research and development	58,634	43,477	29,177
Selling, general and administrative	71,443	56,654	37,948
Total operating expenses	130,077	100,131	67,125
Loss from operations	(48,458)	(40,050)	(51,906)
Interest income	255	76	188
Interest expense	(15,793)	(13,971)	(6,832)
Foreign currency transaction gain (loss)	(287)	261	8
Loss on short-term investments	—	—	(128)
Adjustment to fair value of common stock warrants	(495)	(1,148)	(10,747)
Other income	—	2,346	—
Loss before provision for income taxes	(64,778)	(52,486)	(69,417)
Provision for income taxes	444	54	—
Net Loss	$ (65,222)	$ (52,540)	$ (69,417)
Other comprehensive income (loss):			
Foreign currency translation gain (loss), net of tax	(1,317)	323	(268)
Comprehensive Loss	$ (66,539)	$ (52,217)	$ (69,685)
Net loss per share:			
Basic and diluted	$ (0.83)	$ (0.83)	$ (1.20)
Weighted-average shares outstanding:			
Basic and diluted	78,878,500	63,213,504	57,860,366

The accompanying notes are an integral part of these consolidated financial statements.

RAPTOR PHARMACEUTICAL CORP.
CONSOLIDATED STATEMENT OF STOCKHOLDERS' EQUITY (DEFICIT)
(In thousands, except shares and per share data)

	Common Stock		Additional Paid In	Accumulated Other Comprehensive	Accumulated	
	Shares	Amount	Capital	Income (Loss)	Deficit	Total
Balance at December 31, 2012	**52,425**	**$ 52**	**$ 155,945**	**$ (115)**	**$ (135,938)**	**$ 19,944**
Net loss	—	—	—	—	(69,417)	(69,417)
Other comprehensive income (loss)	—	—	—	(268)	—	(268)
Issuance of common stock:						—
At-the-market financing facility, net of offering costs	4,939	5	38,389	—	—	38,394
Exercise of common stock options	651	1	2,474	—	—	2,475
Exercise of common stock warrants	3,600	4	10,322	—	—	10,326
Reclassification of the fair value of warrant liabilities upon exercise			20,086		—	20,086
Stock-based compensation	—	—	7,030	—	—	7,030
Balance at December 31, 2013	**61,615**	**62**	**234,246**	**(383)**	**(205,355)**	**28,570**
Net loss	—	—	—	—	(52,540)	(52,540)
Other comprehensive income (loss)	—	—	—	323	—	323
Issuance of common stock:						—
Employee stock purchase plan	21	—	179	—	—	179
At-the-market financing facility, net of offering costs	4,970	4	44,459	—	—	44,463
Exercise of common stock options	1,643	2	6,574	—	—	6,576
Exercise of common stock warrants	612	1	1,825	—	—	1,826
Reclassification of the fair value of warrant liabilities upon exercise	—	—	7,503	—	—	7,503
Stock-based compensation	—	—	12,046	—	—	12,046
Balance at December 31, 2014	**68,861**	**69**	**306,832**	**(60)**	**(257,895)**	**48,946**
Net loss	—	—	—	—	(65,222)	(65,222)
Other comprehensive income (loss)	—	—	—	(1,317)	—	(1,317)
Issuance of common stock:						—
Employee stock purchase plan	141	—	938	—	—	938
Sale of common stock	10,925	11	92,038			92,049
Restricted stock units	10	—	—	—	—	—
Exercise of common stock options	1,567	2	6,606	—	—	6,608
Exercise of common stock warrants	284	0	301	—	—	301
Employee stock-based compensation expense	—	—	12,803	—	—	12,803
Consultant stock-based compensation expense	—	—	20	—	—	20
Common stock issued for QUINSAIR acquisition	3,448	3	20,857	—	—	20,860
Reclassification of the fair value of warrant liabilities upon exercise	—	—	1,206	—	—	1,206
Balance at December 31, 2015	**85,236**	**$ 85**	**$ 441,601**	**$ (1,377)**	**$ (323,117)**	**$ 117,192**

The accompanying notes are an integral part of these consolidated financial statements.

RAPTOR PHARMACEUTICAL CORP.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	For the Year Ended December 31,		
	2015	**2014**	**2013**
Cash flows from operating activities:			
Net loss	$ (65,222)	$ (52,540)	$ (69,417)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation expense	12,823	12,046	7,030
Fair value adjustment of common stock warrants	495	1,148	10,747
Amortization of intangible assets	311	239	193
Depreciation of property and equipment	1,310	798	244
Deferred income taxes	303	—	—
Realized loss (gain) on disposal/sale of property and equipment	—	219	(12)
Loss on short-term investments	—	—	128
Amortization of debt issuance cost	1,215	1,626	433
Changes in assets and liabilities:			
Accounts receivable	(5,973)	(1,274)	(6,181)
Inventories	2,627	(6,134)	(3,000)
Prepaid expenses and other assets	438	572	(2,028)
Deposits	(659)		
Accounts payable	2,970	(2,714)	(114)
Accrued liabilities	5,203	3,731	10,683
Deferred revenue	—	(4,698)	4,698
Net cash used in operating activities	(44,159)	(46,981)	(46,596)
Cash flows from investing activities:			
Net purchase of property and equipment	(2,890)	(5,086)	(1,586)
Purchase of short-term investments	—	—	(147)
Sale of short-term investments	—	—	22,114
Intangible assets	—	—	(1,250)
Change in restricted cash	492	(1,062)	(337)
Acquisition of QUINSAIR	(35,370)	—	—
Net cash (used in) provided by investing activities	(37,768)	(6,148)	18,794
Cash flows from financing activities:			
Proceeds from sale of common stock, net	92,049	—	—
Proceeds from sale of common stock under ATM agreement	—	44,463	38,394
Proceeds from the exercise of common stock warrants	301	1,826	10,326
Proceeds from the exercise of common stock options and ESPP	7,546	6,755	2,475
Proceeds from issuance of debt	—	70,000	25,000
Debt issuance costs	—	(3,521)	(1,260)
Principal payments on debt	(9,000)		
Offering costs	-	(156)	(126)
Net cash provided by financing activities	90,896	119,367	74,809
Effect of exchange rates on cash and cash equivalents	(1,230)	323	(268)
Net increase in cash and cash equivalents	7,739	66,561	46,739
Cash and cash equivalents, beginning of period	149,613	83,052	36,313
Cash and Cash Equivalents, End of Period	$ 157,352	$ 149,613	$ 83,052

Supplemental cash flow information:	**2015**	**2014**	**2013**
Interest paid	$ 14,328	$ 11,654	$ 5,412
Income taxes paid	384	176	2
Supplemental disclosure of non-cash investing and financing activities:			
Common stock issued in connection with QUINSAIR acquisition	20,860	—	—
Contingent consideration recognized in connection with QUINSAIR acquisition	166,800	—	—
Fair value of warrant liability reclassified to equity upon exercise	1,206	7,503	20,086

The accompanying notes are an integral part of these consolidated financial statements.

RAPTOR PHARMACEUTICAL CORP.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

December 31, 2015

1. NATURE OF OPERATIONS AND BUSINESS RISKS

The accompanying consolidated financial statements reflect the financial position and results of operations of Raptor Pharmaceutical Corp. (the "Company" or "Raptor") and have been prepared in accordance with the accounting principles generally accepted in the United States of America ("GAAP").

Raptor is a biopharmaceutical company focused on developing and commercializing transformative treatments for people affected by rare and debilitating diseases. The Company's first product, PROCYSBI® (cysteamine bitartrate) delayed-release capsules ("PROCYSBI"), received marketing approval from the U.S. Food and Drug Administration ("FDA") on April 30, 2013 for the management of nephropathic cystinosis in adults and children six years and older. On August 14, 2015 the Company received FDA approval for the expanded use of PROCYSBI to treat children two to six years of age with nephropathic cystinosis. In Europe, PROCYSBI® gastro-resistant hard capsules of cysteamine (as mercaptamine bitartrate), received marketing authorization on September 6, 2013 from the European Commission ("EC"), for marketing in the European Union ("EU") as an orphan medicinal product for the management of proven nephropathic cystinosis. PROCYSBI received seven years of market exclusivity, through 2020, as an orphan drug in the United States and ten years of market exclusivity, through 2023, as an orphan drug in Europe. The Company commenced commercial sales of PROCYSBI in the United States in June 2013, and in Europe in April 2014. For at least the near term, the Company's ability to generate revenue is dependent upon sales of PROCYSBI in the United States for the management of nephropathic cystinosis in adults and children two years and older and in the EU for the management of proven nephropathic cystinosis.

In October 2015, we acquired various assets and rights related to levofloxacin solution for inhalation, a pharmaceutical product also known as "MP-376" and commercially as "QUINSAIR," from Tripex Pharmaceuticals, LLC ("Tripex"). QUINSAIR received marketing authorization by the EC for treating chronic lung infection caused by the bacteria *Pseudomonas aeruginosa* in adults who have cystic fibrosis in March 2015 and Health Canada in June 2015 for the management of cystic fibrosis in patients aged 18 years or older with chronic pulmonary *Pseudomonas aeruginosa* infections. We plan to launch QUINSAIR in Europe in the first half of 2016 and Canada later in 2016. QUINSAIR is not approved in the United States and the Company plans to discuss the path to potential approval in the same indication in the United States with the FDA in 2016.

Raptor's development pipeline includes its proprietary delayed-release form of cysteamine, or RP103, the investigational form of PROCYSBI and MP-376, the investigational form of QUINSAIR. Raptor currently has product candidates in clinical development designed to potentially treat Huntington's disease ("HD") and Leigh syndrome and other mitochondrial disorders. Raptor's preclinical programs are based upon bioengineered novel drug candidates that are designed to address rare and orphan indications.

Basis of Presentation

The Company's consolidated financial statements include the accounts of the Company's direct and indirect wholly owned subsidiaries: Raptor Pharmaceuticals Inc., formerly known as Raptor Therapeutics Inc., which merged with Raptor Discoveries Inc. in December 2012 prior to changing its name, and Raptor European Products, LLC, each of which was incorporated in Delaware on August 1, 2007, and February 14, 2012, respectively, and Raptor Pharmaceuticals Europe B.V. ("BV"), Raptor Pharmaceuticals France SAS ("SAS"), Raptor Pharmaceuticals Germany GmbH ("GMBH") and RPTP European Holdings C.V. ("CV"), domiciled in the Netherlands on December 15, 2009, in France on October 30, 2012, in Germany on October 16, 2013 and in the Cayman Islands on February 16, 2012, respectively. All inter-company accounts have been eliminated. Net assets in foreign countries totaled $ 4.5 million and $5.8 million at December 31, 2015 and 2014, respectively.

RAPTOR PHARMACEUTICAL CORP.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

December 31, 2015

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Use of Estimates

The preparation of financial statements in conformity with U.S. GAAP requires management to make certain estimates and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent assets and liabilities as of the dates of the consolidated financial statements and the reported amounts of revenues and expenses during the reporting period. Actual results could differ from those estimates.

Functional Currency

The Company's consolidated functional currency is the U.S. dollar. BV, SAS, and GMBH, the Company's Dutch subsidiary, French subsidiary, and German subsidiary, respectively, use the European Euro as their functional currency. The CV subsidiary, a Cayman-based subsidiary, uses the U.S dollar as its functional currency. At each quarter end, each foreign subsidiary's balance sheets are translated into U.S. dollars based upon the quarter-end exchange rate, while their statements of operations and comprehensive loss are translated into U.S. dollars based upon an average exchange rate during the period.

Segment Information

The Company has determined that it operates in only one segment, as it only reports profit and loss information on an aggregate basis to its chief operating decision maker. The Company's long-lived assets maintained outside the United States are not material.

Fair Value of Financial Instruments

The carrying amounts of certain of the Company's financial instruments including cash equivalents, restricted cash, accounts receivable, accounts payable and accrued liabilities, approximate fair value due either to length of maturity or interest rates that approximate prevailing market rates. The Company previously recorded a common stock warrant liability which was carried at fair value and, determined using the Black-Scholes option valuation model at the end of each reporting period.

Cash and Cash Equivalents

The Company considers all highly liquid investments with original maturities of three months or less, when purchased, to be cash equivalents. The Company maintains cash and cash equivalents, which consist principally of money market funds, with high credit quality financial institutions. Such amounts exceed Federal Deposit Insurance Corporation insurance limits. As of December 31, 2015, the Company had $157.4 million in cash and cash equivalents, of which $6.9 million was held by its foreign subsidiaries.

Restricted Cash

Restricted cash represents certificates of deposit and compensating balances required by the Company's U.S. and European banks as collateral for credit cards and for access to a value-added tax deferral program.

Accounts Receivable and Allowance for Doubtful Accounts

Accounts receivable are recorded and carried at the original invoiced amount less an allowance for any potential uncollectible amounts. The Company estimates its allowance for doubtful accounts based upon an assessment of various factors, including historical experience, the age of the accounts receivable balances, credit quality of customers, current economic conditions, and other factors that may affect customers' ability to pay. To date, the Company has not experienced significant losses with respect to the collection of accounts receivable.

Revenue Recognition and Accounts Receivable

The Company recognizes revenue in accordance with the Financial Accounting Standards Board ("FASB") Accounting Standards Codification ("ASC") 605, Revenue Recognition, when the following criteria have been met: persuasive evidence of an arrangement exists; delivery has occurred and risk of loss has passed; the seller's price to the buyer is fixed or determinable and collectability is reasonably assured. The Company determines that persuasive evidence of an arrangement exists based on written

contracts that define the terms of its revenue arrangements. Pursuant to the contract terms, the Company determines when title to products and associated risk of loss has passed on to the customer. The Company assesses whether the Company's product and/or revenue fees are fixed or determinable based on the payment terms associated with the corresponding transaction and whether the sales price and/or fees are subject to refund or adjustment. The Company assesses collectability based primarily on the customer's payment history and creditworthiness, and records a reserve for product returns based upon timing and history of similar product sales and returns in the pharmaceutical industry.

PROCYSBI is currently distributed in the U.S. by a specialty pharmacy distributor, the Accredo Health Group, Inc. ("Accredo") which is currently the Company's only U.S. customer and which subsequently ships directly to patients. The Company's distributor in the EU and other territories outside the U.S. is the Almac Group, Ltd., which ships directly to pharmacies after a prescription for PROCYSBI has been received. PROCYSBI is not available in U.S. retail pharmacies. Authorization of coverage by patients' commercial insurance plans, Raptor's patient assistance program ("PAP") or government payors is a prerequisite to the shipment of PROCYSBI to U.S. patients. Prior to the third quarter of 2014, revenue from the sale of PROCYSBI in the U.S. was recognized based on the amount of product sold through to the patients. Beginning July 2014, the Company was able to reasonably estimate and determine sales allowances in the U.S.; therefore the Company began recognizing PROCYSBI revenue in the U.S. at the point of sale to the specialty pharmacy, which resulted in a one-time non-recurring recognition of an additional $4.4 million in net revenues during the three months ended September 30, 2014. Revenue is currently recognized in the EU once confirmed orders from pharmacies have been shipped and invoiced for payment by the distributor on the Company's behalf.

The Company records revenue net of expected discounts, distributor fees, and rebates, including government rebates such as Medicare and Medicaid in the U.S. Allowances are recorded as a reduction of revenue at the time product sales are recognized. Allowances for government rebates and discounts are established based on the actual payor and payor mix information, which is known in the U.S. at the time of shipment to the distributor and in Europe at the time of shipment to pharmacies, and the government-mandated discount rates applicable to government-funded programs. There is a significant time lag in us receiving these rebate notices (generally several months after our sale is made). The Company's estimates are based on our historical claims from participating state governments, as supplemented by management's judgment. The allowances are adjusted to reflect known changes in the factors that may impact such allowances in the quarter the changes are known.

Inventories and Cost of Sales

Inventories are stated at the lower of cost or market price, with cost determined on a first-in, first-out basis. Inventories are reviewed periodically to identify slow-moving inventory based on sales activity, both projected and historical, as well as product shelf-life.

Products that have been approved by the FDA or other regulatory authorities are also used in clinical programs, to assess the safety and efficacy of the products for usage in diseases or patients that have not been approved by the FDA or other regulatory authorities. The form of PROCYSBI utilized for both commercial and clinical programs is identical and, as a result, the inventory has an "alternative future use" as defined in authoritative accounting guidance. Raw materials and purchased drug product associated with clinical development programs are included in inventory and charged to research and development expense when the product enters the research and development process and/or no longer can be used for commercial purposes and, therefore, does not have an "alternative future use."

Upon launching PROCYSBI in June 2013 in the United States and in April 2014 in the EU, the Company began recognizing cost of sales. Cost of sales includes the cost of inventory sold or reserved; manufacturing, manufacturing overhead and supply chain costs; inventory variance amortization; product shipping and handling costs; and amortization of licensing approval milestone payments and licensing royalties payable to the University of California, San Diego ("UCSD").

Property and Equipment

Property and equipment, which mainly consist of leasehold improvements, office furniture, lab equipment and computer hardware and software, are stated at cost. Depreciation is computed using the straight-line method over the related estimated useful lives, except for leasehold improvements, which are depreciated over the shorter of the useful life of the asset or the lease term. Significant additions and improvements that have useful lives estimated at greater than one year are capitalized, while repairs and maintenance are charged to expense as incurred.

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Goodwill and Intangible Assets

Goodwill represents the excess of the consideration transferred over the estimated fair value of assets acquired and liabilities assumed in a business combination. Intangible assets with indefinite useful lives are related to purchased in-process research and development (IPR&D) projects and are measured at their respective fair values as of the acquisition date. The Company does not amortize goodwill and intangible assets with indefinite useful lives. Intangible assets related to IPR&D projects are considered to be indefinite-lived until the completion or abandonment of the associated R&D efforts. If and when development is complete, which generally occurs if and when marketing approval is obtained, the associated assets are deemed finite-lived and are amortized based on their respective estimated useful lives at that point in time. The Company tests goodwill and other indefinite-lived intangible assets for impairment on an annual basis and in between annual tests if any events or changes occur that would indicate the fair values of the assets are below their carrying amounts.

Intangible assets with finite useful lives are amortized over their estimated useful lives on a straight-line basis, and are reviewed for impairment when facts or circumstances suggest that the carrying value of these assets may not be recoverable.

Common Stock Warrant Liabilities

The Company previously issued common stock warrants that contained conditional obligations that may have required the Company to transfer cash to settle the warrants upon the occurrence of certain fundamental transactions. Therefore, the Company classified such warrants as liabilities. At each reporting period, the Company re-measured the common stock warrant liability at the end of every reporting period with the change in value reported in the Company's consolidated statements of operations and comprehensive loss. At the exercise date, the fair values of these warrants were re-measured and reclassified to equity. As of December 31, 2015, all common stock warrants had been exercised or expired.

Debt Issuance Costs

Debt issuance costs are expenses associated with the loan agreements with HC Royalty and the issuance of convertible notes (see Note 8). Debt issuance costs which were capitalized are being amortized over the life of the respective debt to interest expense using the interest method. Debt issuance costs are a component of Other Assets on the Company's consolidated balance sheets.

Other Income

In 2014, the Company recorded other income of $2.3 million related to disgorgement of alleged short-swing profits under Section 16(b) of the Securities Exchange Act of 1934 from a stockholder. This amount is recorded as *Other Income* on the Company's Consolidated Statements of Operations and Comprehensive Loss.

Net Loss per Share

Net loss per share is calculated by dividing net loss by the weighted-average shares of common stock outstanding during the period. Diluted net loss per share is calculated by dividing net loss by the weighted-average shares of common stock outstanding and potential shares of common stock during the period. For all periods presented, potentially dilutive securities are excluded from the computation of fully diluted net loss per share as their effect is anti-dilutive. Potentially dilutive securities include:

	Year Ended December 31,		
	2015	2014	2013
Warrants to purchase common stock	—	334,764	946,370
Options to purchase common stock	8,790,474	8,857,961	8,217,674
Restricted stock unit awards outstanding	448,777		
Convertible debt	3,428,571	3,428,571	—
Total Potentially Dilutive Securities	12,667,822	12,621,296	9,164,044

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Stock-Based Compensation

Compensation costs related to the Company's stock incentive plans are measured at the grant date based on the fair value of the equity instruments awarded and are recognized over the period during which an employee is required to provide service in exchange for the award, or the requisite service period, which is usually the vesting period. Compensation expense for stock-based compensation awards is reduced by an estimate for forfeitures.

Research and Development

Research and development costs are charged to expense as incurred. Research and development expenses primarily include salaries and benefits for medical, clinical, regulatory, quality, pharmacovigilance, preclinical, and research personnel, costs related to research activities, preclinical and nonclinical studies, clinical trials, and drug manufacturing expenses, including certain commercial drug manufacturing expenses prior to obtaining marketing approval.

Advertising Expenses

The Company expenses advertising costs, including promotional expenses, as incurred. For the years ended December 31, 2015, and 2014 advertising expenses were $2.9 million and $1.4 million, respectively.

Income Taxes

Income taxes are recorded under the liability method, under which deferred tax assets and liabilities are determined based on the difference between the financial statement and tax bases of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to affect taxable income. Valuation allowances are established when necessary to reduce deferred tax assets to the amount expected to be realized. Based on the weight of available evidence, including cumulative losses since inception and expected future losses, the Company has determined that it is more likely than not that the deferred tax asset amount will not be realized and therefore a full valuation allowance has been provided on the Company's net deferred tax assets.

The Company identifies uncertain tax positions and discloses any potential tax liability on its financial statements. The Company recognizes interest and/or penalties related to income tax matters as a component of income tax expense. As of December 31, 2015, there were no accrued uncertain tax positions or interest and penalties related to uncertain tax positions.

The Company files U.S. federal, California state, and various other state and foreign country income tax returns. The Company is currently not subject to any income tax examinations. Due to the Company's net operating losses ("NOLs"), generally all tax years remain open.

Reclassifications

Certain amounts previously reported under specific financial statement captions have been reclassified to be consistent with the current period presentation.

Recent Accounting Pronouncements

In May 2014, the FASB issued Accounting Standards Update ("ASU") 2014-09, Revenue from Contracts with Customers, which outlines a single comprehensive model for entities to use in accounting for revenue arising from contracts with customers and supersedes most current revenue recognition guidance, including industry-specific guidance. The core principle of the revenue model is that "an entity recognizes revenue to depict the transfer of promised goods or services to customers in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services." In applying the revenue model to contracts within its scope, the Company will: identify the contract(s) with a customer, identify the performance obligations in the contract, determine the transaction price, allocate the transaction price to the performance obligations in the contract, and recognize revenue when (or as) the entity satisfies a performance obligation. In August 2015, the FASB issued ASU 2015-14, which defers the effective date of ASU 2014-09 by one year for all entities and permits early adoption on a limited basis. ASU 2014-09 will be effective for the Company in the first quarter of 2018, and early adoption permitted in the first quarter of 2017. The Company does not believe the adoption of this ASU will have a material impact on its consolidated financial statements.

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In August 2014, the FASB issued ASU 2014-15, Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern, which provides guidance on determining when and how reporting entities must disclose going-concern uncertainties in their financial statements. The ASU requires management to perform interim and annual assessments of an entity's ability to continue as a going concern within one year of the date of issuance of the entity's financial statements (or within one year after the date on which the financial statements are available to be issued, when applicable). Further, an entity must provide certain disclosures if there is "substantial doubt about the entity's ability to continue as a going concern." This ASU is effective for the Company in the first quarter of 2018, and early adoption permitted. The Company does not expect the adoption of the amendments to have a material effect on its financial condition and results of operations.

In April 2015, the FASB issued ASU 2015-03, Simplifying the Presentation of Debt Issuance Costs, which amends the presentation of debt issuance costs in the balance sheet as a direct deduction from the carrying amount of the related debt liability rather than as a deferred charge as presented under current guidance. ASU 2015-03 is effective for the Company in the first quarter of 2016 and must be applied retrospectively. Early adoption is permitted. In August 2015, the FASB issued ASU 2015-15, Interest - Imputation of Interest, to clarify the SEC staff's position on presenting and measuring debt issuance costs incurred in connection with line-of-credit arrangements given the lack of guidance on this topic in ASU 2015-03. The SEC staff has announced that it would "not object to an entity deferring and presenting debt issuance costs as an asset and subsequently amortizing the deferred debt issuance costs ratably over the term of the line-of-credit arrangement." The adoption of this amendment would result in a balance sheet reclassification of the Company's $3.8 million unamortized debt issuance costs balance of December 31, 2015 to a reduction in the carrying amount of the related debt liability. This amendment will not affect the Company's results of operations.

In July 2015, the FASB issued ASU 2015-11, Simplifying the Measurement of Inventory, which requires entities to measure most inventory "at the lower of cost and net realizable value," thereby simplifying the current guidance under which an entity must measure inventory at the lower of cost or market. ASU 2015-11 is effective for the Company in the first quarter of 2017 and is to be applied prospectively. Early adoption is permitted. The Company does not expect the adoption of this amendment to have a material effect on its financial condition and results of operations.

In September 2015, the FASB issued ASU 2015-16, Simplifying the Accounting for Measurement-Period Adjustments which allows entities to recognize adjustments to provisional amounts in the period adjustment is identified rather than retrospectively. In-period adjustments must be disclosed. This ASU is effective for the Company in the first quarter of 2016. The amendments should be applied prospectively to adjustments to provisional amounts that occur after the effective date of this ASU. Early adoption is permitted for financial statements that have not been issued. The Company does not expect the adoption of this amendment to have a material effect on its financial condition and results of operations.

In November 2015, the FASB issued ASU 2015-17, Balance Sheet Classification of Deferred Taxes. This is part of FASB's simplification initiative. The amendments in this ASU require that deferred tax liabilities and assets be classified as noncurrent in a classified statement of financial position. This ASU is effective for the Company in the first quarter of 2017. Early adoption is permitted. The Company does not expect the adoption of this amendment to have a material effect on its financial condition and results of operations.

In January 2016, the FASB issued ASU 2016-01, Recognition and Measurement of Financial Assets and Financial Liabilities. The purpose is to enhance the reporting model for financial instruments to provide users of financial statements with more decision-useful information. This ASU is effective for the Company in the first quarter of 2018. Early adoption is not permitted except for limited provisions. The Company does not expect the adoption of this amendment to have a material effect on its financial condition and results of operations.

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3. FAIR VALUE MEASUREMENT

The Company uses a fair value approach to value certain assets and liabilities. Fair value is the price that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. As such, fair value is a market-based measurement that should be determined based on assumptions that market participants would use in pricing an asset or liability. The Company uses a fair value hierarchy, which distinguishes between assumptions based on market data (observable inputs) and an entity's own assumptions (unobservable inputs). The hierarchy consists of three levels:

- Level 1 –Quoted market prices in active markets for identical assets or liabilities;
- Level 2 –Inputs other than level one inputs that are either directly or indirectly observable; and
- Level 3 –Unobservable inputs developed using estimates and assumptions, which are developed by the reporting entity and reflect those assumptions that a market participant would use.

Determining which category an asset or liability falls within the hierarchy requires significant judgment. The Company evaluates its hierarchy disclosures each reporting period. There were no transfers between Level 1, 2 or 3 of the fair value hierarchy during the years ended December 31, 2015 and 2014. The following table presents the assets and liabilities recorded that are reported at fair value on our consolidated balance sheets on a recurring basis.

Assets and Liabilities Measured at Fair Value on a Recurring Basis

(In thousands) December 31, 2015	Level 1	Level 2	Level 3	Total
Assets				
Cash equivalents (1)	$ 147,007	$ —	$ —	$ 147,007
Total	$ 147,007	$ —	$ —	$ 147,007
Liabilities				
Contingent Consideration Liability	$ —	$ —	$ 166,800	$ 166,800
Total	$ —	$ —	$ 166,800	$ 166,800

December 31, 2014	Level 1	Level 2	Level 3	Total
Assets				
Cash equivalents (1)	$ 137,938	$ —	$ —	$ 137,938
Total	$ 137,938	$ —	$ —	$ 137,938
Liabilities				
Common stock warrants	$ —	$ —	$ 711	$ 711
Total	$ —	$ —	$ 711	$ 711

(1) Cash equivalents represent the fair value of the Company's investments in money market funds at December 31, 2015 and 2014.

The following table presents a reconciliation of the Company's recurring fair value measurements categorized within Level 3 of the fair value hierarchy (liability-classified common stock warrants). See Note 11 for additional information regarding the fair value of the contingent consideration liability.

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Changes in Level 3 Liabilities Measured at Fair Value on a Recurring Basis – Common Stock Warrants

	Year Ended December 31,		
(In thousands)	2015	2014	2013
Beginning fair value	$ 711	$ 7,066	$ 16,405
Change in fair value recognized in earnings	495	1,148	10,747
Exercises	(1,206)	(7,503)	(20,086)
Ending Fair Value	$ —	$ 711	$ 7,066

Certain of the Company's previously outstanding common stock warrants were classified as liabilities and were, therefore, re-measured using the Black-Scholes option valuation model at the end of each reporting period with the change in value reported in the Company's consolidated statements of operations and comprehensive loss. At December 31, 2015, all common stock warrants subject to liability classification had been exercised or expired.

Effect of Raptor's Stock Price and Volatility Assumptions on the Calculation of Fair Value of Warrant Liabilities

As discussed above, the Company uses the Black-Scholes option pricing model as its method of valuation for warrants that are subject to warrant liability accounting. The determination of fair value as of the reporting date is affected by Raptor's stock price as well as assumptions regarding a number of subjective variables. These variables include, but are not limited to, expected stock price volatility over the term of the security and risk-free interest rate. The primary factors affecting the fair value of the warrant liability are the Company's stock price and volatility.

Fair Value of Certain Financial Liabilities

The following table presents the carrying value and fair value of certain financial liabilities that are recorded on the Company's consolidated balance sheets.

	December 31, 2015		December 31, 2014	
(In thousands)	Carrying Value	Fair Value	Carrying Value	Fair Value
Liabilities				
Note payable	$ 51,000	$ 63,004	$ 60,000	$ 65,522
Convertible notes	60,000	44,975	60,000	56,760

4. INVENTORIES

Inventories consist of raw materials, work-in-process and finished goods related to the manufacture of PROCYSBI. Raw materials include the active pharmaceutical ingredient ("API"), cysteamine bitartrate and materials that may be used for clinical trials, which are charged to research and development expense when consumed. Work-in-process includes third party manufacturing cost and an overhead allocation of the Company's manufacturing and quality testing expenses.

Inventories are summarized as follows:

	December 31,	
(In thousands)	2015	2014
Raw materials	$ 2,681	$ 6,290
Work-in-process	1,824	721
Finished goods	1,919	2,123
Total Inventories	$ 6,424	$ 9,134

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5. PROPERTY AND EQUIPMENT

The following table presents the components of property and equipment and their estimated useful lives.

(In thousands)	December 31, 2015	December 31, 2014	Estimated useful lives
Manufacturing equipment	$ 4,262	$ 2,393	—
Office furniture	2,344	2,198	7 years
Laboratory equipment	1,721	1,373	5 years
Computer hardware and software	1,364	815	3 years
Leasehold improvements	583	470	Lease term
Total at cost	10,274	7,249	
Less: accumulated depreciation	(2,630)	(1,369)	
Total Property and Equipment, Net	$ 7,644	$ 5,880	

Depreciation expense for the years ended December 31, 2015 and 2014 was $1.3 million and $0.8 million, respectively.

6. NET PRODUCT REVENUES BY GEOGRAPHIC REGION AND NET PRODUCT REVENUES BY SIGNIFICANT CUSTOMERS

Net Product Revenues by Geographic Region

(In millions)	For the Year Ended December 31, 2015	2014	2013
United States	$ 86.5	$ 66.8	$ 16.9
International	7.7	2.7	—
Total Net Product Revenues by Geographic Region	$ 94.2	$ 69.5	$ 16.9

Net Product Revenues by Significant Customer

Sales to our significant customer, Accredo Health Services, totaled $86.5 million, or 91.82% for 2015, $66.8 million, or 96.12% for 2014, and $16.8, or 100% for 2013 of net product revenue.

7. GOODWILL AND INTANGIBLE ASSETS

On December 14, 2007, the Company acquired the intellectual property and other rights to develop RP103 to treat various clinical indications from UCSD by way of a merger with Encode Pharmaceuticals, Inc., a privately held development stage company (“Encode”), which held the intellectual property license with UCSD. The fair value of the intangible assets at the time of acquisition was approximately $2.6 million.

Pursuant to the license agreement with UCSD, the Company is obligated to pay an annual maintenance fee until the commencement of commercial sales of any licensed products is developed. The Company is also obligated to pay milestone payments upon the occurrence of certain events, royalties on net sales from products developed pursuant to the license agreement and a percentage of sublicense fees or royalties, if any. The Company is obligated to fulfill predetermined milestones within a specified number of years from the effective date of the license agreement, depending on the indication. To the extent that the Company fails to perform these obligations under the agreement, UCSD may terminate the license or otherwise cause the license to become non-exclusive.

In April 2013, the Company announced that the FDA approved PROCYSBI (cysteamine bitartrate) delayed release capsules for the management of nephropathic cystinosis in adults and children six years and older. Subsequently, in September 2013, the Company announced that the EC approved PROCYSBI® gastro-resistant hard capsules of cysteamine (as mercaptamine bitartrate) as an orphan medicinal product for the management of proven nephropathic cystinosis for marketing in the EU. The Company paid milestone

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payments to UCSD during the second and third quarters of 2013 of $0.8 million and $0.5 million, respectively, in conjunction with these approvals, which were capitalized as intangible assets.

In October 2015, the Company acquired the intellectual property and other rights to develop QUINSAIR from Tripex Pharmaceuticals, LLC ("Tripex") for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adults with cystic fibrosis that has received marketing approval in Europe and Canada. The fair value of the intangible assets at the time of acquisition was approximately $213.8 million.

A summary of intangibles acquired is as follows:

(In thousands)	Useful Life (Years)	December 31, 2015	December 31, 2014
IPR&D QUINSAIR	Indefinite	$ 210,600	$ —
Developed technology - QUINSAIR	11.0	3,200	$ —
IP license for RP103 related to the Encode merger	20.0	2,620	2,620
UCSD license - FDA and EC approval milestones	14.0	1,250	1,250
Other intangible assets	16.0	240	240
Total intangible assets		217,910	4,110
Less accumulated amortization		(1,447)	(1,136)
Intangible Assets, Net		$ 216,463	$ 2,974

The intangible assets (developed technology) related to the QUINSAIR developed technology are being amortized over an estimated useful life of 11 years, which is the life of the intellectual property patents. The intangible assets related to RP103 are being amortized over an estimated useful life of 20 years, which is the life of the intellectual property patents. The 14 year estimated useful life is also based upon the typical development, approval, marketing and life cycle management timelines of pharmaceutical drug products. Other intangible assets are being amortized using the straight-line method over an estimated useful life of 16 years, which is the life of the intellectual property patents. The above definite-lived intangibles do not have any residual value beyond the assets' useful lives.

During the years ended December 31, 2015 and 2014, there was no intangible asset impairment recognized.

During the years ended December 31, 2015 and 2014, the Company amortized $146 thousand, and $146 thousand, respectively, of intangible assets to research and development expense.

Amortization expense for intangible assets for each of the next five years is as follows:

(In thousands)	Amortization Expense
2016	$ 529
2017	529
2018	529
2019	529
2020	529

The changes in the carrying amount of goodwill for the years ended December 31, 2015 and 2014 are as follows:

(In thousands)	
Balance as of December 31, 2014 and 2013	$ 3,275
Goodwill acquired	8,948
Goodwill, Net	$ 12,223

The Company tested the carrying value of goodwill for impairment as of December 31, 2015 and determined that there was no impairment.

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8. ACCRUED LIABILITIES

Accrued liabilities consisted of:

(In thousands)	December 31, 2015	December 31, 2014
Personnel-related costs	$ 7,601	$ 6,879
Rebates and other sales deductions	2,833	3,231
Clinical trials and research and development costs	5,076	2,522
License royalty payable	1,352	972
Royalty-based interest payable	2,008	369
Manufacturing costs	1,577	284
Business development & legal costs	1,030	333
Other	1,153	2,269
Total Accrued Liabilities	$ 22,630	$ 16,859

The roll forward of significant estimated accrued rebates, reserve for cash discounts and product returns for the years ended December 31, 2015, and 2014 were as follows:

	Beginning Balance	Provision for Current Period Sales	Provision for Prior Period Sales	Actual Returns/ Credits Related to Current Period Sales	Actual Returns/ Credits Related to Prior Period Sales	Outstanding Balance at Year End
December 31, 2015						
Accrued rebates	$ 2,935	$ 6,250	$ 239	$ (3,712)	$ (3,174)	$ 2,538
Reserve for cash discounts	215	1,821	41	(1,563)	(256)	258
Product returns	296	—	—	—	—	296
December 31, 2014						
Accrued rebates	$ 2,029	$ 5,950	$ (1,135)	$ (3,388)	$ (521)	$ 2,935
Reserve for cash discounts	126	1,725	—	(1,511)	(125)	215
Product returns	296	—	—	—	—	296

The Company accrued approximately $2.5 million and $2.9 million for estimated rebate payments at December 31, 2015 and 2014, respectively. The Company evaluates its historical rebate payments by product as a percentage of historical sales in order to estimate its accrued rebates in proportion to revenue. Management has determined that a one-year look back represents a reasonable approach for assessing its rebate liabilities, and as of December 31, 2015 believes that it has adequately reserved for known and potentially unknown incurred rebates.

The Company accrued approximately $0.3 million and $0.2 million for the estimated cost of prompt-payment discounts at December 31, 2015 and 2014, respectively. These amounts are estimated based upon payment terms with each of the Company's customers.

The Company considered the need for a reserve for possible product returns sold during the years ended December 31, 2015 and 2014 respectively. The Company determined an allowance of $0.3 million at December 31, 2015 and 2014, respectively, was necessary for possible product returns from its distributor. These amounts are estimated based upon the timing and history of similar product sales in the pharmaceutical industry. As of December 31, 2015, no products had been returned.

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9. NOTE PAYABLE

On December 20, 2012, the Company entered into a loan agreement with HC Royalty, as lender, under which it agreed to borrow $50.0 million in two $25.0 million tranches. The Company received $23.4 million in net proceeds from the first tranche of the loan at closing in December 2012 and an additional $23.7 million in net proceeds in May 2013 from the second tranche upon FDA approval of PROCYSBI.

In July 2014, the Company entered into an amended and restated loan agreement with HC Royalty which revised the terms of the 2012 loan agreement between the Company and HC Royalty, and also provided for an additional $10.0 million in term loan funding. The interest rate was revised to an annual fixed rate of 8.0%, compared to the original interest rate of 10.75%. The loan also contains a synthetic royalty component based on net product revenues, including revenues from the sale of PROCYSBI, in each calendar year, and such royalty is payable quarterly. The variable royalty rate under the amended and restated loan agreement has been revised to 8.0% on the first $50.0 million of revenue and 2.0% on revenue in excess of $50.0 million. The first quarterly principal payment of $3.0 million was paid by the Company in June 2015. All term loans under the amended and restated loan agreement mature on March 31, 2020. The loan and the Company's obligation to make payments thereunder will terminate immediately when all payments received by HC Royalty equal $120.0 million.

Prior to July 1, 2014, with respect to the first $25.0 million tranche, for each calendar year (prorated for any portion thereof), the loan bore a royalty rate of 6.25% of the first $25.0 million of product net revenues, 3.0% of product net revenues for such calendar year in excess of $25.0 million and up to $50.0 million, and 1.0% of product net revenues for such calendar year in excess of $50.0 million, payable quarterly. Prior to July 1, 2014, with respect to the second $25.0 million tranche, for each calendar year (prorated for any portion thereof), the loan bore a variable royalty interest rate of 6.0% of the first $25.0 million of net product revenues for such calendar year, 3.0% of product net revenues for such calendar year in excess of $25.0 million and up to $50.0 million, and 1.0% of product net revenues for such calendar year in excess of $50.0 million, payable quarterly.

The Company's amended and restated loan agreement with HC Royalty includes affirmative and negative covenants, including the use of commercially reasonable efforts to exploit RP103 in specific markets and compliance with laws, as well as restrictions on mergers and sales of assets, incurrence of liens, incurrence of indebtedness and transactions with affiliates and other requirements. To secure the performance of the Company's obligations under the loan, the Company granted a security interest to HC Royalty in substantially all of its assets, the assets of its domestic subsidiaries and a pledge of stock of certain of its domestic subsidiaries. The Company's failure to comply with the terms of the loan and related documents, the occurrence of a change of control of the Company or the occurrence of an uncured material adverse effect on the Company or the occurrence of certain other specified events, will result in an event of default under the loan that, if not cured or waived, could result in the acceleration of the payment of all of its indebtedness, as well as prepayment penalties, to HC Royalty and interest thereon. Under the terms of the security agreement, in an event of default, HC Royalty can potentially take possession of, foreclose on, sell, assign or grant a license to use, the Company's pledged collateral and assign and transfer the pledged stock of certain of its subsidiaries.

The Company received marketing approval of PROCYSBI from the FDA on April 30, 2013 and commenced shipment of PROCYSBI during June 2013, and as a result, variable royalty interest became payable to HC Royalty based upon net revenues of PROCYSBI. Interest expense on the loan, excluding amortization of debt issuance costs, for the years ended December 31, 2015, 2014, and 2013 was approximately $9.8 million, $10.6 million, and $6.8 million, respectively.

The following table presents contractual principal payments of the note payable at December 31, 2015.

(In thousands)	Note Principal Payments
2016	$ 12,000
2017	12,000
2018	12,000
2019	12,000
2020	3,000
Total	$ 51,000

Unamortized debt issuance costs on the loan agreement totaled $1.5 million and $2.3 million at December 31, 2015 and 2014, respectively. Amortization expense was $0.7 million, $1.0 million and $0.4 million for the years ended December 31, 2015, 2014, and 2013, respectively.

10. CONVERTIBLE NOTES

In July 2014, the Company sold $60.0 million aggregate principal amount of 8.0% convertible senior notes due 2019 to HC Royalty and other purchasers. These convertible notes require quarterly interest distributions at a fixed coupon rate equal to 8.0% until maturity or conversion, which will be no later than August 1, 2019. The convertible senior notes are convertible at the option of the holder at a conversion rate of 57.14 common shares per $1,000 principal amount of convertible senior notes at issuance (equivalent to a conversion price of $17.50 per common share), subject to adjustment in certain events. Upon conversion of these convertible senior notes by a holder, the holder will receive shares of the Company's common stock.

In addition, the Company may elect to exercise the optional redemption, as defined in the note purchase agreement, in which case the convertible senior notes will convert into shares of common stock if the price of the common stock is at or above 175% of the applicable conversion price over a 30 consecutive day period. Upon the occurrence of a "change of control", as defined in the note purchase agreement, the holders may require the Company to repurchase all or a portion of the notes for cash at 100% of the principal amount of the notes being purchased, plus a repayment premium and any accrued and unpaid interest. To secure the performance of the Company's obligations under the convertible notes agreement, the Company has assigned certain of its assets as collateral.

Interest expense on convertible notes, excluding amortization of debt issuance costs, was $4.8 million and $2.1 million for the years ended December 31, 2015 and 2014, respectively. Unamortized debt issuance costs on these convertible notes totaled $2.3 million and $2.8 million at December 31, 2015 and 2014, respectively. Amortization expense for the years ended December 31, 2015 and 2014 was $0.5 million and $0.2 million, respectively.

11. BUSINESS COMBINATION

(a) Acquisition of QUINSAIR

Acquisition Overview

On October 5, 2015, the Company completed the acquisition of QUINSAIR from Tripex. The Company acquired exclusive global rights and assets to develop, manufacture and commercialize QUINSAIR a levofloxacin solution for inhalation. At closing, the Company paid Tripex approximately $35.4 million in cash consideration, subject to a deduction for payment of costs for representations and warranties insurance, and an amount to be held in escrow, and issued to Tripex 3,448,001 shares of Raptor common stock. In addition, the purchase agreement provides for contingent payments of up to $350 million associated with development, regulatory and commercial milestones, a portion of which is also payable in Raptor common stock at the Company's election, and a single digit royalty on future global net sales. The Company has single-digit royalty and contingent obligations to two additional parties involved in QUINSAIR's development.

Consideration transferred

The acquisition-date fair value of the consideration transferred consisted of the following items:

(In thousands)		
Cash consideration	**$**	**35,370**
Stock consideration		20,860
Contingent consideration		166,800
Total purchase consideration	$	223,030

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Fair Value Estimate of Assets Acquired and Liability Assumed

Property and equipment	**$**	**282**
Developed Technology		3,200
In-Process Research and Development		210,600
Goodwill		8,948
	$	223,030

	Value of Intangible Assets Acquired	Amortization Period*
Developed technology	$ 3,200	132 months
IPR&D	210,600	(1)
Total identifiable intangible assets	$ 213,800	

* Recognized on a straight-line basis.

(1) IPR&D is an intangible asset classified as indefinite-lived until the completion or abandonment of the associated research and development effort, and will be amortized over an estimated useful life to be determined at the date the project is completed. IPR&D is not amortized during this period, but is periodically tested for impairment.

The fair value of the acquired developed technology and IPR&D assets were estimated using the income approach. The income approach uses valuation techniques to convert future amounts to a single present amount (discounted). The measurement is based on the value indicated by current market expectations about those future amounts. Direct costs of the QUINSAIR acquisition included consulting, legal, and accounting fees which aggregated to $3.9 million. This amount is included in “selling, general and administrative expenses” within the accompanying Consolidated Statements of Operations for the year ended December 31, 2015.

The Company estimated the acquisition date fair value of the contingent consideration payable of $166.8 million on October 5, 2015, which is payable upon the achievement of specified development, regulatory approval, sales-based milestone events or financial results. The model used in valuing this contingent consideration liability requires the use of significant estimates and assumptions including but not limited to:

- estimates of revenues and operating profits related to the products or product candidates;
- the probability of success for unapproved product candidates considering their stages of development;
- the time and resources needed to complete the development and approval of product candidates;
- the life of the potential commercialized products and associated risks, including the inherent difficulties and uncertainties in developing a product candidate such as obtaining FDA and other regulatory approvals; and
- risks related to the viability of and potential alternative treatments in any future target markets.

As of December 31, 2015, the fair value of the contingent consideration liability remained unchanged at $166.8 million due to the limited passage of time from the acquisition date and as there were no changes to the significant estimates and assumptions used in measuring the acquisition date fair value. The contingent consideration liability is recognized on the face of the Company’s consolidated balance sheet.

The acquired assets were pre-revenue as of the acquisition date and the expenses incurred, related to the acquired assets, were insignificant for the period January 1, 2014 to the acquisition date. Subsequent to the acquisition date, the Company has not recognized any revenue and has incurred approximately $1.0 million of expenses through December 31, 2015.

Goodwill

Goodwill presented above of $8.9 million represents the difference of the QUINSAIR total purchase consideration of $223.0 million *minus* the net assets acquired of $214.1 million. This goodwill includes benefits that the Company believes will result from the

know-how associated with the QUINSAIR compound for the impending commercial launch and future product development. In accordance with applicable GAAP, the Company will not amortize goodwill though it will be subjected to annual impairment testing. This goodwill is not deductible for income tax purposes.

12. CAPITAL STRUCTURE

Stockholder Rights Plan

The Company's stockholder rights plan entitled the holder of each outstanding share of common stock of the Company to one stock purchase right (a "Right"). Each Right entitled the registered holder to purchase from the Company one thousandth of a share of the Company's Series A Participating Preferred Stock (the "Preferred Shares") at a price of $15 per one one-thousandth of a Preferred Share (the "Purchase Price"), once the Rights became exercisable. The Rights were not exercisable until the earlier of either (a) 10 days after the public announcement that a person, together with all affiliates or associates of such person, has become an "Acquiring Person" by obtaining beneficial ownership of 15% or more of the Company's outstanding common stock, or (b) 10 business days (or a later date determined by the Board before any person or group becomes an Acquiring Person) after a person or group of affiliated or associated persons began a tender or exchange offer which, if completed, would result in that person or group of affiliated or associated persons becoming an Acquiring Person. Each one one-thousandth of a share preferred stock, if issued, would have the same voting power as one one-hundred thirty-sixth (1/136th) of a share of common stock and would have entitled holders to a per share payment equal to the payment made on one one-hundred thirty-sixth (1/136th) of a share of common stock, so that one full share of preferred stock would be entitled to receive a payment one one-hundred thirty-sixth (1/136th) of 1,000 times the per share payment to a share of common stock, provided that shares of the Company's common stock were exchanged via merger, consolidation or a similar transaction. The Rights expired on May 13, 2015.

2009 Merger and NASDAQ Listing

On September 29, 2009, the Company, formerly known as TorreyPines Therapeutics, Inc. ("TorreyPines") and Raptor Pharmaceutical Corp. ("RPC") completed a reverse merger. The Company changed its name to "Raptor Pharmaceutical Corp." and commenced trading on the NASDAQ Global Market. In connection with the merger, the Company assumed all of the TorreyPines stock options and warrants outstanding at the time of the merger. The remaining warrants outstanding expired on September 26, 2015.

Common Stock Issuance under At-The-Market ("ATM") Agreement

On April 30, 2012, the Company entered into an "At-the-Market" ("ATM") sales agreement, with Cowen and Company, LLC ("Cowen"), under which the Company could, at its discretion, sell its common stock with a sales value of up to a maximum of $40.0 million through ATM offerings on the NASDAQ Stock Market (the "2012 Sales Agreement"). On July 3, 2013, the Company and Cowen amended and restated the 2012 Sales Agreement (the "2012 Amended and Restated Sales Agreement") to increase the aggregate gross sales proceeds that could be raised to $100.0 million. Cowen was the sole sales agent for any sales made under the ATM for a 3.0% commission on gross proceeds. The common stock was sold at prevailing market prices at the time of the sale of common stock, and, as a result, prices varied. Cumulatively through December 31, 2014, we sold 12,569,914 shares under the ATM offerings at a weighted-average selling price of $7.96 per share for net proceeds of approximately $97 million under the 2012 Amended and Restated Sales Agreement.

During the years ended December 31, 2014 and 2013, the Company sold approximately 5.0 million and 4.9 million shares, respectively, under ATM offerings at a weighted-average selling price of $9.29 and $8.09 per share, respectively, for proceeds of approximately $45 million and $38.8 million net of commissions, respectively. As of December 31, 2014, the Company did not have any remaining shares available under the ATM for future sales of the Company's common stock.

On September 4, 2015, the Company entered into a new ATM sales agreement, with Cowen, under which the Company may, at its discretion, sell its common stock with a sales value of up to a maximum of $75.0 million through ATM offerings on the NASDAQ Stock Market (the "2015 Sales Agreement"). Cowen is the sole sales agent for any sales made under the 2015 Sales Agreement, and the Company will pay Cowen a commission, or allow a discount, for its services in acting as agent in the sale of our common stock of up to 3.0% of the gross sales price per share of all shares sold through it as agent under the 2015 Sales Agreement. The common stock will be sold at prevailing market prices at the time of the sale of common stock, and, as a result, prices will vary. During the year ended December 31, 2015, there were no shares sold under the 2015 Sales Agreement and $75.0 million was available for issuance under the 2015 Sales Agreement.

2015 Follow-on Public Offering

On April 8, 2015, the Company closed an underwritten public offering of shares of the Company's common stock at a price to the public of $9.00 per share. The shares sold in the offering included 9.5 million shares of common stock plus an additional 1.43 million shares of common stock pursuant to the exercise by the underwriters of the over-allotment option the Company granted to them. Total gross proceeds to the Company in the offering (including in connection with the sale of the shares of common stock pursuant to the exercise of the over-allotment option) totaled $98.3 million, before underwriting discounts and commissions. The offering resulted in net proceeds to the Company of approximately $92.0 million after deduction of underwriting discounts of 6% and other offering expenses paid by the Company.

Common Stock Warrants

During the years ended December 31, 2015 and 2014, the Company received approximately $0.3 million and $1.8 million from the exercise of warrants in exchange for the issuance of 284,047 and 611,606 shares of the Company's common stock, respectively. There were no common stock warrants outstanding at December 31, 2015.

For the years ended December 31, 2015, 2014 and 2013, the Company recorded losses of approximately $0.5 million, $1.1 million, and $10.7 million, respectively, in its consolidated statements of operations and comprehensive loss from changes in the fair values of liability-classified warrants.

13. STOCK-BASED COMPENSATION

Stock Incentive Plans

The Company's 2010 Stock Incentive Plan, as amended, provides for stock options, restricted stock or RSUs to be granted to its employees, independent contractors, consultants and non-employee directors.

On November 25, 2014, as a key requirement of the Company's strategy of strengthening its leadership team and employee base, continuing the expansion of its commercial activities into new territories, and increasing the expansion of its product development programs, the Company's Board of Directors approved the 2014 Commencement Plan. The plan was approved pursuant to Rule 5635(c)(4) of the Nasdaq Global Select Market for equity grants to induce new employees to enter into employment with the Company. Up to 2,400,000 shares were available to be issued under this plan.

On May 19, 2015, at the Company's Annual Meeting of Stockholders, the stockholders approved amendments to the Company's 2010 Stock Incentive Plan. These amendments were previously approved by the Company's Board of Directors in February 2015. Among other things, the 2015 Plan Amendment increased the share reserve available for issuance by 3,456,620 under the 2010 Stock Incentive Plan to an aggregate of approximately 15.4 million shares plus any shares which are subject to awards under the 2014 Commencement Plan which are forfeited or lapse unexercised and which are not issued under the 2014 Commencement Plan, all of which may be used for any form of award under the 2010 Stock Incentive Plan. Following the approval of the 2015 Plan Amendment by the Company's stockholders, no new equity grants will be made under the 2014 Commencement Plan.

During the year ended December 31, 2015, the Company received approximately $6.6 million from the exercise of stock options. As of December 31, 2015, there were 3,906,512 shares remaining available for issuance under the 2010 Stock Incentive Plan, as amended.

Stock options are granted to recognize the contributions made by its employees, independent contractors, consultants and directors, to provide those individuals with additional incentive to devote themselves to the Company's future success and to improve its ability to attract, retain and motivate individuals upon whom its growth and financial success depends. Employee stock options generally vest over four years with a six-month cliff-vesting period. In general, all options are exercisable over a period not to exceed the contractual term of ten years from the date the stock options are granted at prices not less than the fair market value of the Company's common stock on the grant date. The Company has and may grant options with different vesting terms from time to time.

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The following table presents components of stock-based compensation recorded in our consolidated statements of operations and comprehensive loss.

	Year Ended December 31,		
(In thousands)	**2015**	**2014**	**2013**
Cost of goods sold	$ 186	$ 191	$ —
Research and development	2,526	2,220	1,550
General and administrative	10,111	9,635	5,480
Total Stock-Based Compensation Expense	$ 12,823	$ 12,046	$ 7,030

Stock-based compensation expense was based on the Black-Scholes option-pricing model assuming the following:

Period (1)	Risk-free interest rate	Expected life of stock option	Annual Volatility
Year ended December 31, 2015	1.33% to 2.18%	6 years	67 to 69%
Year ended December 31, 2014	0.0025% to 2.13%	6 years	67 to 68%
Year ended December 31, 2013	0.71% to 1.51%	5 years	66 to 100%

(1) Dividend rate is 0% for all periods presented.

The compensation expense for stock-based compensation awards includes an estimate for forfeitures and is recognized over the requisite service period of the options, which is typically the period over which the options vest, using the straight-line method.

A summary of the activity in the 2014 Employment Commencement Stock Incentive Plan, the 2010 Equity Incentive Plan, as amended, the 2006 Equity Compensation Plan, as amended, and the Company's other stock option plans, is as follows:

	For the Year Ended			
	December 31,2015		December 31,2014	
	Option Shares	Weighted-average Exercise Price	Option Shares	Weighted-average Exercise Price
Beginning balance	8,857,961	$ 7.71	8,217,674	$ 6.05
Granted	2,453,009	9.80	3,356,946	12.03
Exercised	(1,542,603)	4.28	(1,643,464)	4.00
Canceled	(977,893)	11.33	(1,073,195)	14.22
Outstanding Balance at Year End	8,790,474	8.49	8,857,961	7.71

The number of options outstanding, vested and expected to vest as of December 31, 2015 was 8,142,976 and the weighted-average remaining contractual life was 6.9 years. The aggregate intrinsic value and the weighted-average intrinsic value of stock options outstanding, vested and expected to vest as of December 31, 2015 was $2.1 million and $8.37 per option, respectively. The number of options outstanding, vested and expected to vest as of December 31, 2014 was 8,390,147 and the weighted-average remaining contractual life was 6.8 years. The aggregate intrinsic value and the weighted-average intrinsic value of stock options outstanding, vested and expected to vest as of December 31, 2014 was $33.7 million and $7.57 per option, respectively.

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As of December 31, 2015, the options outstanding under all of the Company's stock option plans consisted of the following:

	Options Outstanding			Options Vested and Exercisable		
Range of Exercise Price	Number of Options Outstanding	Weighted-average Remaining Contractual Life	Weighted-average Exercise Price	Number of Options Exercisable	Weighted-average Remaining Contractual Life	Weighted-average Exercise Price
$0 to $3.00	319,755	2.10	$ 2.67	319,755	2.10	$ 2.67
$3.01 to $5.00	1,021,578	5.31	4.05	819,757	4.32	3.89
$5.01 to $6.00	2,384,438	5.62	5.27	2,164,305	5.40	5.26
$6.01 to $9.00	1,146,802	7.72	7.62	546,617	6.92	7.45
$9.01 to $10.00	1,690,699	8.94	9.74	446,466	8.68	9.71
$10.01 to $14.00	969,870	8.64	11.86	292,277	7.67	11.93
$14.01 to $18.00	1,239,639	7.21	14.92	754,730	6.48	14.88
$18.01 to $160.00	17,693	1.22	105.16	17,693	1.22	105.16
Total	8,790,474	6.92	8.49	5,361,600	5.73	7.54

The aggregate intrinsic value of stock options outstanding as of December 31, 2015 was $2.2 million. The aggregate intrinsic value of stock options exercisable as of December 31, 2015 was $2.1 million.

At December 31, 2015, the total unrecognized compensation cost was approximately $20.2 million. The weighted-average period over which it is expected to be recognized is approximately 2.65 years.

The following table presents details on the stock options granted and exercised.

	Year Ended December 31,		
	2015	2014	2013
Weighted-average fair value per share of options granted	$ 5.95	$ 6.50	$ 5.33
Aggregate intrinsic value of options exercised	$ 10,602.00	$ 11,920.00	$ 5,979.00

In the years ended December 31, 2015 and 2014, the Company incurred $1.4 million and $1.3 million, respectively, of incremental stock compensation costs associated with modifications to retiring directors, former directors, and certain employees' stock option grants. These modifications included the acceleration of unvested shares and an extended period to exercise vested options.

Restricted Stock Units

At December 31, 2015, there were 448,777 RSUs outstanding, of which none have vested. There were 509,967 RSUs granted and 51,146 RSUs forfeited related to employee departures during the twelve months ended December 31, 2015. During the twelve months ended December 31, 2015, there were 10,044 RSU distributions. Unvested RSUs at December 31, 2015 will vest through 2019.

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A summary of information related to restricted stock units ("RSUs") for the year ended December 31, 2015 is presented below:

	For the Year Ended December 31,2015	
	Number of Shares Issued Under the 2010 and 2014 Equity Incentive Plan	Weighted-average Grant Date Fair Value Per Share
Unvested balance - December 31, 2014	-	$ -
Granted	509,967	9.28
Vested	(10,044)	9.36
Forfeited	(51,146)	9.32
Unvested balance - December 31, 2015	448,777	9.28

As of December 31, 2015 there was $3.6 million of unrecognized stock-based compensation expense related to RSUs to be recognized over a weighted-average period of 3.3 years. The total fair value of awards vested during the year was $0.1 million.

Employee Stock Purchase Plan

The ESPP allows a maximum of 1,000,000 shares of common stock to be purchased in aggregate for all employees. During the year ended December 31, 2015 and 2014, the Company issued 141,218 and 21,280 shares under the ESPP, respectively. As of December 31, 2015, there were approximately 837,502 shares reserved for future issuance under the ESPP.

The assumptions used to estimate the per share fair value of stock purchase rights granted under the ESPP were as follows:

Period (1)	Risk-free interest rate	Expected life of stock option	Annual Volatility
Year ended December 31, 2015	0.03% to 0.31%	6 months	53% to 71%
Year ended December 31, 2014	0.01% to 0.16%	4 to 6 months	62% to 67%

(1) Dividend rate is 0%.

14. INCOME TAXES

The Company had losses before income taxes for domestic and foreign operations as follows:

	Year Ended December 31,		
(In thousands)	2015	2014	2013
United States	$ 15,968	$ 15,463	$ 33,966
International	48,810	37,023	35,451
Loss before Income Taxes	$ 64,778	$ 52,486	$ 69,417

The provision for income taxes differs from the amount estimated by applying the statutory federal income tax rate to loss before taxes. The following is a reconciliation of the statutory federal and state rates to the effective rates, for the years ended December 31, 2015, 2014, and 2013.

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Reconciliation of Statutory Tax Rate to Effective Tax Rate

	Year Ended December 31,		
(In thousands)	**2015**	**2014**	**2013**
Federal tax (benefit) at statutory rate	(34.00)%	(34.00)%	(34.00)%
State tax (benefit) at statutory rate, net of federal tax benefit	3.65 %	(7.10)%	0.72 %
Change in valuation allowance	5.37 %	14.51 %	20.86 %
Research and development credits	(1.68)%	(2.34)%	(14.92)%
Fair market value of warrants	— %	— %	5.27 %
Intangible asset basis allocation	— %	2.77 %	— %
Stock-based compensation - ISO	— %	— %	1.08 %
Tax attributes not benefited	— %	— %	6.07 %
Foreign losses not benefited	24.92 %	27.11 %	14.94 %
Other	2.49 %	(0.95)%	(0.02)%
Effective Tax Rate	0.75 %	0 %	(0)%

Components of our net deferred tax liabilities are presented in the following table.

Deferred Tax Assets and Liabilities

	December 31,	
(In thousands)	**2015**	**2014**
Net operating loss carryforwards	$ 23,679	$ 22,480
Capitalized start-up costs	9,595	11,057
Stock option expense	5,397	4,435
Research credits	22,495	20,951
Fixed assets and intangible assets	3,333	1,565
Accruals	1,659	1,434
Inventory	434	1,200
In Process R&D	(316)	
Other	161	124
Valuation allowance	(66,740)	(63,246)
Deferred Tax Assets and Liabilities, Net	$ (303)	$ —

As of December 31, 2015, the Company had net operating loss carryforwards for U.S. federal, U.S. state and foreign income tax purposes of approximately $60.6 million, $92.1 million and $4.4 million, respectively, which expire beginning after the year 2022, 2016 and no expiration, respectively. As of December 31, 2015, the Company had federal and state research and development credits of $21.3 million and $1.8 million, respectively. The federal credits expire beginning after the year 2023 and the state credits have no expiration.

As of December 31, 2015, the Company's net operating loss carryforwards for federal and state income tax purposes include approximately $10.3 million on a gross basis, respectively, of losses attributable to stock option tax expense deductions.

The valuation allowance increased by approximately $3.5 million during the period ending December 31, 2015, primarily as a result of current year losses and tax credits.

Utilization of the Company's net operating loss may be subject to substantial annual limitation due to the ownership change limitations provided by the Internal Revenue Code and similar state provisions. Such an annual limitation could result in the expiration of the net operating loss before utilization.

The Company has analyzed its tax positions in all of the federal, state and foreign jurisdictions where it is required to file income tax returns, as well as all open tax years in these jurisdictions.

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As of December 31, 2015, the Company had no unrecognized tax benefits and has recorded no liability related to uncertain tax positions. The Company did not record a change in its unrecorded tax benefits during the year ended December 31, 2015, and expects no change in its unrecorded tax benefits in the next 12 months.

Due to net operating loss and research credit carryforwards, substantially all of the Company's tax years, from 2001 through 2015, remain open to U.S. federal and state tax examinations.

The Company is not aware of any pending income tax audits. Significant components of the Company's deferred tax assets for income tax purposes are net operating loss carryforwards, capitalized start-up costs, and stock-based compensation and research credits. Due to the Company's lack of earning history, any deferred assets recorded have been fully offset by a valuation reserve.

The Company's practice is to recognize interest and/or penalties related to income tax matters as a component of income tax expense. As of December 31, 2015, there were no accrued interest and penalties related to uncertain tax positions.

15. COMMITMENTS AND CONTINGENCIES

Contractual Obligations with UCSD Relating to the Acquisition of the DR Cysteamine (RP103) License

Pursuant to the license agreement with UCSD, the Company is obligated to pay milestone payments upon the occurrence of certain events, royalties on net sales from products developed pursuant to the license agreement and a percentage of sublicense fees or sublicense royalties, if any. The Company is obligated to fulfill predetermined milestones within a specified number of years from the effective date of the license agreement, depending on the indication. Cumulatively, the Company has expensed $2.2 million in milestone payments to UCSD based upon the initiation of clinical trials in cystinosis, Huntington's disease and NASH and on regulatory filings in cystinosis. To the extent that the Company fails to perform any of its obligations under the license agreement, then UCSD may terminate the license or otherwise cause the license to become non-exclusive.

Leases

In January 2016, the Company entered into a four-year lease for additional office space in South San Francisco. The Company anticipates taking occupancy of such facilities in March 2016. The Company will record such rent on a straight-line basis.

In April 2013, the Company executed a seven-year lease for its corporate office facilities in Novato, California. The Company took occupancy of such facilities at the end of June 2013. On June 10, 2013, the Company amended the lease to add space to accommodate its research laboratory and relocated to this space in July 2014. The Company records such rent on a straight-line basis.

In October 2014, the Company executed a three-year lease for its European sales, marketing and administrative headquarters in Utrecht, Netherlands. The Company records such rent on a straight-line basis.

Rent expense for the Company's current and previous facilities was approximately $1.9 million, $1.4 million, and $0.6 million for the years ended December 31, 2015, 2014, and 2013, respectively. Leasehold improvements for our offices are amortized into expense over the lease term. For the years ended December 31, 2015, 2014, and 2013, the Company recognized a negligible amount of leasehold amortization expense.

The Company has outstanding standby letters of credit at December 31, 2015 and 2014, totaling $1.0 million and $1.3 million, respectively of which $0.8 million was unused at December 31, 2015 and $1.3 million unused at December 31, 2014, respectively.

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The following table presents our future lease commitments at December 31, 2015:

(In thousands)	Future Lease Payments
2016	$ 2,286
2017	2,512
2018	2,564
2019	2,382
2020	1,929
2021 and thereafter	3,329
Total	$ 15,002

16. EMPLOYEE BENEFIT PLAN

The Company has a 401(k) tax-deferred savings plan (the "401(k) Plan"), which permits participants to make contributions by salary deduction pursuant to Section 401(k) of the Internal Revenue Code of 1986, as amended. The Company will match pretax employee contributions up to 4% of eligible compensation during each pay period (subject to annual maximums of $10,600, $10,400, $10,200 per employee in 2015, 2014 and 2013, respectively). Matching contributions are immediately vested. The Company's contributions amounted to $0.7 million, $0.5 million and $0.3 million in 2015, 2014 and 2013, respectively.

17. QUARTERLY RESULTS OF OPERATIONS (UNAUDITED)

The following table presents selected unaudited quarterly results of operations in conjunction with the consolidated financial statements and related notes contained elsewhere in this Annual Report on Form 10-K. These unaudited results were prepared on the same basis as the Company's audited consolidated financial statements. The Company's quarterly operating results have fluctuated in the past and may continue to do so in the future as a result of a number of factors, including, but not limited to, the timing and amounts of its revenues and the timing and nature of research and development activities.

	Quarterly Data 2015			
(In millions, except per share data, unaudited)	March 31, 2015	June 30, 2015	September 30, 2015	December 31, 2015
Net sales	$ 20.5	$ 23.3	$ 25.8	$ 24.7
Gross profit	16.7	20.7	23.2	$ 21.0
Net loss	(19.7)	(13.9)	(14.6)	17.0
Net loss per share, basic and diluted	(0.28)	(0.17)	(0.18)	(0.20)

	Quarterly Data 2014			
(In millions, except per share data, unaudited)	March 31, 2014	June 30, 2014	September 30, 2014	December 31, 2014
Net sales	$ 12.1	$ 16.3	$ 23.8	$ 17.3
Gross profit	10.8	15.3	19.8	14.0
Net loss	(14.9)	(12.7)	(6.0)	(18.9)
Net loss per share, basic and diluted	(0.24)	(0.20)	(0.10)	(0.29)

Schedule II: Valuation and Qualifying Accounts

Valuation Allowance for Deferred Tax Assets

(In millions)	Year Ended December 31, 2015	2014	2013
Balance at beginning of year	$ 63	$ 58	$ 43
Additions to charged to expenses/other accounts	4	5	15
Balance at end of year	$ 67	$ 63	$ 58

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2016

or

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to

Commission File Number 001-35238

HORIZON PHARMA PUBLIC LIMITED COMPANY

(Exact name of Registrant as specified in its charter)

Ireland	**Not Applicable**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
Connaught House, 1st Floor 1 Burlington Road, Dublin 4, D04 C5Y6, Ireland	**Not Applicable**
(Address of principal executive offices)	**(zip code)**

011 353 1 772 2100

(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	**Name of Each Exchange on Which Registered**
Ordinary shares, nominal value $0.0001 per share	**The NASDAQ Global Select Market**

Securities registered pursuant to Section 12(g) of the Act:

None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐.

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒.

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company.

Large accelerated filer	☒	Accelerated filer	☐
Non-accelerated filer	☐ (Do not check if a smaller reporting company)	Smaller reporting company	☐

Indicate by check mark whether the registrant is a shell company (as defined by Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

The aggregate market value of the registrant's voting ordinary shares held by non-affiliates of the registrant, based upon the $16.47 per share closing sale price of the registrant's ordinary shares on June 30, 2016 (the last business day of the registrant's most recently completed second quarter), was approximately $2.2 billion. Solely for purposes of this calculation, the registrant's directors and executive officers and holders of 10% or more of the registrant's outstanding ordinary shares have been assumed to be affiliates and an aggregate of 24,135,899 ordinary shares held by such persons on June 30, 2016 are not included in this calculation.

As of February 22, 2017, the registrant had outstanding 162,334,893 ordinary shares.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement for the registrant's 2017 Annual Meeting of Shareholders are incorporated by reference into Part III of this Annual Report on Form 10-K.

HORIZON PHARMA PLC
FORM 10-K — ANNUAL REPORT
For the Fiscal Year Ended December 31, 2016

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PART I

Special Note Regarding Forward-Looking Statements

This Annual Report on Form 10-K contains "forward-looking statements" — that is, statements related to future, not past, events — as defined in Section 21E of the Securities Exchange Act of 1934, as amended, that reflect our current expectations regarding our future growth, results of operations, financial condition, cash flows, performance, business prospects, and opportunities, as well as assumptions made by, and information currently available to, our management. Forward-looking statements include any statement that does not directly relate to a current or historical fact. We have tried to identify forward-looking statements by using words such as "believe," "may," "could," "will," "estimate," "continue," "anticipate," "intend," "seek," "plan," "expect," "should," or "would." Among the factors that could cause actual results to differ materially from those indicated in the forward-looking statements are risks and uncertainties inherent in our business including, without limitation: our ability to successfully execute our sales and marketing strategy, including continuing to successfully recruit and retain sales and marketing personnel and to successfully build the market for our medicines; whether we will be able to realize the expected benefits of strategic transactions, such as our acquisitions of Hyperion Therapeutics Inc., Crealta Holdings LLC and Raptor Pharmaceutical Corp., including whether and when such transactions will be accretive to our net income; the rate and degree of market acceptance of, and our ability and our distribution and marketing partners' ability to obtain coverage and adequate reimbursement and pricing for, our medicines from government and third-party payers and risks relating to the success of our patient access programs; our ability to maintain regulatory approvals for our medicines; our ability to conduct clinical development and obtain regulatory approvals for our medicine candidates, including potential delays in initiating and completing studies and filing for and obtaining regulatory approvals and whether data from clinical studies will support regulatory approval; our need for and ability to obtain additional financing; the accuracy of our estimates regarding future financial results; our ability to successfully execute our strategy to develop or acquire additional medicines or companies, including disruption from any future acquisition or whether any acquired development programs will be successful; our ability to manage our anticipated future growth; the ability of our medicines to compete with generic medicines, especially those representing the active pharmaceutical ingredients in our medicines as well as new medicines that may be developed by our competitors; our ability and our distribution and marketing partners' ability to comply with regulatory requirements regarding the sales, marketing and manufacturing of our medicines and medicine candidates; the performance of our third-party distribution partners, licensees and manufacturers over which we have limited control; our ability to obtain and maintain intellectual property protection for our medicines; our ability to defend our intellectual property rights with respect to our medicines; our ability to operate our business without infringing the intellectual property rights of others; the loss of key commercial or management personnel; regulatory developments in the United States and other countries, including potential changes in healthcare laws and regulations; and other risks detailed below in Part I — Item 1A. "Risk Factors."

Although we believe that the expectations reflected in our forward-looking statements are reasonable, we cannot guarantee future results, events, levels of activity, performance or achievement. We undertake no obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, unless required by law.

Item 1. Business

Unless otherwise indicated or the context otherwise requires, references to the "Company", "we", "us" and "our" refer to Horizon Pharma plc and its consolidated subsidiaries, including its predecessor Horizon Pharma, Inc., or HPI. All references to "Vidara" are references to Horizon Pharma plc (formerly known as Vidara Therapeutics International Public Limited Company) and its consolidated subsidiaries prior to the effective time of the merger of the businesses of HPI and Vidara on September 19, 2014, or the Vidara Merger. The disclosures in this report relating to the pre-Vidara Merger business of Horizon Pharma plc, unless noted as being the business of Vidara prior to the Vidara Merger, pertain to the business of HPI prior to the Vidara Merger.

Overview

We are a biopharmaceutical company focused on improving patients' lives by identifying, developing, acquiring and commercializing differentiated and accessible medicines that address unmet medical needs. We market eleven medicines through our orphan, rheumatology and primary care business units. Our marketed medicines are ACTIMMUNE® (interferon gamma-1b), BUPHENYL® (sodium phenylbutyrate) Tablets and Powder, DUEXIS® (ibuprofen/famotidine), KRYSTEXXA® (pegloticase), MIGERGOT® (ergotamine tartrate & caffeine suppositories), PENNSAID® (diclofenac sodium topical solution) 2% w/w, or PENNSAID 2%, PROCYSBI® (cysteamine bitartrate) delayed-release capsules, QUINSAIR™ (aerosolized form of levofloxacin), RAVICTI® (glycerol phenylbutyrate) Oral Liquid, RAYOS® (prednisone) delayed-release tablets and VIMOVO® (naproxen/esomeprazole magnesium).

Our Strategy

Our strategy is to continue to build a well-balanced, diversified, high-growth biopharmaceutical company. We are executing our strategy through the successful commercialization of our existing medicines, a strong commitment to patient access and support and business development efforts focused on transformative acquisitions to accelerate our rare disease leadership as well as on-market and development-stage medicines to fill out our pipeline.

We are building a sustainable biopharmaceutical company by helping ensure that patients have access to their medicines and support services, and by investing in the further development of medicines for patients with rare or underserved diseases. Our growing business is diversified across three business units: orphan, rheumatology and primary care, and is driven by a successful commercial model that focuses on differentiated, long-life medicines, innovative patient access programs and a disciplined business development strategy. Our key areas of focus are:

Revenue diversification – We have successfully diversified our portfolio of medicines from two in 2013 to eleven in December 2016. Our intent is to continue to generate organic growth, broaden our medicine portfolio to ensure net revenues are not dominated by any one medicine and increase the proportion of net revenues derived from our orphan medicines.

Clinical development – We work diligently to unlock the full therapeutic potential of our medicines by working closely with regulatory agencies, premier academic centers with established study consortiums, healthcare professionals and patient groups to facilitate our clinical development programs and generate data for possible new indications that may help more patients in need. We also continue to look at opportunities to augment our rare disease pipeline through development-stage acquisitions.

Business development – We have a disciplined and robust acquisition strategy, and our focus is on rapid value creation and improving the performance of each of the medicines we acquire. We have completed seven acquisitions over the past five years, including two transformative transactions in 2016 that brought us three new rare disease medicines. While we remain focused on acquiring clinically-differentiated medicines and executing transactions that are accretive and net present value positive, we have expanded our acquisition criteria to potentially include medicines in late-stage development.

Our Company

We are a public limited company formed under the laws of Ireland. Our predecessor, HPI, was originally incorporated in Delaware in March 2010 and Vidara was originally incorporated in Ireland in December 2011. We operate through a number of international and U.S. subsidiaries with principal business purposes to perform research and development or manufacturing operations, serve as distributors of our medicines, hold intellectual property assets or provide us with services and financial support.

Our principal executive offices are located at Connaught House, 1st Floor, 1 Burlington Road, Dublin 4, D04 C5Y6, Ireland and our telephone number is 011 353 1 772 2100. Our website address is *www.horizonpharma.com*. Information found on, or accessible through, our website is not a part of, and is not incorporated into, this Annual Report on Form 10-K.

Mergers and Acquisitions

The Vidara Merger occurred on September 19, 2014 and was accounted for as a reverse acquisition under the acquisition method of accounting for business combinations, with HPI treated as the acquiring company for accounting purposes. As part of the Vidara Merger, a wholly owned subsidiary of Vidara merged with and into HPI, with HPI surviving the Vidara Merger as a wholly owned subsidiary of Vidara. Prior to the Vidara Merger, Vidara changed its name to Horizon Pharma plc. Upon the consummation of the Vidara Merger, the historical financial statements of HPI became our historical financial statements. Accordingly, the historical financial statements of HPI are included in the 2014 comparative periods.

On October 17, 2014, we acquired the U.S. rights to PENNSAID 2% from Nuvo Research Inc., or Nuvo, for $45.0 million in cash.

On May 7, 2015, we completed our acquisition of Hyperion Therapeutics Inc., or Hyperion, in which we acquired all of the issued and outstanding shares of Hyperion's common stock for $46.00 per share in cash or approximately $1.1 billion on a fully-diluted basis. Hyperion marketed RAVICTI and BUPHENYL. Following the completion of the acquisition, Hyperion became our wholly owned subsidiary and was renamed Horizon Therapeutics, Inc. (which subsequently converted to a limited liability company, Horizon Therapeutics, LLC).

On January 13, 2016, we completed our acquisition of Crealta Holdings LLC, or Crealta, for approximately $539.7 million, including cash acquired of $24.9 million. Crealta marketed KRYSTEXXA and MIGERGOT. Following the completion of the acquisition, Crealta became our wholly owned subsidiary and was renamed Horizon Pharma Rheumatology LLC.

On October 25, 2016, we completed our acquisition of Raptor Pharmaceutical Corp., or Raptor, in which we acquired all of the issued and outstanding shares of Raptor's common stock for $9.00 per share in cash. The total consideration was $860.8 million, including cash acquired of $24.9 million and $56.0 million to repay Raptor's outstanding debt. Raptor marketed PROCYSBI and QUINSAIR. Following completion of the acquisition, Raptor became our wholly owned subsidiary and converted to a limited liability company, changing its name to Horizon Pharmaceutical LLC.

The consolidated financial statements presented herein include the results of operations of the acquired Vidara, Hyperion, Crealta and Raptor businesses from the applicable dates of acquisition.

Our Medicines

We believe our medicines address unmet therapeutic needs in orphan diseases, arthritis, pain and inflammation and inflammatory diseases and provide significant advantages over existing therapies.

Our current marketed medicine portfolio consists of the following:

Medicine	Disease	Marketing Rights
ORPHAN BUSINESS UNIT MEDICINES:		
ACTIMMUNE	Chronic granulomatous disease and severe, malignant osteopetrosis	United States and selected foreign countries
BUPHENYL	Urea cycle disorders	Worldwide (1)
PROCYSBI	Nephropathic cystinosis	Worldwide
QUINSAIR	Treatment of chronic pulmonary infections due to pseudomonas aeruginosa in cystic fibrosis patients	Worldwide (2)
RAVICTI	Urea cycle disorders	Worldwide (3)
RHEUMATOLOGY BUSINESS UNIT MEDICINES:		
KRYSTEXXA	Chronic refractory gout	Worldwide
RAYOS/LODOTRA	Rheumatoid arthritis, polymyalgia rheumatic, systemic lupus erythematosus and multiple other indications	Worldwide (4)
PRIMARY CARE BUSINESS UNIT MEDICINES:		
DUEXIS	Signs and symptoms of osteoarthritis and rheumatoid arthritis	Worldwide (5)
MIGERGOT	Vascular headache	United States
PENNSAID 2%	Pain of osteoarthritis of the knee(s)	United States
VIMOVO	Signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis	United States

(1) BUPHENYL is known as AMMONAPS in certain European countries. The distribution rights for BUPHENYL in Europe, certain Asian, Latin American, Middle Eastern, North African and other countries have been granted to Swedish Orphan Biovitrum AB, or SOBI. Orphan Pacific, Inc. holds an exclusive distribution agreement for the distribution of AMMONAPS in Japan.

(2) We have not received regulatory approval to distribute QUINSAIR in the United States.

(3) RAVICTI distribution rights in the Middle East and North Africa have been granted to SOBI. In June 2016, we partnered with Clinigen Group plc's Idis managed access division to initiate a managed access program in selected European countries, which agreement terminates on April 10, 2017 and after which we will partner with SOBI to continue our managed access program in selected European countries. We expect to commercially launch RAVICTI in Europe in 2017 through an exclusive distribution agreement with SOBI.

(4) Mundipharma International Corporation Limited, or Mundipharma, is our exclusive distributor for LODOTRA in Europe, Asia and Latin America. The majority of LODOTRA sales are in Germany and Italy where reimbursement has been approved.

(5) DUEXIS rights in Latin America have been licensed to Grünenthal S.A., or Grünenthal.

ORPHAN BUSINESS UNIT

Market

Chronic Granulomatous Disease

Chronic granulomatous disease, or CGD, is a genetic disorder of the immune system. It is described as a primary immunodeficiency disorder, which means it is not caused by another disease or disorder. In people who have CGD, a type of white blood cell, called a phagocyte, is defective. These defective phagocytes cannot generate superoxide, leading to an inability to kill harmful microorganisms such as bacteria and fungi. As a result, the immune system is weakened. People with CGD are more likely to have certain problems such as recurrent severe bacterial and fungal infections and chronic inflammatory conditions. These patients are prone to developing masses called granulomas, which can occur repeatedly in organs throughout the body and cause a variety of problems. CGD is considered to be a condition that patients can live with and manage. Studies suggest overall survival has improved over the last decade with more patients living well into adulthood. Approximately 1 out of every 100,000 to 200,000 babies in the United States is born with CGD.

Severe, Malignant Osteopetrosis

Severe, malignant osteopetrosis, or SMO, is a form of osteopetrosis and is sometimes referred to as marble bone disease or malignant infantile osteopetrosis because it occurs in very young children. While exact numbers are not known, it has been estimated that 1 out of 250,000 children is born with SMO. During normal bone development, existing bone material is constantly being replaced by new bone. Cells called osteoblasts cause new bone formation while other cells called osteoclasts remove old bone through a process called resorption. In people with osteopetrosis, this balance is not maintained because their osteoclasts do not function properly. As a result, resorption of old bone material decreases while the formation of new bone continues. This leads to an abnormal increase in bone mass, which can make the bones more brittle. Because abnormal bone development affects many different systems in the body, osteopetrosis may cause problems such as blood disorders, decreased ability to fight infection, bone fractures, problems with vision and hearing, and abnormal appearance of the face and head.

Urea Cycle Disorders

Urea cycle disorders, or UCDs, are inherited metabolic diseases caused by a deficiency of one of the enzymes or transporters that constitute the urea cycle. The urea cycle involves a series of biochemical steps in which ammonia, a potent neurotoxin, is converted to urea, which is excreted in the urine. UCD patients may experience episodes where they get symptoms from the ammonia in their blood being excessively high – called hyperammonemic crises – which may result in irreversible brain damage, coma or death. UCD symptoms may first occur at any age depending on the severity of the disorder, with more severe defects presenting earlier in life. We estimate that there are approximately 2,000 patients with UCDs living in the United States.

Nephropathic Cystinosis

We estimate that there are approximately 500 patients diagnosed with cystinosis living in the United States and an estimated 2,000 patients worldwide. Nephropathic cystinosis comprises ninety-five percent of known cases of cystinosis. In these patients, elevated cystine leads to cellular dysfunction and death; without treatment, the disease is usually fatal by the end of the first decade of life. Cystinosis is progressive, eventually causing irreversible tissue damage and multi-organ failure, including kidney failure, blindness, muscle wasting and premature death. Nephropathic cystinosis is usually diagnosed in infancy after children display symptoms to physicians, including markedly increased urination, thirst, dehydration, gastrointestinal distress, failure to thrive, rickets, photophobia and kidney symptoms specific to Fanconi syndrome. Management of cystinosis requires lifelong therapy.

Pseudomonas Aeruginosa Infection in Cystic Fibrosis

Cystic fibrosis is a rare, life-threatening genetic disease affecting approximately 70,000 people worldwide. Cystic fibrosis is caused by a mutation in the cystic fibrosis transmembrane conductance regulator, or CFTR, gene. Defective or missing CFTR protein causes poor flow of salt and water into or out of the cell in several organs, including the lungs. This leads to the buildup of abnormally thick secretions that can cause chronic lung infections and progressive lung damage in many patients that eventually leads to death.

Patients with cystic fibrosis are highly susceptible to colonization with bacterial infections of the lung, largely because their pulmonary mucous secretions are thicker, stickier, and more difficult to expectorate than those of healthy individuals. This creates an environment in the lung that favors bacterial proliferation. As of 2014, a median of approximately thirty-five percent of all patients with cystic fibrosis in the European Union, or EU, were colonized with *Pseudomonas aeruginosa*, a gram-negative bacterial infection. Infection rates climb as patients age.

Our Solutions

ACTIMMUNE

ACTIMMUNE is a biologically manufactured protein called interferon gamma-1b that is similar to a protein the human body makes naturally. In the body, interferon gamma is produced by cells of the immune system and helps to prevent infection in patients with CGD and enhances osteoclast function in patients with SMO. ACTIMMUNE is approved by the U.S. Food and Drug Administration, or FDA, to reduce the frequency and severity of serious infections associated with CGD and for delaying time to disease progression in patients with SMO. The precise way that ACTIMMUNE works to help prevent infection in patients with CGD and slow the worsening of SMO is not fully understood, but ACTIMMUNE is believed to work by modifying the cellular function of various cells, including those in the immune system and those that help form bones.

Efficacy in CGD

The International Chronic Granulomatous Disease Cooperative Study Group conducted a controlled clinical trial in 128 patients (ages ranging from one to forty-four years old) at thirteen medical centers across four countries. The purpose of this clinical trial was to evaluate the safety and efficacy of ACTIMMUNE in reducing the frequency and severity of serious infections in patients with CGD. Patients enrolled in the trial were randomly selected to receive either ACTIMMUNE or placebo in addition to antibiotics. The number and timing of serious infections were tracked in all patients for up to 1 year. Investigators concluded that ACTIMMUNE is an effective and safe therapy for patients with CGD, because the therapy statistically reduced the frequency of serious infections.

Efficacy in SMO

In a controlled clinical trial, sixteen patients were randomized to receive either ACTIMMUNE with calcitriol or calcitriol alone. The age of patients ranged from one month to eight years; with a mean age of one and one-half years. The median time to progression in the ACTIMMUNE plus calcitriol arm was 165 days versus a median of sixty-five days in the calcitriol only arm. In a separate analysis that combined data from a second trial, nineteen of twenty-four patients on ACTIMMUNE therapy (with or without calcitriol) for at least six months had reduced trabecular bone volume compared to baseline.

Commercial Status

ACTIMMUNE is the only drug currently approved by the FDA for the treatment for CGD and SMO. Our licenses allow us to market and sell ACTIMMUNE in the United States, Canada and Japan. We currently commercialize ACTIMMUNE in the United States and also supply ACTIMMUNE to patients in Canada, if so requested by way of a prescription from their treating physicians, through Health Canada's, or HC, Special Access Program, which provides access to non-marketed drugs in Canada for practitioners treating patients with serious or life-threatening conditions when conventional therapies have failed, are unsuitable or are unavailable. We have not registered or sold ACTIMMUNE in Japan.

On May 18, 2016, we entered into a definitive agreement with Boehringer Ingelheim International GmbH, or Boehringer Ingelheim International, to acquire certain rights to interferon gamma-1b, which Boehringer Ingelheim International currently commercializes under the trade names IMUKIN, IMUKINE, IMMUKIN and IMMUKINE in an estimated thirty countries, primarily in Europe and the Middle East. The transaction is expected to close in 2017 and we are continuing to work with Boehringer Ingelheim International to enable the transfer of applicable marketing authorizations.

BUPHENYL

BUPHENYL tablets for oral administration and BUPHENYL powder for oral, nasogastric, or gastrostomy tube administration are indicated as adjunctive therapy in the chronic management of patients with UCDs involving deficiencies of carbamoyl phosphate synthetase, ornithine transcarbamylase or argininosuccinic acid synthetase.

BUPHENYL is indicated in all patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy. It is important that the diagnosis be made early and treatment initiated immediately to improve chances of survival. BUPHENYL must be combined with dietary protein restriction and, in some cases, essential amino acid supplementation.

Commercial Status

BUPHENYL was approved by the FDA in the United States in 1996 and by the European Medicines Agency, or EMA, in Europe in 1999. We commercially market and distribute BUPHENYL in the United States. BUPHENYL is known as AMMONAPS in certain European countries, and the marketing and distribution rights are granted to SOBI through the end of 2021. We provide BUPHENYL in certain other countries through various Special Access Programs and licensed distributors.

PROCYSBI

PROCYSBI is an approved therapy for the management of nephropathic cystinosis. PROCYSBI capsules contain cysteamine bitartrate in the form of innovative microspheronized beads that are individually coated to create delayed and extended-release properties, allowing patients to maintain consistent therapeutic systemic drug levels over a twelve-hour dosing period. The enteric-coated beads are pH sensitive and bypass the stomach for dissolution and absorption in the more alkaline environment of the proximal small intestine. Randomized controlled clinical trials and extended treatment with PROCYSBI therapy demonstrated consistent cystine depletion as monitored by levels of the biomarker (and surrogate marker), white blood cell cystine.

In addition to the population of patients who have already been identified, we believe that a number of patients with atypical phenotypic presentation and end-stage renal disease have their condition as a result of undiagnosed late-onset nephropathic cystinosis, and would benefit from treatment with PROCYSBI.

Commercial Status

PROCYSBI received marketing approval from the FDA in April 2013 for the management of nephropathic cystinosis in adults and children six years and older. In August 2015, the FDA approved PROCYSBI for expanded use to treat children two to six years of age with nephropathic cystinosis. In Europe, PROCYSBI received marketing authorization in September 2013 from the European Commission, or EC, for marketing in the EU countries as an orphan medicine for the management of proven nephropathic cystinosis. The EU marketing authorization allows us to commercialize PROCYSBI in the 28 Member States of the EU plus Norway, Liechtenstein and Iceland. PROCYSBI received seven years of market exclusivity, through 2020, for patients six years of age and older as an orphan drug in the United States, and ten years of market exclusivity, through 2023, as an orphan drug in Europe. PROCYSBI received orphan drug designation in the United States for the treatment of patients aged two to six years of age, through 2022.

QUINSAIR

QUINSAIR is a formulation of the antibiotic drug levofloxacin, suitable for inhalation via a nebulizer. This route of delivery allows higher concentrations of drug in the lung sputum than can be achieved via systemic (for example, oral) administration. QUINSAIR, as approved, is administered twice daily in twenty-eight-day cycles, using a hand-held nebulizer with a disposable handset known as the Zirela® device, manufactured by our partner PARI Pharma GmbH, or PARI, and configured specifically for use with QUINSAIR.

Commercial Status

QUINSAIR is the first fluoroquinolone inhaled antibiotic to be approved in Canada and the EU for the treatment of chronic pulmonary infections due to *Pseudomonas aeruginosa* in cystic fibrosis patients. QUINSAIR was approved in the EU and Canada on the basis of three randomized, controlled studies, one Phase 2 and two Phase 3. In the EU, QUINSAIR is eligible for "new data" regulatory exclusivity of ten years after approval, beginning with its March 2015 marketing authorization, a period which is concurrent with, and independent from, the period of any applicable patent. QUINSAIR is not approved in the United States. Raptor launched QUINSAIR in Germany and Denmark in the first half of 2016 and we launched QUINSAIR in Canada in December 2016. We do not plan to pursue approval in the United States for QUINSAIR as a treatment of pseudomonas aeruginosa in adults with cystic fibrosis.

RAVICTI

RAVICTI is indicated for use as a nitrogen-binding agent for chronic management of adult and pediatric patients two years of age and older (two months of age and older in Europe) with UCDs that cannot be managed by dietary protein restriction and/or amino acid supplementation alone. RAVICTI must be used with dietary protein restriction and, in some cases, dietary supplements (for example, essential amino acids, arginine, citrulline or protein-free calorie supplements).

Efficacy in the Treatment of UCDs in Adult Patients

A randomized, double-blind, active-controlled, crossover, non-inferiority study compared RAVICTI to sodium phenylbutyrate by evaluating venous ammonia levels in patients with UCDs that had been on sodium phenylbutyrate prior to enrollment for control of their UCD. Patients adhered to a low-protein diet and received amino acid supplements throughout the study. After two weeks of dosing, by which time patients had reached a steady state on each treatment, all patients had twenty-four hours of ammonia measurements.

Another study was conducted to assess monthly ammonia control and hyperammonemic crisis over a twelve-month period. A total of fifty-one adults were in the study and all but six had been converted from sodium phenylbutyrate to RAVICTI. Venous ammonia levels were monitored monthly. Of fifty-one adult patients participating in the twelve-month, open-label treatment with RAVICTI, seven patients (fourteen percent) reported a total of ten hyperammonemic crises.

The efficacy of RAVICTI in pediatric patients two to seventeen years of age was evaluated in two fixed-sequence, open-label, sodium phenylbutyrate to RAVICTI switchover studies, seven and ten days in duration. These studies compared blood ammonia levels of patients on RAVICTI to venous ammonia levels of patients on sodium phenylbutyrate in twenty-six pediatric UCD patients. Twenty-four hour blood ammonia levels of UCD patients six to seventeen years of age (Study 3) and patients two to five years of age (Study 4) were similar between treatments but trended higher with sodium phenylbutyrate.

Long-term (twelve-month), uncontrolled, open-label studies were conducted to assess monthly ammonia control and hyperammonemic crisis over a twelve-month period. Of the twenty-six pediatric patients six to seventeen years of age participating in these two trials, five patients (nineteen percent) reported a total of five hyperammonemic crises.

Commercial Status

RAVICTI was approved for marketing in the United States in 2013. Current FDA approval is for patients from two years of age and older only.

In November 2015, the EC adopted a binding decision to approve RAVICTI for use as an adjunctive therapy for chronic management of adult and pediatric patients two months of age and older with six subtypes of UCDs. This decision followed the Positive Opinion previously adopted on September 24, 2015 by the Committee for Medicinal Products for Human Use, or CHMP, of the EMA. The approval authorizes us to market RAVICTI in all twenty-eight Member States of the EU and the centralized marketing authorization will form the basis for recognition by the Member States of the European Economic Area, or EEA, namely Norway, Iceland and Liechtenstein, for the medicine to be placed on the market. In June 2016, we partnered with Clinigen Group plc's Idis managed access division to initiate a managed access program in selected European countries, which agreement will terminate on April 10, 2017 and after which we will partner with SOBI to continue our managed access program in selected European countries. We expect to commercially launch RAVICTI in Europe in 2017 through an exclusive distribution agreement with SOBI.

We have worldwide rights to market and distribute RAVICTI. In relation to marketing and distribution rights in the Middle East and North Africa region, we have entered into a distribution agreement with SOBI through 2018. In March 2016, HC issued a Notice of Compliance for RAVICTI for use as an adjunctive therapy for chronic management of adult and pediatric patients two years of age and older with UCDs, and we launched RAVICTI in Canada in November 2016.

We are in the process of seeking approval for label expansions for RAVICTI, with assessments in progress studying the use of RAVICTI in patients both from two months to two years (on June 29, 2016 we submitted a supplemental new drug application, or sNDA, with the FDA for this indication) and from birth to two months (targeted sNDA submission in the first quarter of 2018). In patients with UCDs for which RAVICTI is an FDA-approved medicine, there is a variable age of diagnosis (from newborn to adulthood), and the severity of the disease can be associated with the age of onset and enzymatic deficit. However, a prompt diagnosis and careful management of the disease can lead to good clinical outcomes.

Competition

ACTIMMUNE presently faces limited competition. ACTIMMUNE is the only drug currently approved by the FDA specifically for the treatment for CGD and SMO. While there are additional or alternative approaches used to treat patients with CGD and SMO, including the increasing trend towards the use of bone marrow transplants in patients with CGD, there are currently no medicines on the market that compete directly with ACTIMMUNE.

In the United States, RAVICTI and BUPHENYL compete with generic forms of sodium phenylbutyrate. In Europe and certain other countries, RAVICTI and BUPHENYL compete with Pheburane, which is a sugar-coated version of sodium phenylbutyrate. Pheburane claims a taste advantage over BUPHENYL. However the volume of Pheburane that must be ingested multiple times per day is much greater than BUPHENYL, and significantly greater than RAVICTI, and is a barrier to patient compliance.

Other than PROCYSBI, we are aware of two pharmaceutical products currently approved to treat cystinosis. Cystagon® (immediate-release cysteamine bitartrate capsules), is a systemic cystine-depleting therapy for cystinosis in the United States manufactured by Mylan N.V., and by Orphan Europe SARL in markets outside of the United States. Cystagon was approved by the FDA in 1994 and by the EC in 1997. Cystaran® (cysteamine ophthalmic solution) was approved by FDA in 2012 for treatment of corneal crystal accumulation in patients with cystinosis and is marketed by Sigma Tau Pharmaceuticals, Inc.

While we believe that PROCYSBI will continue to be well received in the market, Cystagon remains on the market and we expect it will compete with PROCYSBI for the foreseeable future. We are not aware of any pharmaceutical company with an active program to develop an alternative therapy for cystinosis. Academic researchers in the United States and Europe are pursuing gene therapy and stem cell therapy, as well as pro-drug and PEGylated drug approaches as alternatives to cysteamine bitartrate. We believe that the development timeline to an approved product for these approaches is many years with substantial uncertainty.

In relation to QUINSAIR, chronic pulmonary infections due to *Pseudomonas aeruginosa* are currently treated primarily with inhaled antibiotics, including tobramycin, an aminoglycoside-class antibiotic sold by Novartis Pharmaceuticals Corporation as TOBI® or in dry-powder-inhalation format as TOBI Podhaler® and sold by others in generic form, aztreonam, a monobacter-class antibiotic which is marketed in an inhaled formulation by Gilead Sciences, Inc. under the tradename Cayston®, and colistimethate sodium, a polymixin-class antibiotic which is approved and marketed in inhaled formulations in Europe. Tobramycin, aztreonam and colistimethane are primarily effective against gram-negative bacteria such as *Pseudomonas aeruginosa*. However, the prevalence of multi-drug-resistant *Pseudomonas aeruginosa* is growing. Thus, we believe there is an unmet need that might be addressed with a new class of inhaled antibiotic such as the fluoruquinolone class that levofloxacin represents.

RHEUMATOLOGY BUSINESS UNIT

Market

Chronic Refractory Gout

Chronic refractory gout, or CRG, is a type of arthritis that occurs when uric acid build-up in the blood remains high and inflammation persists even after treatment with conventional therapies. Gout is one of the most common forms of inflammatory arthritis, estimated to affect 8.3 million in the United States, with CRG impacting 40,000 to 50,000 people in the United States. CRG frequently causes crippling disabilities and significant joint damage.

Rheumatoid Arthritis

Rheumatoid arthritis, or RA, is a chronic disease that causes pain, stiffness and swelling, primarily in the joints. According to a 2006 DataMonitor report, 2.9 million people in the United States suffer from RA, of which 1.8 million are diagnosed and treated with various drugs. RA has no known cause, but unlike osteoarthritis, or OA, RA is not associated with factors such as aging. RA occurs when the body's immune system malfunctions, attacking healthy tissue and causing inflammation, which leads to pain and swelling in the joints and may eventually cause permanent joint damage and painful disability. The primary symptoms of RA include progressive immobility and pain, especially in the morning, with long-term sufferers experiencing continual joint destruction for the remainder of their lives. There is no known cure for RA. Once the disease is diagnosed, treatment is prescribed for life to alleviate symptoms and/or to slow or stop disease progression. RA treatments include medications, physical therapy, exercise, education and sometimes surgery. Early, aggressive treatment of RA can delay joint destruction. Treatment of RA usually includes multiple drug therapies taken concurrently. Disease-modifying anti-rheumatic drugs, or DMARDs, are the current standard of care for the treatment of RA, in addition to rest, exercise and anti-inflammatory drugs such as nonsteroidal anti-inflammatory drugs, or NSAIDs.

Polymyalgia Rheumatica

Polymyalgia rheumatica, or PMR, is an inflammatory disorder that causes significant muscle pain and stiffness. The pain and stiffness often occur in the shoulders, neck, upper arms and hip with pronounced morning stiffness lasting at least one hour. Most people who develop PMR are older than sixty-five years of age. It rarely affects people younger than fifty. There are approximately 1.1 million patients with PMR in the United States and it afflicts one in every 133 people over the age of fifty. Prednisone is the standard of care for treating PMR and treatment is generally initiated at a relatively high dose (for example, 10-20 mg per day) and reduced as clinical improvement is seen. Treatment usually lasts eighteen to twenty-four months. Similar to RA, PMR is associated with circadian patterns of Interleukin 6, or IL-6, elevation in early morning hours.

Systemic Lupus Erythematosus

Systemic lupus erythematosus, or SLE, is a chronic autoimmune disease that causes inflammation and pain in the joints and muscles as well as overall fatigue. SLE affects from 161,000 to 322,000 adults in the United States. More than 90 percent of cases of SLE occur in women, frequently starting at childbearing age. In addition to affecting the muscles and joints, it can affect other organs in the body such as the kidneys, tissue lining the lungs (pleura), heart (pericardium), and brain. Most patients feel fatigue and have rashes, arthritis (painful and swollen joints) and fever. SLE flares vary from mild to serious.

In November 2015, we announced our collaboration with the Alliance for Lupus Research, or ALR, to study the effect of RAYOS on the fatigue experienced by SLE patients. SLE is a chronic autoimmune disease that causes inflammation and pain in the joints and muscles, as well as overall fatigue. RAYOS is currently indicated for patients with SLE. The first study planned as part of the collaboration is an investigator-initiated, randomized, double-blind, active comparator, cross-over study in which patients will be randomized to receive either prednisone for three months or RAYOS at 10 p.m. for three months, and then switched to the alternative medication for an additional three months. Approximately sixty-two patients across twenty-five sites will be enrolled in the United States. Fatigue will be measured by the Functional Assessment of Chronic Illness Therapy-Fatigue and the Fatigue Severity Scale, as well as the Vitality scale of the Medical Outcome Study thirty-six-item short form health survey.

Market Opportunity and Limitations of Existing Treatments

Morning Stiffness, Pain and Immobility

A Medical Marketing Economics May 2008 study of 150 RA patients in the United States, which we sponsored, showed that despite the use of a combination of currently available treatments for RA, more than ninety percent of the patients reported suffering from morning stiffness, pain and immobility, which is linked to peak IL-6 levels in the early morning hours. We believe an optimal treatment would reduce IL-6 levels in the early morning hours.

Side Effects of Current High-Dose Corticosteroid Treatments

According to the 2006 DataMonitor report, approximately 50 percent of RA patients in the United States, Japan, France, Italy, Spain, Germany and the United Kingdom are prescribed combination therapy which often includes corticosteroids, with prednisone being one of the most common. Corticosteroids, including prednisone, are used to suppress various autoimmune, inflammatory and allergic disorders by inhibiting the production of various pro-inflammatory cytokines. Joint inflammation in RA is driven by excessive production of inflammatory mediators and cytokines, such as IL-6 and TNF-alpha. While corticosteroids are potent and effective agents to treat patients with RA, they are often used at high doses to treat RA flares or significant inflammation. High-dose oral corticosteroid treatment is not a viable long-term treatment option due to adverse side effects such as osteoporosis, cardiovascular disease and weight gain. However, clinical studies have shown that the long-term use of low-dose prednisone (<10 mg per day) does not dramatically increase total adverse events. In addition, low doses, typically less than 10 mg daily, of corticosteroids such as prednisone have been shown to treat the symptoms of RA while slowing the overall progression of the disease.

Our Solutions

KRYSTEXXA

KRYSTEXXA is an orphan biologic medicine which is the first and only FDA-approved medicine for the treatment of CRG. KRYSTEXXA is a PEGylated uric acid specific enzyme (uricase) indicated for the treatment of CRG in adult patients that are refractory to conventional therapy. Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated. KRYSTEXXA has a unique mechanism of action which rapidly reverses disease progression. A PEGylated uric acid specific enzyme catalyzes the conversion of serum uric acid to allantoin, which is then excreted in urine. This PEGylated uric acid specific enzyme is given via an intravenous infusion to patients every two weeks.

Commercial Status

KRYSTEXXA was launched in the United States in January 2011.

RAYOS/LODOTRA

The medicine sold and marketed as RAYOS in the United States is known as LODOTRA outside the United States. While the FDA has approved RAYOS for the treatment of RA, ankylosing spondylitis, or AS, PMR, primary systemic amyloidosis, asthma, chronic obstructive pulmonary disease, SLE and a number of other conditions, we have focused our promotion of RAYOS/LODOTRA on rheumatology indications, including RA and PMR.

The proprietary formulation technology of RAYOS/LODOTRA enables a delayed-release of prednisone approximately four hours after administration. The RAYOS/LODOTRA proprietary delivery system synchronizes the prednisone delivery time with the patient's elevated cytokine levels, thereby taking effect at a physiologically optimal point to inhibit cytokine production, and thus significantly reduces the signs and symptoms of RA and PMR.

RAYOS/LODOTRA was developed using Vectura Group plc's (as successor in interest to SkyePharma AG, or SkyePharma), or Vectura, proprietary GeoClock™ and GeoMatrix™ technologies, for which we hold an exclusive worldwide license for the delivery of glucocorticoid, a class of corticosteroid. RAYOS/LODOTRA is composed of an active core containing prednisone, which is encapsulated by an inactive porous shell. The inactive shell acts as a barrier between the medicine's active core and a patient's gastrointestinal, or GI, fluids. RAYOS/LODOTRA is intended to be administered at bedtime. At approximately four hours following bedtime administration of RAYOS/LODOTRA, water in the digestive tract diffuses through the shell, causing the active core to expand, which leads to a weakening and breakage of the shell and allows the release of prednisone from the active core. Our pharmacokinetic studies have shown that the blood concentration of prednisone from RAYOS/LODOTRA is similar to immediate release prednisone except for the intended time delay of medicine release after administration.

Commercial Status

We began marketing RAYOS to U.S. rheumatologists in December 2012. LODOTRA received its first approval in Europe in March 2009. Mundipharma is our exclusive distributor for LODOTRA in Europe, Asia and Latin America. The majority of LODOTRA sales are in Germany and Italy where reimbursement has been approved.

Competition

As the only FDA approved medication for the treatment of CRG, KRYSTEXXA faces limited direct competition. We believe that the complexity of manufacturing KRYSTEXXA provides a barrier to potential generic competition. However, a number of competitors have medicines in Phase 1 or Phase 2 trials. On December 22, 2015, AstraZeneca AB, or AstraZeneca, secured approval from the FDA for Zurampic® (lesinurad) 200mg tablets in combination with a xanthine oxidase inhibitor, or XOI, for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with an XOI alone. In April 2016, the U.S. rights to Zurampic were licensed to Ironwood Pharmaceuticals Inc. Although Zurampic is not a direct competitor because it has not been approved for CRG, this therapy could be used prior to use of KRYSTEXXA, and if effective, could reduce the target patient population for KRYSTEXXA.

RAYOS/LODOTRA competes with a number of medicines in the market to treat RA, including corticosteroids, such as prednisone, traditional DMARDs, such as methotrexate, and biologic agents, such as Humira and Enbrel. The majority of RA patients are treated with DMARDs, which are typically used as initial therapy in patients with RA. Biologic agents are typically added to DMARDs as combination therapy. It is common for an RA patient to take a combination of a DMARD, an oral corticosteroid, an NSAID, and/or a biologic agent. We are not currently aware of any other delayed-release prednisone medicine in development.

PRIMARY CARE BUSINESS UNIT

Market

Pain is a serious and costly public health concern. In 2010, the U.S. National Center for Health Statistics reported that approximately 30 percent of U.S. adults 18 years of age and over reported recent symptoms of pain, aching or swelling around a joint within the past 30 days.

Some of the most common and debilitating chronic inflammation and pain-related diseases are OA, RA and acute and chronic pain. According to National Health Interview Survey data analyzed by the U.S. Centers for Disease Control and Prevention, from 2010-2012, 52.5 million U.S. adults eighteen years of age and over had reported being diagnosed with some form of arthritis. With the aging of the U.S. population, the prevalence of arthritis is expected to rise by approximately forty percent by 2030, impacting sixty-seven million people in the United States.

Osteoarthritis

OA is a type of arthritis that is caused by the breakdown and eventual loss of the cartilage of one or more joints. Cartilage is a protein substance that serves as a cushion between the bones of the joints. Among the over 100 different types of arthritis conditions, OA is the most common and occurs more frequently with age. OA commonly affects the hands, feet, spine and large weight-bearing joints, such as the hips and knees. Symptoms of OA manifest in patients as joint pain, tenderness, stiffness, limited joint movement, joint cracking or creaking (crepitation), locking of joints and local inflammation. OA can also lead to joint deformity in later stages of the disease. Many drugs are used to treat the inflammation and pain associated with OA, including aspirin and other NSAIDs, such as ibuprofen, naproxen and diclofenac that have a rapid analgesic and anti-inflammatory response.

Rheumatoid Arthritis

The market for RA has been discussed above in the Rheumatology Business Unit section (refer to Page 10).

Ankylosing Spondylitis

AS is a type of arthritis that affects the spine. AS symptoms include pain and stiffness from the neck down to the lower back. The spine's bones (vertebrae) may grow or fuse together, resulting in a rigid spine. These changes may be mild or severe, and may lead to a stooped-over posture. Early diagnosis and treatment helps control pain and stiffness and may reduce or prevent significant deformity.

Market Opportunity and Limitations of Existing Treatments

GI-Associated Adverse Events

NSAIDs are very effective at providing pain relief, including pain associated with OA and RA; however, there are significant upper GI-associated adverse events that can result from the use of NSAIDs. According to a 2004 article published in Alimentary Pharmacology & Therapeutics, significant GI side effects, including serious ulcers, afflict up to approximately twenty-five percent of all chronic arthritis patients treated with NSAIDs for three months, and OA and RA patients are two to five times more likely than the general population to be hospitalized for NSAID-related GI complications. It is estimated that NSAID-induced GI toxicity causes over 16,500 related deaths in OA and RA patients alone and over 107,000 hospitalizations for serious GI complications each year. In more than seventy percent of patients with these serious GI complications, there are no prior symptoms.

Despite the fact that GI ulcers are one of the most prevalent adverse events resulting from the use of NSAIDs in the United States, according to a 2006 article published in BMC Muskoskeletal Disorders, eleven observational studies indicated that physicians do not commonly co-prescribe GI protective agents to high-risk patients. Physicians prescribe concomitant therapy to only twenty-four percent of NSAID users, and studies show sub-optimal patient compliance with concomitant prophylaxis therapy. According to a 2003 article published in Alimentary Pharmacology & Therapeutics, in a study of 784 patients, thirty-seven percent of patients were non-compliant, a rate increasing to sixty-one percent in patients treated with three or more drugs. This noncompliance results in a substantial unmet clinical need, which we believe can be appropriately addressed with DUEXIS or VIMOVO, creating smarter solutions for both patients and physicians.

Topical NSAIDs

Within the NSAID market there exists a significant niche for topical NSAIDs, which are prescribed more than five million times per year. Topical NSAID treatment may be appropriate for some patients, such as patients who may benefit from the lower systemic exposure in a topical NSAID, patients with OA in just one joint such as the knee, patients who have trouble taking oral medications, or patients who are older. However, applying the correct dosage of the topical NSAID amount can often be a barrier to patient compliance, and there exists a market for a more convenient and more accurate application technique.

Our Solutions

DUEXIS

DUEXIS tablets are a proprietary, single-tablet combination containing a fixed-dose combination of ibuprofen, the most widely prescribed NSAID, and famotidine, a well-established GI agent used to treat dyspepsia, gastroesophageal reflux disease and active ulcers, in one pill. Based on clinical study results, DUEXIS has been proven to reduce the risk of ibuprofen-induced upper GI ulcers in patients taking ibuprofen for OA or RA.

Ibuprofen: One of the World's Most Widely Prescribed NSAIDs

Ibuprofen continues to be one of the most widely prescribed NSAIDs worldwide. According to Intercontinental Marketing Services, or IMS, in the United States alone, there were over 42 million prescriptions written for ibuprofen in 2015. Ibuprofen's flexible three times daily dosing allows it to be used for both chronic conditions such as arthritis and chronic back pain, and acute conditions such as sprains and strains.

Famotidine: A Safe and Effective GI Agent

Famotidine is the most potent marketed drug in the class of histamine-2 receptor antagonists, or H2RA. H2RAs are a class of drugs used to block the action of histamine on the cells in the stomach that secrete gastric acid. Famotidine was chosen as the ideal GI protectant to be combined with ibuprofen as it is a well-studied compound with an estimated 18.8 million patients treated worldwide that provides distinct advantages including:

- rapid onset of action; and
- well-tolerated with a low incidence of adverse drug reactions and a demonstrated safety margin of up to eight times the approved prescription dose for an extended period of greater than twelve months.

Although famotidine as a standalone product is not indicated for risk reduction of GI ulcers, two well-controlled clinical trials of famotidine formulated in DUEXIS found a significant decrease in the risk of developing upper GI ulcers, which in the clinical trials was defined as a gastric and/or duodenal ulcer in patients who are taking ibuprofen for those indications. Additionally, over-the-counter dosages of famotidine have been shown to be ineffective.

Benefits of a Fixed-Dose Combination Therapy

Numerous studies have demonstrated that fixed-dose combination therapy provides significant advantages over taking multiple pills. Specifically, fixed-dose combinations can reduce the number of pills, ensure that the correct dosage of each component is taken at the correct time and improve compliance, often associated with better treatment outcomes. DUEXIS has been formulated to provide an optimal dosing regimen of ibuprofen and famotidine together in the convenience of a single pill. Data shows that physicians co-prescribe GI protective agents less than twenty-five percent of the time when prescribing an NSAID. On occasions where a patient is co-prescribed a GI protective agent, data shows that after three prescriptions, sixty-one percent of patients no longer take a GI protective agent.

Commercial Status

DUEXIS is indicated for the relief of signs and symptoms of RA and OA and to decrease the risk of developing upper-GI ulcers (which in the clinical trials was defined as a gastric and/or duodenal ulcer) in patients who are taking ibuprofen for these indications. We began marketing DUEXIS to U.S. physicians in December 2011.

In June 2012, we licensed DUEXIS rights in Latin America to Grünenthal, a private company focused on the promotion of pain medicines.

PENNSAID 2%

PENNSAID 2% is a topical NSAID that is applied directly to the knee and is indicated for the treatment of pain of OA of the knee(s). PENNSAID 2% contains diclofenac sodium, a commonly prescribed NSAID to treat OA pain. PENNSAID 2% also includes dimethyl sulfoxide, or DMSO, a penetrating agent that helps ensure that diclofenac sodium is absorbed through the skin to the site of inflammation and pain. Topical NSAIDs such as PENNSAID 2% are an alternative to oral NSAID treatment because they reduce systemic exposure to a fraction of that provided by an oral NSAID. PENNSAID 2% is the only topical NSAID offered with the convenience of a metered-dose pump, which ensures that the patient will get the correct amount of PENNSAID 2% solution each time. PENNSAID 2% is easy to apply for patients because PENNSAID 2% is applied in two pumps, twice daily, delivering relief right to the site of OA knee pain.

Commercial Status

On January 16, 2014, the FDA approved PENNSAID 2% for the treatment of the pain of OA of the knee(s). We acquired the U.S. rights to PENNSAID 2% in October 2014, and began marketing PENNSAID 2% with our primary care sales force in early January 2015.

VIMOVO

VIMOVO is a proprietary, fixed-dose, delayed-release tablet. VIMOVO combines enteric-coated naproxen, an NSAID, surrounded by a layer of immediate-release esomeprazole magnesium surrounding the core. Naproxen has proven anti-inflammatory and analgesic properties and esomeprazole magnesium reduces the stomach acid secretions that can cause upper GI ulcers. Both naproxen and esomeprazole magnesium have well-documented and excellent long-term safety profiles and both medicines have been used by millions of patients worldwide. Based on clinical trial results, VIMOVO has been shown to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID associated gastric ulcers.

Naproxen: One of the World's Most Widely Prescribed NSAIDs

Naproxen is another of the most widely prescribed NSAIDs worldwide. According to IMS, in the United States alone, there were more than seventeen million prescriptions written for naproxen in 2015. In addition, naproxen's twice daily dosing allows it to be used for chronic conditions such as arthritis and AS.

Esomeprazole Magnesium: A Safe and Effective GI Agent

Esomeprazole magnesium, a gastroprotective agent, is a proton pump inhibitor, or PPI, that works by inhibiting the secretion of gastric acid thus decreasing the amount of acid in the stomach. PPIs are considered to be very potent inhibitors of acid secretion. Esomeprazole magnesium is indicated for reducing the risk of NSAID-induced gastric ulcers.

Benefits of a Fixed-Dose Combination Therapy

VIMOVO is specifically formulated to allow esomeprazole magnesium to achieve its gastroprotective impact before naproxen is released into the system. VIMOVO's design is intended to produce a sequential delivery of gastroprotective esomeprazole before exposure to naproxen. Data shows that physicians co-prescribe GI protective agents less than 25 percent of the time when prescribing an NSAID. On occasions where a patient is co-prescribed a GI protective agent, data shows that after three prescriptions, 61 percent of patients no longer take a GI protective agent.

Commercial Status

Following our acquisition of the U.S. rights to VIMOVO in November 2013, we began marketing VIMOVO in early January 2014. VIMOVO is indicated for the relief of signs and symptoms of OA, RA and AS and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers. VIMOVO is not interchangeable with the individual components of naproxen and esomeprazole magnesium.

MIGERGOT

MIGERGOT is indicated as therapy to abort or prevent vascular headaches, such as migraines, migraine variants or so-called "histaminic cephalalgia". MIGERGOT is not promoted by our sales representatives.

Competition

Our competitors in our primary care markets include large pharmaceutical and biotechnology companies, specialty pharmaceutical companies and generic drug companies, although we are not currently aware of any other ibuprofen/famotidine combination medicine or naproxen/esomeprazole magnesium combination medicine in development.

DUEXIS and VIMOVO compete with other NSAIDs, including Celebrex® which was marketed by Pfizer Inc., and is also a generic medicine known as celecoxib and supplied by other pharmaceutical companies. Celecoxib is an NSAID that selectively inhibits the COX-2 enzyme and is an effective anti-arthritic agent that reduces the risk of ulceration compared to traditional NSAIDs such as ibuprofen. DUEXIS and VIMOVO also compete with TIVORBEX™ (indomethacin) capsules, marketed by Iroko Pharmaceuticals, LLC.

In general, DUEXIS and VIMOVO also face competition from the separate use of NSAIDs for pain relief and GI medications to address the risk of NSAID-induced ulcers. Use of these therapies separately in generic form may be less expensive than DUEXIS and VIMOVO. We expect to compete with the separate use of NSAIDs and ulcer medications primarily through DUEXIS' and VIMOVO's advantages in dosing convenience and patient compliance, and by educating physicians about such advantages. DUEXIS is the only NSAID medicine containing a histamine-2 receptor antagonist with an indication to reduce the risk of NSAID-induced upper GI ulcers and VIMOVO is the only NSAID medicine containing a PPI with an indication to reduce the risk of NSAID-induced ulcers. Data shows that physicians co-prescribe GI protective agents less than twenty-five percent of the time when prescribing an NSAID. On occasions where a patient is co-prescribed a GI protective agent, data shows that after three prescriptions, sixty-one percent of patients no longer take a GI protective agent.

PENNSAID 2% faces competition from generic versions of diclofenac sodium topical solutions which are priced significantly lower than the price we charge for PENNSAID 2%. PENNSAID 2% competes primarily with Diclofenac, a market leader in the topical NSAID category. We expect to compete with these other medicines primarily through PENNSAID 2%'s dosing convenience and patient compliance. Unlike the other two medicines that are dosed four times per day and require the patient to measure out the correct dose, only PENNSAID 2% is easy to apply with the convenience of twice-daily dosing and a metered-dose pump, which ensures that the patient will get the correct amount of PENNSAID 2% solution each time.

Distribution

Finished tablets of DUEXIS, VIMOVO, RAYOS, MIGERGOT, BUPHENYL and PROCYSBI, vials of ACTIMMUNE and KRYSTEXXA, bottles of RAVICTI, PENNSAID 2% and QUINSAIR and powder of BUPHENYL are shipped to central third-party logistics FDA-compliant warehouses for storage and distribution into the supply chain. Our third-party logistics providers specialize in integrated operations that include warehousing and transportation services that can be scaled and customized to our needs based on market conditions and the demands and delivery service requirements for our medicines and materials. Their services eliminate the need to build dedicated internal infrastructures that would be difficult to scale without significant capital investment. Our third-party logistics providers warehouse all medicines in controlled FDA-registered facilities. Incoming orders are prepared and shipped through an order entry system to ensure just in time delivery of the medicines.

Sales and Marketing

As of December 31, 2016, our sales force was composed of approximately 480 sales representatives consisting of approximately 20 orphan disease sales representatives, 100 rheumatology sales specialists and 360 primary care sales representatives.

Our orphan disease representatives focus on marketing our orphan medicines to a limited number of healthcare practitioners who specialize in fields such as pediatric immunology, allergy, infectious diseases and metabolic disorders to help them understand the potential benefits of our medicines. We have entered into, and may continue to enter into, agreements with third parties for commercialization of our medicines outside the United States.

Part of our commercial strategy for RAYOS and our primary care medicines is to offer physicians the opportunity to have their patients fill prescriptions through pharmacies participating in our HorizonCares patient access program. For commercial patients who are prescribed our primary care medicines or RAYOS, the HorizonCares program offers co-pay assistance when a third-party commercial payer covers a prescription but requires an eligible patient to pay a co-pay or deductible, and offers full subsidization when a third-party commercial payer rejects coverage for an eligible patient. During 2016, we entered into business arrangements with pharmacy benefit managers, or PBMs, and other payers to secure formulary status and reimbursement of our medicines, such as our arrangements with Express Scripts, Inc., CVS Caremark and Prime Therapeutics LLC. While we believe that this strategy will result in broader inclusion of certain of our primary care medicines on healthcare plan formularies, and therefore increase payer reimbursement and lower our cost of providing patient access programs, these arrangements generally require us to pay administrative and rebate payments to the PBMs and/or other payers and regardless of our agreements with the PBMs, the extent of formulary status and reimbursement will ultimately depend to a large extent upon individual healthcare plan formulary decisions.

We have a comprehensive compliance program in place to address adherence with various laws and regulations relating to our sales, marketing, and manufacturing of our medicines, as well as certain third-party relationships, including pharmacies. Specifically with respect to pharmacies, the compliance program utilizes a variety of methods and tools to monitor and audit pharmacies, including those that participate in our patient access programs, to confirm their activities, adjudication and practices are consistent with our compliance policies and guidance.

Manufacturing, Commercial and Supply Agreements

We have agreements with third parties for active pharmaceutical ingredients, or APIs, and manufacturing of our medicines, formulation and development services, fill, finish and packaging services, transportation, and distribution and logistics services for certain medicines. In most cases, we retain certain levels of safety stock or maintain alternate supply relationships that we can utilize without undue disruption of our manufacturing processes if a third party fails to perform its contractual obligations.

ACTIMMUNE

ACTIMMUNE is a recombinant protein that is produced by fermentation of a genetically engineered Escherichia coli bacterium containing the DNA which encodes for the human protein. Purification of the active drug substance is achieved by conventional column chromatography. The resulting active drug substance is then formulated as a highly purified sterile solution and filled in a single-use vial for subcutaneous injection, which is the ACTIMMUNE finished drug medicine. In support of its manufacturing process, we and Boehringer Ingelheim RCV GmbH & Co KG, or Boehringer Ingelheim, store multiple vials of the Escherichia coli bacterium master cell bank and working cell bank in order to ensure that it will have adequate backup should any cell bank be lost in a catastrophic event.

Boehringer Ingelheim Supply Agreement

In July 2013, Vidara and Boehringer Ingelheim entered into an exclusive supply agreement, which we assumed as a result of the Vidara Merger and amended effective as of June 1, 2015. Pursuant to the agreement, Boehringer Ingelheim manufactures the ACTIMMUNE active drug substance and commercial quantities of the ACTIMMUNE finished drug medicine. Boehringer Ingelheim is our sole source supplier for ACTIMMUNE active drug substance and finished drug medicine. Under the terms of this agreement, we are required to purchase minimum quantities of finished drug medicine of 75,000 vials per annum. Boehringer Ingelheim manufactures our commercial requirements of ACTIMMUNE on an annual basis, and based on our forecasts and the annual contractual minimum purchase quantity. The supply agreement has a term that runs until July 31, 2020 and which can be further renewed by agreement between parties. Under this supply agreement, either we or Boehringer Ingelheim may terminate the agreement for an uncured material breach by the other party or upon the other party's bankruptcy or insolvency.

In October 2016, we committed to purchase additional units of ACTIMMUNE from Boehringer Ingelheim in 2017. These additional units of ACTIMMUNE were intended to cover anticipated demand should the results of the Phase 3 trial, Safety, Tolerability and Efficacy of ACTIMMUNE Dose Escalation in Friedreich's Ataxia study, or STEADFAST, evaluating ACTIMMUNE for the treatment of Friedreich's ataxia, or FA, be successful and U.S. marketing approval for FA subsequently be received. In December 2016, we announced topline results from the study, and, based on the trial results, the decision to discontinue the STEADFAST program.

License Agreements

As a result of the Vidara Merger, we acquired a license agreement, as amended, with Genentech, Inc., or Genentech, who was the original developer of ACTIMMUNE. Under such agreement, we are or were obligated to pay royalties to Genentech on our net sales of ACTIMMUNE as follows:

- For the period from November 26, 2014 through May 5, 2018, a royalty in the twenty percent to thirty percent range for the first $3.7 million in net sales achieved in any calendar year, and in the one percent to nine percent range for all additional net sales in any year; and
- From May 6, 2018 and for so long as we continue to commercially sell ACTIMMUNE, an annual royalty in the low-single digits as a percentage of annual net sales.

Either Genentech or we may terminate the agreement if the other party becomes bankrupt or defaults, however, in the case of a default, the defaulting party has thirty days to cure the default before the license agreement may be terminated.

Under the terms of an assignment and option agreement with Connetics Corporation (which was the predecessor parent company to InterMune Pharmaceuticals Inc. and is now part of GlaxoSmithKline), or Connetics, we are obligated to pay royalties to Connetics on our net sales of ACTIMMUNE as follows:

- Low-single digits as a percentage of net sales of ACTIMMUNE in the United States.

RAVICTI

We have clinical and commercial supplies of glycerol phenylbutyrate API manufactured for us by two alternate suppliers, Helsinn Advanced Synthesis SA (Switzerland) and DSM Fine Chemicals Austria (now Patheon Austria GmbH & Co KG) on a purchase order basis. We have finished RAVICTI drug medicine manufactured by Lyne Laboratories, Inc. under a manufacturing agreement and we have an agreement in place for a fill/finish supplier, Halo Pharmaceuticals, Inc., for European supplies.

Ucyclyd Asset Purchase Agreement

As a result of the Hyperion acquisition, we acquired an asset purchase agreement with Ucyclyd Pharma, Inc., or Ucyclyd, pursuant to which we are obligated to pay to Ucyclyd tiered mid- to high- single digit royalties on our global net sales of RAVICTI. The asset purchase agreement cannot be terminated for convenience by either party. However, we have a license to certain Ucyclyd manufacturing technology, and Ucyclyd may have a license to certain of our technology, and the party granting a license is permitted to terminate the license if the other party fails to comply with any payment obligations relating to the license and does not cure such failure within a defined time period.

Brusilow License Agreement

As a result of the Hyperion acquisition, we acquired a license agreement with Saul W. Brusilow, M.D. and Brusilow Enterprises, Inc., or Brusilow, pursuant to which we license patented technology related to RAVICTI from Brusilow. Under such agreement, we are obligated to pay low-single digit royalties to Brusilow on net sales of RAVICTI that are covered by a valid claim of a licensed patent. The license agreement may be terminated for any uncured breach as well as bankruptcy. We may also terminate the agreement at any time by giving Brusilow prior written notice, in which case all rights granted to us would revert to Brusilow.

BUPHENYL

When Hyperion purchased BUPHENYL, Hyperion assumed all of Ucyclyd's rights and obligations under its manufacturing agreements for the medicine. We assumed these agreements when we acquired Hyperion. We purchase API for BUPHENYL from CU Chemie Uetikon GmbH and final manufacturing, testing and packaging of the medicine is provided by Pharmaceutics International Inc.

Amended and Restated Collaboration Agreement

Under the terms of an amended and restated collaboration agreement with Ucyclyd, we are obligated to pay to Ucyclyd tiered mid to high single-digit royalties on our net sales in the United States of BUPHENYL to UCD patients outside of the FDA approved labeled age range for RAVICTI.

PROCYSBI

PROCYSBI drug product is comprised of enteric coated beads of cysteamine bitartrate encapsulated in gelatin capsules. PROCYSBI drug product and API, cysteamine bitartrate, are manufactured on a contract basis by third parties.

Patheon Manufacturing Services Agreement

As a result of the Raptor acquisition, we assumed a manufacturing services agreement, as amended, with Patheon Pharmaceuticals Inc., or Patheon. Pursuant to the agreement, we must provide a rolling, non-binding forecast of PROCYSBI, with a portion of the forecast being a firm written order. The agreement has an initial term that runs until December 31, 2017 and which automatically renews for successive two year terms if not terminated at least eighteen months in advance. Notice of termination of the agreement was not given by any party by June 30, 2016, therefore the agreement will be in force until at least December 31, 2019.

Cambrex Profarmaco Milano Supply Agreement

As a result of the Raptor acquisition, we assumed an API supply agreement, as amended, with Cambrex Profarmaco Milano, or Cambrex. Pursuant to the agreement, we must provide rolling, non-binding forecasts, with a portion of the forecast being the minimum floor of the firm order that must be placed. The Cambrex supply agreement has an initial term that runs until November 30, 2020 and which automatically renews for successive two-year terms if not terminated at least one year in advance.

UCSD License Agreement

As a result of the Raptor acquisition, we assumed a license agreement, as amended, with The Regents of the University of California, San Diego, or UCSD. We must pay UCSD a royalty in the mid-single digits on net sales of PROCYSBI in countries where PROCYSBI is covered by a patent right, and a royalty in the low-single digits on net sales of PROCYSBI in countries where PROCYSBI is not covered by a patent right. We must pay UCSD a minimum annual royalty in an amount less than $0.1 million. Royalties terminate upon the later of (a) the expiration date of the longest-lived patent rights on a country-by-country basis; and (b) ten years after first commercial sale of PROCYSBI. We may also be obligated to pay UCSD milestone payments for each orphan indication and for each non-orphan indication. We are also subject to diligence obligations relating to performing activities for specified indications, marketing licensed medicines in the United States, filling market demand for licensed medicines following commencement of marketing at any time during the agreement and obtaining all necessary governmental approvals for the manufacture, use and sale of licensed medicines.

QUINSAIR

QUINSAIR drug product, its API, levofloxacin hemihydrate, and the Zirela nebulizer device are all manufactured on a contract basis by third parties.

Teva Supply Agreement

The API is exclusively supplied by TEVA API Inc.. We must provide a twelve-month rolling forecast, and the first three months of this forecast is binding. The term of the TEVA supply agreement runs until April 11, 2021 with automatic one-year renewal periods unless notice is provided six months before termination.

Catalent Supply Agreement

QUINSAIR drug product is manufactured by Catalent Pharma Solutions, LLC. The term of the Catalent supply agreement runs until March 10, 2019. We must provide a twelve-month rolling forecast, and the first four months of this forecast is binding.

PARI Supply Agreement

Nebulizers are supplied by PARI in Starnberg, Germany. We are obligated to provide a twelve-month rolling forecast, and the first three months of this forecast is binding. The supply agreement runs until at least April 12, 2026.

RAYOS/LODOTRA

We rely on well-established third-party manufacturers for the manufacture of RAYOS/LODOTRA. We purchase the API for RAYOS/LODOTRA from Tianjin Tianyao Pharmaceuticals Co., Ltd. in China and from Sanofi Chimie SA in France. We have contracted with Jagotec AG, or Jagotec, for the production of RAYOS/LODOTRA tablets through its affiliate Vectura, and we entered into an agreement with Patheon for the packaging and assembling of RAYOS/LODOTRA.

Vectura and Jagotec Agreements

Development and License Agreement

In August 2004, we entered into a development and license agreement with Vectura, as successor in interest to SkyePharma, and Jagotec, a wholly owned subsidiary of Vectura, regarding certain proprietary technology and know-how owned by Vectura for the delayed-release of corticosteroids. Under the agreement, which was amended in August 2007, we received an exclusive, sub-licensable worldwide license to the oral formulation of any glucocorticoid, including prednisone, prednisolone, methylprednisolone and/or cortisone, with delayed-release technology covered by intellectual property rights and know-how owned by Vectura. We were also granted an option to acquire a royalty-free, exclusive and sub-licensable right to license and manufacture RAYOS/LODOTRA which we could exercise any time upon specified prior written notice, expiring no earlier than five years after the first launch of RAYOS/LODOTRA. We have exercised the option to acquire the manufacturing license, which became effective in April 2014.

In return for the grant of the license, Jagotec has the right to manufacture, package and supply RAYOS/LODOTRA to us in accordance with terms and conditions of a separate manufacturing and supply agreement we entered into with Jagotec. In addition, Jagotec is entitled to receive a single-digit percentage royalty on net sales of RAYOS/LODOTRA and on any sub-licensing income, which includes any payments not calculated based on the net sales of RAYOS/LODOTRA, such as license fees, and lump sum and milestone payments.

The agreement expires on a country-by-country basis, upon the expiration of the last patent rights for RAYOS/LODOTRA, which will occur between 2024 and 2028. In the event of expiration, the licenses under the agreement will be perpetual, fully paid-up and royalty-free. Either party may also terminate the agreement in the event of a liquidation or bankruptcy of the other party or upon an uncured breach by the other party.

Manufacturing and Supply Agreement

In August 2007, we entered into a manufacturing and supply agreement with Jagotec for RAYOS/LODOTRA. Under the agreement, which was amended in March 2011 and in January 2017, Jagotec or its affiliates manufacture and supply RAYOS/LODOTRA to us in bulk. The term of the agreement is to December 31, 2023, and the minimum purchase commitment is in force until that date. As of December 31, 2016, our total remaining minimum purchase commitment was approximately $6.9 million based on tablet pricing under the agreement as of that date, which amount is subject to volume and price adjustments due to, among other things, inflation, order quantities and launch and approval in certain EU countries. We also supply the prednisone API to Jagotec at our expense for use in the manufacture of RAYOS/LODOTRA.

We pay Jagotec, exclusive of any value added tax or similar governmental charges, a price for RAYOS/LODOTRA representing a negotiated mark-up over manufacturing costs. The price is adjusted annually to reflect changes in both manufacturing and materials costs as measured by the Ensemble price index. If Jagotec makes a major capital expenditure during the contract term to fulfill increased orders forecast by us, the price per unit will increase if the actual order falls short of the forecast.

KRYSTEXXA

KRYSTEXXA is a pegylated, recombinant protein that is produced by fermentation of a genetically engineered Escherichia coli bacterium containing the DNA which encodes for uricase. The cDNA coding for the uricase is based on mammalian sequences. Uricase is purified and is then PEGylated with a PEGylation agent to produce the bulk medicine, pegloticase. Pegylation and purification of the active drug substance is achieved by conventional column chromatography. The resulting highly purified sterile solution is filled in a single-use vial for intravenous infusion following dilution. In support of its manufacturing process, we store multiple vials of the Escherichia coli bacterium master cell bank and working cell bank at multiple locations in order to ensure that it will have adequate backup should any cell bank be lost in a catastrophic event.

NOF Supply Agreement

In August 2015, Crealta and NOF Corporation, or NOF, in Japan, entered into an exclusive supply agreement for the PEGylation agent used in the manufacture of KRYSTEXXA. Under the terms of this agreement, we are required to issue NOF forecasts of our requirements for the PEGylation agent, a portion of which are binding. The agreement expires in August 2020, however, either we or NOF may terminate the agreement for any reason upon 24 months' prior notice. Either we or NOF may also terminate the agreement upon a material breach, if not cured within a specified period of time, or in the event of the other party's insolvency. While there are no minimum purchase obligations under the agreement, we are required to use NOF as our exclusive supplier for the PEGylation agent, subject to certain exceptions if NOF is unable to supply the PEGylation agent.

Bio-Technology General (Israel) Supply Agreement

In March 2007, Savient Pharmaceuticals, Inc. (as predecessor in interest to Crealta), entered into a commercial supply agreement with Bio-Technology General (Israel) Ltd, or BTG Israel, for the production of the bulk KRYSTEXXA medicine, or bulk product. We assumed this agreement as part of the Crealta acquisition and amended the agreement in September 2016. Under this agreement, we have agreed to purchase certain minimum annual order quantities and are obligated to purchase at least 80 percent of our annual world-wide bulk product requirements from BTG Israel. The term of the agreement runs until December 31, 2030, and will automatically renew for successive three year periods unless earlier terminated by either party upon three years prior written notice. The agreement may be terminated earlier by either party in the event of a force majeure, liquidation, dissolution, bankruptcy or insolvency of the other party, uncured material breach by the other party or after January 1, 2024, upon three years prior written notice. Under the agreement if the manufacture of the bulk product is moved out of Israel, we may be required to obtain the approval of the Israeli Office of the Chief Scientist, or OCS, because certain KRYSTEXXA intellectual property was initially developed with a grant funded by the OCS and we may be required to pay the OCS additional amounts as a repayment for the OCS grant funding. We issue eighteen-month forecasts of the volume of KRYSTEXXA that we expect to order. The first six months of the forecast are considered binding firm orders.

Exelead PharmaSource Supply Agreement

In October 2008, Savient and Exelead, Inc. (formerly known as Sigma Tau PharmaSource, Inc. (as successor in interest to Enzon Pharmaceuticals, Inc.)), or Exelead, entered into a commercial supply agreement for the packaging and supply of the final drug medicine KRYSTEXXA, which we acquired as part of the Crealta acquisition. This agreement remains in effect until terminated, and either we or Exelead may terminate the agreement with three years notice, given thirty days prior to the agreement anniversary date. Either we or Exelead may also terminate the agreement upon a material default, if not cured within a specified period of time, or in the event of the other party's insolvency or bankruptcy.

Duke University and Mountain View Pharmaceutical License Agreement

In August 1998, Savient entered into an exclusive, worldwide license agreement with Duke University, or Duke, and Mountain View Pharmaceuticals Inc., or MVP. Duke developed the recombinant uricase enzyme used in KRYSTEXXA and MVP developed the PEGylation technology used in the manufacture of KRYSTEXXA. Duke and MVP may terminate the agreement if we commit fraud or for our willful misconduct or illegal conduct; upon our material breach of the agreement, if not cured within a specified period of time; upon written notice if we have committed two or more material breaches under the agreement; or in the event of our bankruptcy or insolvency. Under the terms of the agreement, we are obligated to pay Duke a mid-single digit percentage royalty on our global net sales of KRYSTEXXA and a low-double digit percentage royalty on any global sublicense revenue. We are also obligated to pay MVP a mid-single digit percentage royalty on our net sales of KRYSTEXXA outside of the United States and a low-double digit percentage royalty on any sublicense revenue outside of the United States. Royalties terminate upon last to expire of licensed patents on a country-by-country basis, and royalties are reduced by a mid-double digit percentage in countries that never had patents.

DUEXIS

We purchase DUEXIS in final, packaged form exclusively from Sanofi-Aventis U.S. LLC, or Sanofi, for our commercial requirements in North America. The first API in DUEXIS is ibuprofen in a direct compression blend called DC85 and is supplied to Sanofi by BASF Corporation, or BASF, in Bishop, Texas. The second API in DUEXIS is famotidine, which is available from a number of international suppliers. Famotidine is currently sourced from two manufacturers, Dr. Reddy's in India and also from Quimica Syntetica (Chemo) in Spain. We currently receive both APIs in powder form and each is blended with a number of U.S. Pharmacopeia inactive ingredients.

BASF Contract

In July 2010, we entered into a contract with BASF for the purchase of DC85, which was subsequently amended effective as of January 2016. Pursuant to the agreement, we are obligated to source a significant majority of our commercial demand for DC85 from BASF. The contract expires in December 2018. Thereafter, the agreement automatically renews for successive renewal terms of three years each until terminated by either party giving specified prior written notice to the other party. Either party may also terminate the agreement in the event of uncured breach by the other party.

M*anufacturing and Supply Agreement with Sanofi*

In May 2011, we entered into a manufacturing and supply agreement with Sanofi, which was amended in September 2013. Pursuant to the agreement, Sanofi is obligated to manufacture and supply DUEXIS to us in final, packaged form, and we are obligated to purchase DUEXIS exclusively from Sanofi for our commercial requirements in North America and certain countries and territories in Europe, including the EU member states and Scandinavia, and South America. Sanofi must acquire the components necessary to manufacture DUEXIS, including the APIs, and is obligated to acquire all DC85 under the terms of our agreements with suppliers, including the current BASF contract. In order to allow Sanofi to perform its obligations under the agreement, we granted Sanofi a non-exclusive license to our related intellectual property. The price for DUEXIS under the agreement varies depending on the volume of DUEXIS we purchase and is subject to annual adjustments to reflect changes in costs as measured by the Producer Price Index published by the U.S. Department of Labor, Bureau of Labor Statistics, and certain other changes and events set forth in the agreement. We have paid for the purchase and installation of equipment necessary to manufacture DUEXIS tablets, and Sanofi is obligated to pay the costs of routine maintenance of the equipment. Upon expiration or termination of the agreement we may also be obligated to reimburse Sanofi for the depreciated net book value of any other equipment purchased by Sanofi in order to fulfill its obligations under the agreement.

The agreement term extends until May 2019, and automatically extends for successive two-year terms unless terminated by either party upon two years prior written notice. Either party may terminate the agreement upon thirty days prior written notice to the other party in the event of breach by the other party that is not cured within thirty days of notice (which notice period may be longer in certain, limited situations) or in the event we lose regulatory approval to market DUEXIS in all countries worldwide, and either party may terminate the agreement without cause upon two years prior written notice to the other party at any time after the third anniversary of the first commercial sale of DUEXIS in any country worldwide.

VIMOVO

AstraZeneca License Agreement

In November 2013, we entered into a license agreement with AstraZeneca, or the AstraZeneca license agreement, pursuant to which AstraZeneca granted us an exclusive license under certain intellectual property (including patents, know-how, trademarks, copyrights and domain names) of AstraZeneca and its affiliates to develop, manufacture and commercialize VIMOVO in the United States. AstraZeneca also granted us a non-exclusive license under certain intellectual property of AstraZeneca and its affiliates to manufacture, import, export and perform research and development activities with respect to VIMOVO outside the United States but solely for purposes of commercializing VIMOVO in the United States. In addition, AstraZeneca granted us a non-exclusive right of reference and use under certain regulatory documentation controlled by AstraZeneca and its affiliates to develop, manufacture and commercialize VIMOVO in the United States and to manufacture, import, export and perform research and development activities with respect to VIMOVO outside the United States but solely for purposes of commercializing VIMOVO in the United States.

Under the AstraZeneca license agreement, we granted AstraZeneca a non-exclusive sublicense under such licensed intellectual property and a non-exclusive right of reference under certain regulatory documentation controlled by us to manufacture, import, export and perform research and development activities with respect to VIMOVO in the United States but solely for purposes of commercializing VIMOVO outside the United States.

Under the AstraZeneca license agreement, we and our affiliates are subject to certain limitations and restrictions on our ability to develop, commercialize and seek regulatory approval with respect to VIMOVO or other medicines that contain gastroprotective agents in a single fixed combination oral solid dosage form with NSAIDs (excluding DUEXIS). These limitations and restrictions include, among other things, restrictions on indications for which we may commercialize VIMOVO or any such other medicines, restrictions on our ability to develop or seek regulatory approval with respect to such other medicines that contain esomeprazole, restrictions on our ability to develop or seek regulatory approval for VIMOVO for any indications other than the indications for which NSAIDs are indicated, and restrictions on our marketing activities with respect to VIMOVO and any such other medicines.

The AstraZeneca license agreement continues in full force and effect until terminated in accordance with its terms. Under the AstraZeneca license agreement, the parties may terminate upon mutual written agreement by the parties, or either party may terminate rights granted to us with respect to licensed trademarks and licensed domain names under the AstraZeneca license agreement upon uncured material breach by the other party of certain specified provisions of the AstraZeneca license agreement.

Amended and Restated Collaboration and License Agreement with Aralez; Letter Agreement with AstraZeneca and Aralez

We entered into a license agreement with Pozen Inc., who subsequently entered into a business combination with Tribute Pharmaceuticals Canada Inc. to become known as Aralez Pharmaceuticals Inc., or Aralez. Under this agreement, we were granted an exclusive, royalty-bearing license under certain of Aralez's intellectual property in the United States to manufacture, develop and commercialize VIMOVO and other medicines controlled by us that contain gastroprotective agents in a single fixed combination oral solid dosage form with NSAIDs, excluding DUEXIS, in the United States.

Under the Aralez license agreement, we are required to pay Aralez a flat ten percent royalty based on net sales of VIMOVO and such other medicines sold by us, our affiliates or sublicensees during the royalty term, subject to minimum annual royalty obligations of $7.5 million, which minimum royalty obligations will continue for each year during which one of Aralez's patents covers such medicines in the United States and there are no competing medicines in the United States. The royalty rate may be reduced to a mid-single digit royalty rate as a result of loss of market share to competing medicines. Our obligation to pay royalties to Aralez will expire upon the later of (a) expiration of the last-to-expire of certain patents covering such medicines in the United States, and (b) ten years after the first commercial sale of such medicines in the United States. In addition, we will be obligated to reimburse Aralez for costs, including attorneys' fees, incurred by Aralez in connection with VIMOVO patent litigation moving forward, subject to agreed caps.

We are responsible for, and are required to use diligent and reasonable efforts directed to commercializing VIMOVO or another qualified medicine in the United States. We also own and maintain all regulatory filings and marketing approvals in the United States for any such medicines, including all investigational new drugs, or INDs, and new drug applications, or NDAs, for VIMOVO. Aralez covenanted that it will not at any time prior to the expiration of the royalty term, and will ensure that its affiliates do not, directly or indirectly, develop or commercialize or license any third party to develop or commercialize certain competing medicines in the United States.

The Aralez license agreement, unless earlier terminated, will expire upon expiration of the royalty term for all such medicines in the United States. Either party has the right to terminate the agreement upon uncured material breach by the other party or upon the bankruptcy or similar proceeding of the other party. We also have the right to terminate the Aralez license agreement for cause upon certain defined medicine failures.

In November 2013, we, AstraZeneca and Aralez entered into a letter agreement in which Aralez consented to AstraZeneca's assignment of the Aralez license agreement to us and that addresses the rights and responsibilities of the parties in relation to the Aralez license agreement and the amended and restated collaboration and license agreement between Aralez and AstraZeneca for territories outside the United States, or the Aralez-AstraZeneca license agreement. Under the letter agreement, we and AstraZeneca agreed to pay Aralez milestone payments upon the achievement by us and AstraZeneca, collectively, of certain annual aggregate global net sales thresholds ranging from $550.0 million to $1.25 billion with respect to medicines licensed by Aralez to us under the Aralez license agreement and to AstraZeneca under the Aralez-AstraZeneca license agreement. The aggregate milestone payment amount that may be owed by AstraZeneca and us, collectively, under the letter agreement is $260.0 million, with the amount payable by each of us and AstraZeneca with respect to each milestone to be based upon the proportional sales achieved by each of us and AstraZeneca, respectively, in the applicable year.

The letter agreement will terminate with respect to Aralez and us upon the termination of the Aralez license agreement.

Patheon Agreement

In November 2013, we entered into a master manufacturing services agreement and product agreement, or, collectively, the Patheon manufacturing agreement, with Patheon who was AstraZeneca's contract manufacturer of VIMOVO, for the manufacture and supply of VIMOVO. Under the Patheon manufacturing agreement, we agreed to purchase a specified percentage of our VIMOVO requirements for the United States from Patheon or its affiliates. In addition, under the terms of the Patheon manufacturing agreement, we are able to enter into individual product agreements with Patheon for the manufacture of specific medicines in addition to VIMOVO if agreed by us and Patheon.

Pursuant to the Patheon manufacturing agreement, we are required to supply Patheon with any active materials for VIMOVO. We must pay an agreed price for final, packaged VIMOVO supplied by Patheon subject to adjustments, including certain unilateral adjustments by Patheon, such as annual adjustments for inflation and adjustments to account for certain increases in the cost of components of VIMOVO other than active materials.

The Patheon manufacturing agreement will be effective until December 31, 2019 and will automatically renew for successive terms of three years each if there is any product agreement in effect, unless either party gives written notice to the other party of its intention to terminate the agreement at least twenty-four months prior to the end of the then current term. Either party may terminate the Patheon manufacturing agreement or any product agreement early for uncured material breach by the other party or upon the other party's bankruptcy or insolvency. We may terminate any product agreement if any regulatory authority takes any action or raises any objection that prevents us from commercializing the medicines. Additionally, Patheon may terminate the Patheon manufacturing agreement or any product agreement early if we assign our rights or obligations under the Patheon manufacturing agreement or such product agreement to a competitor of Patheon or to a party that, in the reasonable opinion of Patheon, is not a credit worthy substitute for us, or in certain other circumstances where we assign the Patheon manufacturing agreement or product agreement without Patheon's consent.

Divis Agreement

In March 2014, we entered into a manufacturing and supply agreement with Divis Laboratories Limited, or Divis, in India for the supply of naproxen. Our contract term with Divis runs through December 2018, with provisions for a three-year extension at our sole option upon written notice at least six months prior to expiration of the then current term.

Minakem Agreement

In March 2014, we entered into a manufacturing and supply agreement with Minakem Holding SAS, or Minakem, in France for the supply of esomeprazole magnesium trihydrate. Our contract term with Minakem runs through December 2018, with provisions for a three-year extension at our sole option upon written notice at least six months prior to expiration of the then current term.

PENNSAID 2%

Nuvo Supply Agreement

In October 2014, in connection with the acquisition of the U.S. rights to PENNSAID 2% from Nuvo, we entered into an exclusive supply agreement with Nuvo, which was amended in February 2016, under which Nuvo will manufacture and supply PENNSAID 2% to us. We have committed to a binding purchase order to Nuvo for delivery of PENNSAID 2%. In addition, at least ninety days prior to the first day of each calendar month during the term of the supply agreement, we are required to submit a binding written purchase order to Nuvo for PENNSAID 2% in minimum batch quantities. The term of our supply agreement is through December 31, 2029, but the agreement may be terminated earlier by either party for any uncured material breach by the other party of its obligations under the supply agreement or upon the bankruptcy or similar proceeding of the other party.

A key excipient used in PENNSAID 2% as a penetration enhancer is DMSO. We and Nuvo rely on a sole proprietary form of DMSO for which we maintain a substantial safety stock. However, should this supply become inadequate, damaged, destroyed or unusable, we and Nuvo may not be able to qualify a second source.

MIGERGOT

MIGERGOT drug product is ergotamine tartrate and caffeine-containing suppositories. The APIs, ergotamine tartrate and caffeine, are sourced from Teva in Czech Republic and from BASF in Germany, respectively. G&W Laboratories Inc., or G&W, performs the sourcing and procurement of the APIs. MIGERGOT drug product is manufactured by G&W in South Plainfield, New Jersey under a supply agreement that expires on December 31, 2023.

Customers and Information About Geographic Areas

Information regarding our total revenues attributed to United States and non-United States sources in the years ended December 31, 2016, 2015 and 2014, as well as the location of our long-lived assets, is included in Note 13 to our consolidated financial statements included in Item 15 in this Annual Report on Form 10-K.

Research and Development

We devote significant resources to research and development activities associated with our current branded medicines. For the years ended December 31, 2016, 2015 and 2014, we incurred $60.7 million, $41.9 million and $17.5 million, respectively, in research and development expenses.

ACTIMMUNE

In July 2015, we announced our collaboration with Fox Chase Cancer Center to study ACTIMMUNE in combination with PD-1/PD-L1 inhibitors in various forms of cancer including advanced urothelial carcinoma (bladder cancer) and renal cell carcinoma (kidney cancer). Pre-clinical cell line research has indicated that interferon gamma enhances cellular PD-L1 expression on endothelial cells (inner lining of the blood vessel) and on some tumor cells. By enhancing cellular PD-L1 expression on tumor cells, interferon gamma may promote or enhance the effect of the PD-1 or PD-L1 inhibitors. In December 2015, we announced that an investigator-initiated Phase 1 clinical study had been initiated to evaluate ACTIMMUNE in combination with OPDIVO® (nivolumab), marketed by Bristol-Meyers Squibb, in advanced solid tumors. The Phase 1 open label study will evaluate the combination of ACTIMMUNE and nivolumab in patients with advanced solid tumors who have progressed on at least one prior systemic therapy, which may include prior immunotherapy. Patients will be treated with a one week induction phase of ACTIMMUNE (starting dose 50 mcg/m^2 subcutaneously every other day), followed by a combination phase with ACTIMMUNE and nivolumab (3 mg/kg intravenously) for three cycles, followed by a single-agent phase of nivolumab alone for up to one year. The study will primarily assess the safety and tolerability of the combination of ACTIMMUNE and nivolumab. Secondary objectives, including overall response rate, progression free survival and overall survival, will also be assessed, as will various correlative analyses. Initial subject enrollment will occur using a modified 3+3 design, and if endpoints for safety (using dose-limiting toxicity criteria) are met, expansion cohorts in renal cell carcinoma and urothelial carcinoma are planned for up to fifteen patients per cohort. On February 23, 2017, at the American Society for Clinical Oncology - Society for Immunotherapy of Cancer meeting, investigators from Fox Chase Cancer Center presented safety data from the first two cohorts of the Phase 1 dose escalation trial evaluating ACTIMMUNE as part of a combination therapy in solid tumors for certain cancers. The preliminary data showed that combination therapy of ACTIMMUNE with nivolumab, a PD-1 inhibitor, was safe and well-tolerated in the first two cohorts. The third cohort of patients receiving ACTIMMUNE is still under study.

We are supporting Indiana University to study ACTIMMUNE in the treatment of type 2 osteopetrosis, autosomal dominant osteopetrosis, or ADO2. ADO2 is a genetic condition characterized by generalized osteosclerosis predominating in some skeletal sites such as the spine and pelvis. The short-term, open label treatment trial in ADO2 patients aims to determine if administration of ACTIMMUNE increases biochemical markers of bone turnover, and thus determine if the medicine can completely or partially reverse the defective osteoclastic bone resorption in ADO2 patients. The clinical study is expected to run over a period of three years, and commenced in July 2016.

On December 8, 2016, we announced that the STEADFAST study evaluating ACTIMMUNE for the treatment of FA, did not meet its primary endpoint of a statistically significant change from baseline in the modified Friedreich's Ataxia Rating Scale at twenty-six weeks versus treatment with placebo. In addition, the secondary endpoints did not meet statistical significance. No new safety findings were identified on initial review of data other than those already noted in the ACTIMMUNE prescribing information for approved indications. We, in conjunction with the independent Data Safety Monitoring Board, the principal investigator and the Friedreich's Ataxia Research Alliance Collaborative Clinical Research Network in FA, determined that, based on the trial results, the STEADFAST program would be discontinued, including the twenty-six week extension study and the long-term safety study.

RAVICTI

We are in the process of seeking approval for label expansions for RAVICTI, with assessments in progress studying the use of RAVICTI in patients both from two months to two years (sNDA submitted on June 29, 2016) and from birth to two months (targeted sNDA submission in the first quarter of 2018). Current FDA approval is for patients from two years of age and older only. In patients with UCDs for which RAVICTI is an FDA-approved medicine, there is a variable age of diagnosis (from newborn to adulthood), and the severity of the disease can be associated with the age of onset and enzymatic deficit. However, a prompt diagnosis and careful management of the disease can lead to good clinical outcomes.

RAYOS

In November 2015, we announced our collaboration with the ALR to study the effect of RAYOS on the fatigue experienced by SLE patients. SLE is a chronic autoimmune disease that causes inflammation and pain in the joints and muscles, as well as overall fatigue. RAYOS is currently indicated for patients with SLE. The first study planned as part of the collaboration is an investigator-initiated, randomized, double-blind, active comparator, cross-over study in which patients will be randomized to receive either prednisone for three months or RAYOS at 10 p.m. for three months, and then switched to the alternative medication for an additional three months. Approximately sixty-two patients across twenty-five sites will be enrolled in the United States. Fatigue will be measured by the Functional Assessment of Chronic Illness Therapy-Fatigue and the Fatigue Severity Scale, as well as the Vitality scale of the Medical Outcome Study thirty-six-item short form health survey. The study is expected to start in the first quarter of 2017.

KRYSTEXXA

In January 2016, following our acquisition of Crealta, we assumed responsibility for a study designed to test the potential reduction of immunogenicity in KRYSTEXXA patients, known as the Tolerization Reduces Intolerance to Pegloticase and Prolongs the Urate Lowering Effect, or TRIPLE, study. The TRIPLE study is an investigator-initiated, post-market interventional, exploratory open-label, multicenter adaptive design study of approximately fifty-three patients to evaluate the effectiveness of a sixteen-week high zone tolerance regimen of KRYSTEXXA on response to therapy (serum uric acid <6 mg/dL) in adult hyperuricemic patients, < 120 kg and ≥ 120 kg in weight, with gout refractory to conventional therapy. We are also developing a potential registration study to expand the label should the TRIPLE study show positive results. Success in the TRIPLE study and the subsequent registration study would have the potential to significantly expand the patient population and usage of KRYSTEXXA.

As part of the TRIPLE study, initial, more frequent dosing is being examined to determine if this reduces antibody formation by inducing antigen specific non-responsiveness. This would prevent the formation of anti-pegloticase antibodies and prevent the loss of drug response. This involves evaluating the drug's lowest trough level, which pharmacokinetically occurs between the first and second doses. Increasing this trough level should suppress the high titer antibody formation. Current labelling states that KRYSTEXXA should be given every two weeks. This study adds one extra dose that occurs one week after the initial dose.

Intellectual Property

Our objective is to aggressively patent the technology, inventions and improvements that we consider important to the development of our business. We have a portfolio of patents and applications based on clinical and pharmacokinetic/pharmacodynamic modeling discoveries, and our novel formulations. We intend to continue filing patent applications seeking intellectual property protection as we generate anticipated formulation refinements, new methods of manufacturing and clinical trial results.

We will only be able to protect our technologies and medicines from unauthorized use by third parties to the extent that valid and enforceable patents or trade secrets cover them. As such, our commercial success will depend in part on receiving and maintaining patent protection and trade secret protection of our technologies and medicines as well as successfully defending these patents against third-party challenges.

We have licenses to U.S. patents covering ACTIMMUNE. If not otherwise invalidated, those patents expire in 2022. We continue to prosecute and pursue patent protection to obtain additional patent coverage on ACTIMMUNE and its uses.

We have U.S. and foreign patents and patent applications covering PROCYSBI, as well as licenses from the University of California, San Diego to U.S. and foreign patents and patent applications covering PROCYSBI. If not otherwise invalidated, those patents expire between 2027 and 2034. We continue to prosecute and pursue patent protection to obtain additional patent coverage on PROCYSBI and its uses.

PROCYSBI received marketing authorization in September 2013 from the EC for marketing in the EU as an orphan medicinal product for the management of proven nephropathic cystinosis.

PROCYSBI received seven years of market exclusivity, through 2020, for patients six years and older as an orphan drug in the United States, and ten years of market exclusivity, through 2023, as an orphan drug in Europe.

We also have U.S. and foreign patents and patent applications covering QUINSAIR, as well as licenses from PARI to U.S. and foreign patents and patent applications covering QUINSAIR. If not otherwise invalidated, those patents expire between 2020 and 2037. We continue to prosecute and pursue patent protection to obtain additional patent coverage on QUINSAIR and its uses.

QUINSAIR received ten years of market exclusivity in the EU, beginning with its March 2015 marketing authorization.

We also have an exclusive license to U.S. and foreign patents from Brusilow Enterprises LLC covering RAVICTI which expire in the United States in 2018 and if extended, in certain countries in Europe in 2021. We also have ownership of U.S. and foreign patents and patent applications covering RAVICTI. If not otherwise invalidated, those patents expire between 2030 and 2032. We continue to prosecute and pursue patent protection to obtain additional patent coverage on RAVICTI and its uses.

In the United States, RAVICTI has been granted seven years of orphan drug exclusivity, which will expire in 2020. In the EU, RAVICTI received ten years of marketing exclusivity protection, beginning with its December 2015 marketing authorization.

We also have licenses to U.S. and foreign patents and applications covering KRYSTEXXA. If not otherwise invalidated, those patents expire between 2019 and 2030. We continue to prosecute and pursue patent protection to obtain additional patent coverage on KRYSTEXXA and its uses.

In the United States, KRYSTEXXA has received twelve years of biologic exclusivity, expiring in 2022, and seven years of orphan drug exclusivity, expiring in September 2017.

We have an exclusive license to U.S. and foreign patents and patent applications from Vectura covering RAYOS/LODOTRA. If not otherwise invalidated, those in-licensed patents expire between 2024 and 2028. We continue to prosecute and pursue additional patent coverage on RAYOS/LODOTRA and its uses. However, under the Settlement Agreement with Actavis Laboratories FL, Inc. (formerly known as Watson Laboratories, Inc. – Florida), or Actavis, Actavis may enter the market on December 23, 2022, or earlier under certain circumstances.

In the EU, LODOTRA has received ten years of marketing exclusivity protection, beginning with its March 2009 marketing authorization in Germany.

We have multiple patents and patent applications related to DUEXIS. Unless otherwise invalidated, those patents expire in 2026. However, under the license agreement with Par Pharmaceutical, Inc. and Par Pharmaceutical Companies, Inc., or collectively Par, Par may enter the market on January 1, 2023, or earlier under certain circumstances.

We also have ownership of U.S. patents and patent applications covering PENNSAID 2% from Nuvo. We also co-own other U.S. patent applications with Mallinckrodt LLC. If not otherwise invalidated, those patents expire between 2027 and 2030. However, under the settlement agreements with Perrigo Company plc, or Perrigo, Taro Pharmaceuticals USA, Inc. and Taro Pharmaceutical Industries, Ltd., or collectively Taro, Amneal Pharmaceuticals LLC, or Amneal, and Teligent, Inc., or Teligent, Perrigo, Taro, Amneal, and/or Teligent may enter the market on January 10, 2029, or earlier under certain circumstances. We continue to prosecute and pursue patent protection in the United States to obtain additional patent coverage on PENNSAID 2% and its uses.

We also have licenses to U.S. patents and patent applications and trademarks covering VIMOVO from Aralez and AstraZeneca. We co-own other U.S. patents and patent applications with Aralez. If not otherwise invalidated, those in-licensed patents expire between 2018 and 2031. We continue to prosecute and pursue patent protection in the United States to obtain additional patent coverage on VIMOVO and its uses.

The patent positions of life sciences companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in such companies' patents has emerged to date in the United States. The patent situation outside the United States is even more uncertain. Changes in either the patent laws or in interpretations of patent laws in the United States or other countries may diminish the value of our intellectual property. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in our patents or in third-party patents. For example:

- we or our licensors might not have been the first to make the inventions covered by each of our pending patent applications and issued patents;
- we or our licensors might not have been the first to file patent applications for these inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies;
- it is possible that none of our pending patent applications or the pending patent applications of our licensors will result in issued patents;
- our issued patents and the issued patents of our licensors may not provide a basis for commercially viable drugs, or may not provide us with any competitive advantages, or may be challenged and invalidated by third parties;
- we may not be successful in any patent litigation to enforce our patent rights, including our pending patent litigation regarding, PENNSAID 2%, RAVICTI and/or VIMOVO;
- we may not develop additional proprietary technologies or medicine candidates that are patentable; or
- the patents of others may have an adverse effect on our business.

For a description of our legal proceedings, see Note 16 of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K.

Third-Party Coverage and Reimbursement

In both U.S. and foreign markets, our ability to commercialize our medicines successfully depends in significant part on the availability of coverage and adequate reimbursement to healthcare providers from third-party payers, including, in the United States, government payers such as the Medicare and Medicaid programs, managed care organizations and private health insurers. Third-party payers are increasingly challenging the prices charged for medicines and examining their cost effectiveness, in addition to their safety and efficacy. This is especially true in markets where over-the-counter and generic options exist. Even if coverage is made available by a third-party payer, the reimbursement rates paid for covered medicines might not be adequate. For example, third-party payers may use tiered coverage and may adversely affect demand for our medicines by not covering our medicines or by placing them in a more expensive formulary tier relative to competitive medicines (where patients have to pay relatively more out of pocket than for medicines in a lower tier). We cannot be certain that our medicines will be covered by third-party payers or that such coverage, where available, will be adequate, or that our medicines will successfully be placed on the list of drugs covered by particular health plan formularies. Many states have also created preferred drug lists and include drugs on those lists only when the manufacturers agree to pay a supplemental rebate. The industry competition to be included on such formularies and preferred drug lists often leads to downward pricing pressures on pharmaceutical companies. Also, third-party payers may refuse to include a particular branded drug on their formularies or otherwise restrict patient access to a branded drug when a less costly generic equivalent or other therapeutic alternative is available. In addition, because each third-party payer individually approves coverage and reimbursement levels, obtaining coverage and adequate reimbursement is a time-consuming and costly process. We may be required to provide scientific and clinical support for the use of any medicine to each third-party payer separately with no assurance that approval would be obtained, and we may need to conduct pharmacoeconomic studies to demonstrate the cost effectiveness of our medicines for formulary coverage and reimbursement. Even with studies, our medicines may be considered less safe, less effective or less cost-effective than competitive medicines, and third-party payers may not provide coverage and adequate reimbursement for our medicines or our medicine candidates. These pricing and reimbursement pressures may create negative perceptions to any medicine price increases, or limit the amount we may be able to increase our medicine prices, which may adversely affect our medicine sales and results of operations. Where coverage and reimbursement are not adequate, physicians may limit how much or under what circumstances they will prescribe or administer such medicines, and patients may decline to purchase them. This, in turn, could affect our ability to successfully commercialize our medicines and impact our profitability, results of operations, financial condition, and future success.

The U.S. market has seen a trend in which retail pharmacies have become increasingly involved in determining which prescriptions will be filled with the requested medicine or a substitute medicine, based on a number of factors, including potentially perceived medicine costs and benefits, as well as payer medicine substitution policies. Many states have in place requirements for prescribers to indicate "dispense as written" on their prescriptions if they do not want pharmacies to make medicine substitutions; these requirements are varied and not consistent across states. We may need to increasingly spend time and resources to ensure the prescriptions written for our medicines are filled as written, where appropriate.

Coverage policies, third-party reimbursement rates and medicine pricing regulation have been subject to significant change, and may change further at any time, particularly given recent political focus on the pharmaceutical industry. Even if favorable coverage and adequate reimbursement status is attained for one or more medicines, less favorable coverage policies and reimbursement rates may be implemented in the future.

Government Regulation

The FDA and comparable regulatory agencies in state and local jurisdictions and in foreign countries impose extensive requirements upon the clinical development, pre-market approval, manufacture, labeling, marketing, promotion, pricing, import, export, storage and distribution of medicines. These agencies and other regulatory agencies regulate research and development activities and the testing, approval, manufacture, quality control, safety, effectiveness, labeling, storage, recordkeeping, advertising and promotion of drugs and biologics. Failure to comply with applicable FDA or foreign regulatory agency requirements may result in Warning Letters, fines, civil or criminal penalties, additional reporting obligations and/or agency oversight, suspension or delays in clinical development, recall or seizure of medicines, partial or total suspension of production or withdrawal of a medicine from the market.

In the United States, the FDA regulates drug products under the Federal Food, Drug, and Cosmetic Act and its implementing regulations and biologics additionally under the Public Health Service Act. The process required by the FDA before medicine candidates may be marketed in the United States generally involves the following:

- submission to the FDA of an IND, which must become effective before human clinical trials may begin and must be updated annually;
- completion of extensive preclinical laboratory tests and preclinical animal studies, all performed in accordance with the FDA's Good Laboratory Practice, or GLP, regulations;
- performance of adequate and well-controlled human clinical trials to establish the safety and efficacy of the medicine candidate for each proposed indication;
- submission to the FDA of an NDA or biologics license application, or BLA, as appropriate, after completion of all pivotal clinical trials to demonstrate the safety, purity and potency of the medicine candidate for the indication for use;
- a determination by the FDA within 60 days of its receipt of an NDA or BLA to file the application for review;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facilities to assess compliance with the FDA's current good manufacturing practices regulations for pharmaceuticals, or cGMPs; and
- FDA review and approval of an NDA or BLA prior to any commercial marketing or sale of the medicine in the United States.

The development and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our medicine candidates will be granted on a timely basis, if at all.

The results of preclinical tests (which include laboratory evaluation as well as GLP studies to evaluate toxicity in animals) for a particular medicine candidate, together with related manufacturing information and analytical data, are submitted as part of an IND to the FDA. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises concerns or questions about the conduct of the proposed clinical trial, including concerns that human research subjects will be exposed to unreasonable health risks. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. IND submissions may not result in FDA authorization to commence a clinical trial. A separate submission to an existing IND must also be made for each successive clinical trial conducted during medicine development. Further, an independent institutional review board, or IRB, for each medical center proposing to conduct the clinical trial must review and approve the plan for any clinical trial before it commences at that center and it must monitor the study until completed. The FDA, the IRB or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk. Clinical testing also must satisfy extensive good clinical practice regulations and regulations for informed consent and privacy of individually identifiable information. Similar requirements to the U.S. IND are required in the EEA and other jurisdictions in which we may conduct clinical trials.

Clinical Trials. For purposes of NDA or BLA submission and approval, clinical trials are typically conducted in the following sequential phases, which may overlap:

- *Phase 1*. Studies are initially conducted in a limited population to test the medicine candidate for safety, dose tolerance, absorption, distribution, metabolism, and excretion, typically in healthy humans, but in some cases in patients.
- *Phase 2*. Studies are generally conducted in a limited patient population to identify possible adverse effects and safety risks, explore the initial efficacy of the medicine for specific targeted indications and to determine dose range or pharmacodynamics. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more expensive Phase 3 clinical trials.
- *Phase 3*. These are commonly referred to as pivotal studies. When Phase 2 evaluations demonstrate that a dose range of the medicine is effective and has an acceptable safety profile, Phase 3 clinical trials are undertaken in large patient populations to further evaluate dosage, provide substantial evidence of clinical efficacy and further test for safety in an expanded and diverse patient population at multiple, geographically dispersed clinical trial centers.
- *Phase 4*. The FDA may approve an NDA or BLA for a medicine candidate, but require that the sponsor conduct additional clinical trials to further assess the medicine after approval under a post marketing commitment or post marketing requirement. In addition, a sponsor may decide to conduct additional clinical trials after the FDA has approved a medicine. Post-approval trials are typically referred to as Phase 4 clinical trials.

The results of drug development, preclinical studies and clinical trials are submitted to the FDA as part of an NDA or BLA, as appropriate. Applications also must contain extensive chemistry, manufacturing and control information. Applications must be accompanied by a significant user fee. Once the submission has been accepted for filing, the FDA's goal is to review applications within 12 months of submission or, if the application relates to an unmet medical need in a serious or life-threatening indication, eight months from submission. The review process is often significantly extended by FDA requests for additional information or clarification. The FDA will typically conduct a pre-approval inspection of the manufacturer to ensure that the medicine can be reliably produced in compliance with cGMPs and will typically inspect certain clinical trial sites for compliance with good clinical practice, or GCP. The FDA may refer the application to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it typically follows such recommendations. The FDA may deny approval of an application by issuing a Complete Response Letter if the applicable regulatory criteria are not satisfied. A Complete Response Letter may require additional clinical data and/or trial(s), and/or other significant, expensive and time- consuming requirements related to clinical trials, preclinical studies or manufacturing. Data from clinical trials are not always conclusive and the FDA may interpret data differently than we or our collaborators interpret data. Approval may occur with boxed warnings on medicine labeling or Risk Evaluation and Mitigation Strategies, or REMS, which limit the labeling, distribution or promotion of a medicine. Once issued, the FDA may withdraw medicine approval if ongoing regulatory requirements are not met or if safety problems occur after the medicine reaches the market. In addition, the FDA may require testing, including Phase 4 clinical trials, and surveillance programs to monitor the safety effects of approved medicines which have been commercialized and the FDA has the power to prevent or limit further marketing of a medicine based on the results of these post-marketing programs or other information.

Orphan Medicines. Under the Orphan Drug Act, the FDA may designate a medicine as an "orphan drug" if it is intended to treat a rare disease or condition, meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a medicine available in the United States for treatment of the disease or condition will be recovered from sales of the medicine. A company must request orphan drug designation before submitting an NDA for the drug and rare disease or condition. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan drug designation does not shorten the Prescription Drug User Fee Act, or PDUFA, goal dates for the regulatory review and approval process, although it does convey certain advantages such as tax benefits and exemption from the PDUFA application fee.

If a medicine with orphan designation receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the medicine generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor's marketing application for the same drug for the same indication for seven years, except in certain limited circumstances. Orphan exclusivity does not block the approval of a different drug for the same rare disease or condition, nor does it block the approval of the same drug for different indications. If a drug designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity. Orphan exclusivity will not bar approval of another medicine under certain circumstances, including if a subsequent medicine with the same drug for the same indication is shown to be clinically superior to the approved medicine on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand.

In the EU, Regulation (EC) No 141/2000 and Regulation (EC) No. 847/2000 provide that a medicine can be designated as an orphan medicinal product by the EC if its sponsor can establish: that the medicine is intended for the diagnosis, prevention or treatment of (1) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the EU when the application is made, or (2) a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives the medicinal product is unlikely to be developed. For either of these conditions, the applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the EU or, if such method exists, the medicinal product will be of significant benefit to those affected by that condition. Once authorized, orphan medicinal products are entitled to ten years of market exclusivity in all EU Member States (extendable to twelve years for medicines that have complied with an agreed pediatric investigation plan pursuant to Regulation 1901/2006) and in addition a range of other benefits during the development and regulatory review process including scientific assistance for study protocols, authorization through the centralized marketing authorization procedure covering all member countries and a reduction or elimination of registration and marketing authorization fees. However, marketing authorization may be granted to a similar medicinal product with the same orphan indication during the ten year period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if this medicine is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if, at the end of the fifth year, it can be demonstrated on the basis of available evidence that the criteria for its designation as an orphan medicine are no longer satisfied, for example if the original orphan medicinal product has become sufficiently profitable not to justify maintenance of market exclusivity.

Other Regulatory Requirements. Medicines manufactured or distributed pursuant to FDA approvals are subject to continuing regulation by the FDA, including recordkeeping, annual medicine quality review, payment of medicine and manufacturing establishment fees and reporting requirements. Adverse event experience with the medicine must be reported to the FDA in a timely fashion and pharmacovigilance programs to proactively look for these adverse events are mandated by the FDA. Our medicines may be subject to REMS requirements that affect labeling, distribution or post market reporting. Drug manufacturers and their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMPs, which impose certain procedural and documentation requirements upon us and our third-party manufacturers. Following such inspections, the FDA may issue notices on Form 483 and Untitled Letters or Warning Letters that could cause us or our third-party manufacturers to modify certain activities. A Form 483 notice, if issued at the conclusion of an FDA inspection, can list conditions the FDA investigators believe may have violated cGMP or other FDA regulations or guidelines. In addition to Form 483 notices and Untitled Letters or Warning Letters, failure to comply with the statutory and regulatory requirements can subject a manufacturer to possible legal or regulatory action, such as suspension of manufacturing, seizure of medicine, injunctive action, additional reporting requirements and/or oversight by the agency, import alert or possible civil penalties. The FDA may also require us to recall a drug from distribution or withdraw approval for that medicine.

The FDA closely regulates the post-approval marketing and promotion of pharmaceuticals, including standards and regulations for direct-to-consumer advertising, dissemination of off-label information, industry-sponsored scientific and educational activities and promotional activities involving the Internet, including certain social media activities. Medicines may be marketed only for the approved indications and in accordance with the provisions of the approved label. Further, if there are any modifications to the medicine, including changes in indications, labeling, or manufacturing processes or facilities, we may be required to submit and obtain FDA approval of a new or supplemental application, which may require us to develop additional data or conduct additional preclinical studies and clinical trials. Failure to comply with these requirements can result in adverse publicity, Warning Letters or "untitled letters", corrective advertising and potential administrative, civil and criminal penalties, as well as damages, fines, withdrawal of regulatory approval, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs, additional reporting requirements and/or oversight by the agency, and imprisonment, any of which could adversely affect our ability to sell our medicines or operate our business and also adversely affect our financial results.

Physicians may, in their independent medical judgment, prescribe legally available pharmaceuticals for uses that are not described in the medicine's labeling and that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, impose stringent restrictions on manufacturers' communications regarding off-label use. Additionally, a significant number of pharmaceutical companies have been the target of inquiries and investigations by various U.S. federal and state regulatory, investigative, prosecutorial and administrative entities in connection with the promotion of medicines for off-label uses and other sales practices. These investigations have alleged violations of various U.S. federal and state laws and regulations, including claims asserting antitrust violations, violations of the Food, Drug and Cosmetic Act, false claims laws, the Prescription Drug Marketing Act, anti-kickback laws, and other alleged violations in connection with the promotion of medicines for unapproved uses, pricing and Medicare and/or Medicaid reimbursement. If our promotional activities, including any promotional activities that a contracted sales force may perform on our behalf, fail to comply with these regulations or guidelines, we may be subject to warnings from, or enforcement action by, these authorities. In addition, our failure to follow FDA rules and guidelines relating to promotion and advertising may cause the FDA to issue warning letters or untitled letters, suspend or withdraw an approved medicine from the market, require corrective advertising or a recall or institute fines or civil fines, additional reporting requirements and/or oversight or could result in disgorgement of money, operating restrictions, injunctions or criminal prosecution, any of which could harm our business. In addition, the distribution of prescription medicines is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription medicine samples and impose requirements to ensure accountability in distribution, including a drug pedigree which tracks the distribution of prescription drugs. Further, under the Drug Quality and Security Act, drug manufacturers are subject to a number of requirements, including, medicine identification, tracing and verification, among others, that are designed to detect and remove counterfeit, stolen, contaminated or otherwise potentially harmful drugs from the U.S. drug supply chain. These requirements will be phased in over several years and compliance will likely increase the costs of the manufacture and distribution of drug medicines.

Outside the United States, the ability of our partners and us to market a medicine is contingent upon obtaining marketing authorization from the appropriate regulatory authorities. The requirements governing marketing authorization, pricing and reimbursement vary widely from country to country and region to region.

The EU and the EEA consist of the 28 Member States of the EU, plus Norway, Iceland and Liechtenstein which are Member States of the EEA. These Member States have all acceded to the single market rules governing the supervision of medicinal products. Under the prevailing rules, medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. There are three procedures for an MA to be obtained:

- the Centralized MA, which is issued by the EC through the Centralized Procedure, based on the scientific opinion of the CHMP of the EMA, and which is valid throughout the entire territory of the EU/EEA. When decisions on granting of a Centralized MA are taken by the EU, the EEA Member States will take corresponding decisions on the basis the relevant acts to permit marketing of medicinal products. The Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products, and medicinal products containing a new active substance indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune and viral diseases. The Centralized Procedure is optional for products containing a new active substance not yet authorized in the EU/EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU.

- Decentralized Procedure MAs are available for products not falling within the mandatory scope of the Centralized Procedure. An identical dossier is submitted to the competent authorities of each of the Member States in which the MA is sought, one of which is selected by the applicant as the Reference Member State, or RMS, to lead the evaluation of the regulatory submission. The competent authority of the RMS prepares a draft assessment report, a draft summary of the product characteristics, or SmPC, and a draft of the labeling and package leaflet as distilled from the preliminary evaluation, which are sent to the other Member States (referred to as the Concerned Member States, or CMS) for their approval. If the CMS raise no objections, based on a potential serious risk to public health, to the assessment, SmPC, labeling, or packaging proposed by the RMS, the RMS records the agreement, closes the procedure and informs the applicant accordingly. Each Member State concerned by the procedure is required to adopt a national decision to grant a national MA in conformity with the approved assessment report, SmPC and the labeling and package leaflet as approved. Where a product has already been authorized for marketing in a Member State of the EEA, the granted national MA can be used for mutual recognition in other Member States through the Mutual Recognition Procedure, or MRP, resulting in progressive national approval of the product in the EU/EEA.
- National MAs, which are issued by a single competent authority of the Member States of the EEA and only covers their respective territory, are also available for products not falling within the mandatory scope of the Centralized Procedure. Once a product has been authorized for marketing in a Member State of the EEA through the National Procedure, this National MA can also be recognized in other Member States through the MRP.

Under the procedures described above, before granting the MA, the EMA or the competent authority(ies) of the Member State(s) of the EEA prepare an assessment of the risk-benefit balance of the product against the scientific criteria concerning its quality, safety and efficacy.

Under Regulation (EC) No 726/2004/EC and Directive 2001/83/EC (each as amended), the EU has adopted a harmonized approach to data and market protection or exclusivity (known as the 8 + 2 + 1 formula). The data exclusivity period begins to run on the date when the first MA is granted in the EU. It confers on the MA holder of the reference medicinal product eight years of data protection and ten years of market protection. A reference medicinal product is defined to mean a medicinal product authorized based on a full dossier consisting of pharmaceutical and preclinical testing results and clinical trial data, such as a medicinal product containing a new active substance. The ten-year market protection can be extended cumulatively to a maximum period of eleven years if during the first eight years of those ten years of protection period, the MA holder obtains an authorization for one or more new therapeutic indications that are deemed to bring a significant clinical benefit compared to existing therapies.

The protection period means that an applicant for a generic medicinal product is not permitted to rely on preclinical pharmacological, toxicological, and clinical data contained in the file of the reference medicinal product of the originator until the first eight years of data protection have expired. Thereafter, a generic product application may be submitted and generic companies may rely on the preclinical and clinical data relating to the reference medicinal product to support approval of the generic product. However, a generic cannot market until ten years have elapsed from the initial authorization of the reference medicinal product or eleven years if the protection period is extended, based on the formula of 8+2+1.

In addition to the above, where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication. Finally, where a change of classification of a medicinal product has been authorized on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorization for a change of classification of the same substance for one year after the initial change was authorized.

The 8 + 2 + 1 exclusivity scheme applies to products that have been authorized in the EU by either the EMA through the Centralized Procedure or the competent authorities of the Member States of the EEA nationally, including through the Decentralized and Mutual Recognition procedures.

For a medicinal product which is designated as orphan under Regulation 141/2000, it will benefit from a period of ten years of orphan market exclusivity which essentially constitutes a period of market monopoly. During this period of orphan market exclusivity, no EU regulatory authority is permitted to accept or approve an application for marketing authorization for a similar medicinal product or an extension application for the same therapeutic indication. This period can be extended cumulatively to a total of twelve years if the marketing authorization holder or applicant complies with the requirements for an agreed pediatric investigation plan pursuant to Regulation 1901/2006.

The holder of a Centralized MA or National MA is subject to various obligations under the applicable EU laws, such as pharmacovigilance obligations, requiring it to, among other things, report and maintain detailed records of adverse reactions, and to submit periodic safety update reports to the competent authorities. The holder must also ensure that the manufacturing and batch release of its product is in compliance with the applicable requirements. The MA holder is further obligated to ensure that the advertising and promotion of its products complies with applicable EU laws and industry code of practice as implemented in the domestic laws of the Member States of the EU/EEA. The advertising and promotional rules are enforced nationally by the EU/EEA Member States.

Healthcare Fraud and Abuse Laws. As a pharmaceutical company, certain federal and state healthcare laws and regulations pertaining to fraud and abuse and patients' rights are and will be applicable to our business. We may be subject to various federal and state laws targeting fraud and abuse in the healthcare industry. For example, in the United States, there are federal and state anti-kickback laws that prohibit the payment or receipt of kickbacks, bribes or other remuneration intended to induce the purchase or recommendation of healthcare products and services or reward past purchases or recommendations. Violations of these laws can lead to civil and criminal penalties, including fines, imprisonment, additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement, and exclusion from participation in federal healthcare programs. These laws are applicable to manufacturers of products regulated by the FDA, such as us, and pharmacies, hospitals, physicians and other potential purchasers of such products.

The federal Anti-Kickback Statute prohibits persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, to induce either the referral of an individual, or the furnishing, recommending, or arranging for a good or service, for which payment may be made under a federal healthcare program, such as the Medicare and Medicaid programs. The term "remuneration" is defined as any remuneration, direct or indirect, overt or covert, in cash or in kind, and has been broadly interpreted to include anything of value, including for example, gifts, discounts, the furnishing of supplies or equipment, credit arrangements, payments of cash, waivers of payment, ownership interests and providing anything at less than its fair market value. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute may have been violated, and enforcement will depend on the relevant facts and circumstances. The Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the ACA, among other things, amended the intent requirement of the federal Anti-Kickback Statute to state that a person or entity need not have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the ACA provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act (discussed below) or the civil monetary penalties statute, which imposes penalties against any person who is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent, or to have offered improper inducements to federal health care program beneficiaries to select a particular provider or supplier. The federal Anti-Kickback Statute is broad, and despite a series of narrow safe harbors, prohibits many arrangements and practices that are lawful in businesses outside of the healthcare industry. Many states have also adopted laws similar to the federal Anti-Kickback Statute, some of which apply to the referral of patients for healthcare items or services reimbursed by any source, not only the Medicare and Medicaid programs, and do not contain identical safe harbors. In addition, where such activities involve foreign government officials, they may also potentially be subject to the Foreign Corrupt Practices Act. Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities, including our activities with physician customers, pharmacies, and patients, as well as our activities pursuant to partnerships with other companies and pursuant to contracts with contract research organizations, could be subject to challenge under one or more of such laws.

The federal False Claims Act prohibits any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. A claim includes "any request or demand" for money or property presented to the U.S. government. In addition, the ACA specified that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act. The federal False Claims Act has been the basis for numerous enforcement actions and settlements by pharmaceutical and other healthcare companies in connection with various alleged financial relationships with customers. In addition, a number of pharmaceutical manufacturers have reached substantial financial settlements in connection with allegedly causing false claims to be submitted because of the companies' marketing of products for unapproved, and thus non-reimbursable, uses. Certain marketing practices, including off-label promotion, may also violate false claims laws, as might violations of the federal physician self-referral laws, such as the Stark laws, which prohibit a physician from making a referral to certain designated health services with which the physician or the physician's family member has a financial interest and prohibit submission of a claim for reimbursement pursuant to the prohibited referral. The "qui tam" provisions of the False Claims Act allow a private individual to bring civil actions on behalf of the federal government alleging that the defendant has submitted a false claim to the federal government, and to share in any monetary recovery. In addition, various states have enacted similar fraud and abuse statutes or regulations, including, without limitation, false claims laws analogous to the False Claims Act, and laws analogous to the federal Anti-Kickback Statute, that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payer, and there are also federal criminal false claims laws.

Separately, there are a number of other fraud and abuse laws that pharmaceutical manufacturers must be mindful of, particularly after a medicine candidate has been approved for marketing in the United States. For example, a federal criminal law enacted as part of, the Health Insurance Portability and Accountability Act of 1996, or HIPAA, prohibits knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payers. The false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. There are also federal civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payers that are false or fraudulent, as well as federal and state consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

Healthcare Privacy and Security Laws. We may be subject to, or our marketing activities may be limited by, HIPAA, as amended by the Health Information Technology and Clinical Health Act and their respective implementing regulations, which established uniform standards for certain "covered entities" (healthcare providers, health plans and healthcare clearinghouses) governing the conduct of certain electronic healthcare transactions and protecting the security and privacy of protected health information. Among other things, HIPAA's privacy and security standards are directly applicable to "business associates" — independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. In addition to possible civil and criminal penalties for violations, state attorneys general are authorized to file civil actions for damages or injunctions in federal courts to enforce HIPAA and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. In the EU/EEA, Directive 95/46/EEC (as amended) or its successor applies to identified or identifiable personal data processed by automated means (for example, a computer database of customers) and data contained in, or intended to be part of, non-automated filing systems (traditional paper files) as well as transfer of such data to a country outside of the EU/EEA.

"Sunshine" and Marketing Disclosure Laws. There are an increasing number of federal and state "sunshine" laws that require pharmaceutical manufacturers to make reports to states on pricing and marketing information. Several states have enacted legislation requiring pharmaceutical companies to, among other things, establish marketing compliance programs, file periodic reports with the state, and make periodic public disclosures on sales and marketing activities, and prohibiting certain other sales and marketing practices. In addition, a similar federal requirement requires manufacturers, including pharmaceutical manufacturers, to track and report to the federal government certain payments and other transfers of value made to physicians and other healthcare professionals and teaching hospitals and ownership or investment interests held by physicians and their immediate family members. The federal government began disclosing the reported information on a publicly available website in 2014. These laws may adversely affect our sales, marketing, and other activities with respect to our medicines in the United States by imposing administrative and compliance burdens on us. If we fail to track and report as required by these laws or otherwise comply with these laws, we could be subject to the penalty provisions of the pertinent state and federal authorities. In the EU/EEA, declaration of transfers of value to healthcare professionals is subject to the requirements under the voluntary industry code of practice. France however has a statutory regime similar to the U.S. Sunshine Act.

Government Price Reporting. For those marketed medicines which are covered in the United States by the Medicaid programs, we have various obligations, including government price reporting and rebate requirements, which generally require medicines be offered at substantial rebates/discounts to Medicaid and certain purchasers (including "covered entities" purchasing under the 340B Drug Discount Program). We are also required to discount such medicines to authorized users of the Federal Supply Schedule of the General Services Administration, under which additional laws and requirements apply. These programs require submission of pricing data and calculation of discounts and rebates pursuant to complex statutory formulas, as well as the entry into government procurement contracts governed by the Federal Acquisition Regulations, and the guidance governing such calculations is not always clear. Compliance with such requirements can require significant investment in personnel, systems and resources, but failure to properly calculate our prices, or offer required discounts or rebates could subject us to substantial penalties. One component of the rebate and discount calculations under the Medicaid and 340B programs, respectively, is the "additional rebate", a complex calculation which is based, in part, on the rate at which a branded drug price increases over time more than the rate of inflation (based on the CPI-U). This comparison is based on the baseline pricing data for the first full quarter of sales associated with a branded drug's NDA, and baseline data cannot generally be reset, even on transfer of the NDA to another manufacturer. This "additional rebate" calculation can, in some cases where price increase have been relatively high versus the first quarter of sales of the NDA, result in Medicaid rebates up to 100 percent of a drug's "average manufacturer price" and 340B prices of one penny. Subject to the control of Directive 89/105/EEC, pricing and reimbursement in the EU/EEA is governed by national rules and policy and may vary from Member State to Member State.

In General. Because of the breadth of these laws and the narrowness of available statutory and regulatory exemptions, it is possible that some of our business activities, in the United States, could be subject to challenge under one or more of such laws. If we or our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including significant civil and criminal penalties, damages, fines, imprisonment, exclusion from participation in U.S. federal or state healthcare programs, additional reporting requirements and/or oversight and the curtailment or restructuring of our operations. To the extent that any medicine we make is sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals. Any penalties, damages, fines, curtailment or restructuring of our operations could materially adversely affect our ability to operate our business and our financial results. Although compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. Moreover, achieving and sustaining compliance with applicable federal and state privacy, security, sunshine, government price reporting, and fraud laws may prove costly.

Impact of Healthcare Reform and Recent Public Scrutiny of Specialty Drug Pricing on Coverage, Reimbursement, and Pricing. In the United States and other potentially significant markets for our medicines, government authorities and third-party payers are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative medicines and therapies, which has resulted in lower average selling prices. Further, the increased scrutiny of prescription drug pricing practices and emphasis on managed healthcare in the United States and on country-specific and regional pricing and reimbursement controls in the EU will put additional pressure on medicine pricing, reimbursement and usage, which may adversely affect our future medicine sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical reimbursement policies and pricing in general.

The U.S. and some foreign jurisdictions are considering or have enacted a number of additional legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our medicines profitably. Among policy makers and payers in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs (including a number of proposals pertaining to prescription drugs, specifically), improving quality and/or expanding access. There has been particular and increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices over the course of 2015 and 2016, particularly with respect to drugs that have been subject to relatively large price increases over relatively short time periods. There have been several recent U.S. Congressional inquiries and proposed legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient assistance programs, and reform government program reimbursement methodologies for drugs. In the United States, the pharmaceutical industry has already been significantly affected by major legislative initiatives, including, for example, the ACA. The ACA, among other things, imposes a significant annual fee on companies that manufacture or import branded prescription drug medicines. It also contains substantial provisions intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, and impose additional health policy reforms, any or all of which may affect our business. Since its enactment, there have been judicial and Congressional challenges to numerous provisions of the ACA. In January, Congress voted to adopt a budget resolution for fiscal year 2017, or the Budget Resolution, that authorizes the implementation of legislation that would repeal portions of the ACA. The Budget Resolution is not a law, but it is widely viewed as the first step toward the passage of legislation that would repeal certain aspects of the ACA. Further, on January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. Congress also could consider subsequent legislation to replace elements of the ACA that are repealed. We will continue to evaluate the effect that the ACA and any future measures to repeal or replace the ACA have on our business. The intense public scrutiny of drug pricing in the United States, is likely to continue the downward pressure on pharmaceutical pricing, especially under the Medicare program, and may also increase our regulatory burdens and operating costs.

Other legislative changes have also been proposed and adopted since the ACA was enacted. For example, the Budget Control Act of 2011 resulted in aggregate reductions in Medicare payments to providers of up to two percent per fiscal year, starting in 2013, and the American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Such laws, and others that may affect our business that have been recently enacted or may in the future be enacted, may result in additional reductions in Medicare and other healthcare funding. In the future, there will likely continue to be additional proposals relating to the reform of the U.S. healthcare system, some of which could further limit coverage and reimbursement of medicines, including our medicine candidates. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payers. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our medicines.

Irish Law Matters

As a result of the Vidara Merger, the outstanding shares of the common stock of HPI were canceled and automatically converted into the right to receive our ordinary shares. As we are an Irish-incorporated company, the following matters of Irish law are relevant to the holders of our ordinary shares.

Irish Restrictions on Import and Export of Capital. Except as indicated below, there are no restrictions imposed specifically on non-residents of Ireland dealing in Irish domestic securities, which includes ordinary shares of Irish companies. Dividends and redemption proceeds also continue to be freely transferable to non-resident holders of such securities. The Financial Transfers Act 1992 gives power to the Minister for Finance of Ireland to restrict financial transfers between Ireland and other countries and persons. Financial transfers are broadly defined and include all transfers that would be movements of capital or payments within the meaning of the treaties governing the member states of the EU. The acquisition or disposal of interests in shares issued by an Irish incorporated company and associated payments falls within this definition. In addition, dividends or payments on redemption or purchase of shares and payments on a liquidation of an Irish incorporated company would fall within this definition. The Criminal Justice (Terrorist Offences) Act 2005 also gives the Minister of Finance of Ireland the power to take various measures, including the freezing or seizure of assets, in order to combat terrorism. At present the Financial Transfers Act 1992 and the Criminal Justice (Terrorist Offences) Act 2005 prohibit financial transfers involving the late Slobodan Milosevic and associated persons, Republic of Guinea-Bissau, Myanmar/Burma, Belarus, certain persons indicted by the International Criminal Tribunal for the former Yugoslavia, the late Osama bin Laden, Al-Qaida, the Taliban of Afghanistan, Democratic Republic of Congo, Democratic People's Republic of Korea (North Korea), Iran, Iraq, Côte d'Ivoire, Lebanon, Liberia, Zimbabwe, Sudan, Somalia, Republic of Guinea, Afghanistan, Egypt, Eritrea, Libya, Syria, Tunisia, Burundi, the Central African Republic, Ukraine, Yemen, certain known terrorists and terrorist groups, and countries that harbor certain terrorist groups, without the prior permission of the Central Bank of Ireland or the Minister of Finance (as applicable).

Any transfer of, or payment in respect of, a share or interest in a share involving the government of any country that is currently the subject of United Nations sanctions, any person or body controlled by any of the foregoing, or by any person acting on behalf of the foregoing, may be subject to restrictions pursuant to such sanctions as implemented into Irish law.

Irish Taxes Applicable to U.S. Holders

Withholding Tax on Dividends. While we have no current plans to pay dividends, dividends on our ordinary shares would generally be subject to Irish Dividend Withholding Tax, or DWT, at the standard rate of income tax (currently twenty percent), unless an exemption applies.

Dividends on our ordinary shares that are owned by residents of the United States and held beneficially through the Depositary Trust Company, or DTC, will not be subject to DWT provided that the address of the beneficial owner of the ordinary shares in the records of the broker is in the United States.

Dividends on our ordinary shares that are owned by residents of the United States and held directly (outside of DTC) will not be subject to DWT provided that the shareholder has completed the appropriate Irish DWT form and this form remains valid. Such shareholders must provide the appropriate Irish DWT form to our transfer agent at least seven business days before the record date for the first dividend payment to which they are entitled.

If any shareholder who is resident in the United States receives a dividend subject to DWT, he or she should generally be able to make an application for a refund from the Irish Revenue Commissioners on the prescribed form.

While the U.S./Ireland Double Tax Treaty contains provisions regarding withholding, due to the wide scope of the exemptions from DWT available under Irish domestic law, it would generally be unnecessary for a U.S. resident shareholder to rely on the treaty provisions.

Income Tax on Dividends. A shareholder who is neither resident nor ordinarily resident in Ireland and who is entitled to an exemption from DWT generally has no additional liability to Irish income tax or to the universal social charge on a dividend from us unless that shareholder holds our ordinary shares through a branch or agency in Ireland through which a trade is carried on.

A shareholder who is neither resident nor ordinarily resident in Ireland and who is not entitled to an exemption from DWT generally has no additional liability to Irish income tax or to the universal social charge on a dividend from us. The DWT deducted by us discharges the liability to Irish income tax and to the universal social charge. This however is not the case where the shareholder holds the ordinary shares through a branch or agency in Ireland through which a trade is carried on.

Irish Tax on Capital Gains. A shareholder who is neither resident nor ordinarily resident in Ireland and does not hold our ordinary shares in connection with a trade or business carried on by such shareholder in Ireland through a branch or agency should not be within the charge to Irish tax on capital gains on a disposal of our ordinary shares.

Capital Acquisitions Tax. Irish capital acquisitions tax, or CAT, is composed principally of gift tax and inheritance tax. CAT could apply to a gift or inheritance of our ordinary shares irrespective of the place of residence, ordinary residence or domicile of the parties. This is because our ordinary shares are regarded as property situated in Ireland as our share register must be held in Ireland. The person who receives the gift or inheritance has primary liability for CAT.

CAT is levied at a rate of 33 percent above certain tax-free thresholds. The appropriate tax-free threshold is dependent upon (i) the relationship between the donor and the donee and (ii) the aggregation of the values of previous gifts and inheritances received by the donee from persons within the same category of relationship for CAT purposes. Gifts and inheritances passing between spouses are exempt from CAT. Our shareholders should consult their own tax advisers as to whether CAT is creditable or deductible in computing any domestic tax liabilities.

Stamp Duty. Irish stamp duty (if any) may become payable in respect of ordinary share transfers. However, a transfer of our ordinary shares from a seller who holds shares through DTC to a buyer who holds the acquired shares through DTC will not be subject to Irish stamp duty. A transfer of our ordinary shares (i) by a seller who holds ordinary shares outside of DTC to any buyer, or (ii) by a seller who holds the ordinary shares through DTC to a buyer who holds the acquired ordinary shares outside of DTC, may be subject to Irish stamp duty (currently at the rate of one percent of the price paid or the market value of the ordinary shares acquired, if greater). The person accountable for payment of stamp duty is the buyer or, in the case of a transfer by way of a gift or for less than market value, all parties to the transfer.

A shareholder who holds ordinary shares outside of DTC may transfer those ordinary shares into DTC without giving rise to Irish stamp duty provided that the shareholder would be the beneficial owner of the related book-entry interest in those ordinary shares recorded in the systems of DTC (and in exactly the same proportions) as a result of the transfer and at the time of the transfer into DTC there is no sale of those book-entry interests to a third party being contemplated by the shareholder. Similarly, a shareholder who holds ordinary shares through DTC may transfer those ordinary shares out of DTC without giving rise to Irish stamp duty provided that the shareholder would be the beneficial owner of the ordinary shares (and in exactly the same proportions) as a result of the transfer, and at the time of the transfer out of DTC there is no sale of those ordinary shares to a third party being contemplated by the shareholder. In order for the share registrar to be satisfied as to the application of this Irish stamp duty treatment where relevant, the shareholder must confirm to us that the shareholder would be the beneficial owner of the related book-entry interest in those ordinary shares recorded in the systems of DTC (and in exactly the same proportions) (or vice-versa) as a result of the transfer and there is no agreement for the sale of the related book-entry interest or the ordinary shares or an interest in the ordinary shares, as the case may be, by the shareholder to a third party being contemplated.

Employees

As of December 31, 2016, we had approximately 1,050 full-time employees. Of our employees as of December 31, 2016, approximately 185 were engaged in development, regulatory and manufacturing activities, approximately 650 were engaged in sales and marketing and approximately 215 were engaged in administration, including business development, finance, legal, information systems, facilities and human resources. None of our employees is subject to a collective bargaining agreement. We consider our employee relations to be satisfactory.

Available Information

We make available free of charge on or through our internet website our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and all amendments to those reports as soon as reasonably practicable after such material is electronically filed with or furnished to the Securities and Exchange Commission. We also regularly post copies of our press releases as well as copies of presentations and other updates about our business on our website. Our website address is www.horizonpharma.com. The information contained in or that can be accessed through our website is not part of this report. Information is also available through the Securities and Exchange Commission's website at www.sec.gov or is available at the Securities and Exchange Commission's Public Reference Room located at 100 F Street, NE, Washington DC, 20549. Information on the operation of the Public Reference Room is available by calling the Securities and Exchange Commission at 800-SEC-0330.

Item 1A. Risk Factors

Certain factors may have a material adverse effect on our business, financial condition and results of operations, and you should carefully consider them. Accordingly, in evaluating our business, we encourage you to consider the following discussion of risk factors in its entirety, in addition to other information contained in this report as well as our other public filings with the Securities and Exchange Commission, or SEC.

Risks Related to Our Business and Industry

Our ability to generate revenues from our medicines is subject to attaining significant market acceptance among physicians, patients and healthcare payers.

Our current medicines, and other medicines or medicine candidates that we may develop or acquire, may not attain market acceptance among physicians, patients, healthcare payers or the medical community. We have a limited history of commercializing medicines and most of our medicines have not been on the market for an extensive period of time, which subjects us to numerous risks as we attempt to increase our market share. We believe that the degree of market acceptance and our ability to generate revenues from our medicines will depend on a number of factors, including:

- timing of market introduction of our medicines as well as competitive medicines;
- efficacy and safety of our medicines;
- continued projected growth of the markets in which our medicines compete;
- prevalence and severity of any side effects;
- if and when we are able to obtain regulatory approvals for additional indications for our medicines;
- acceptance by patients, primary care physicians and key specialists;
- availability of coverage and adequate reimbursement and pricing from government and other third-party payers;
- potential or perceived advantages or disadvantages of our medicines over alternative treatments, including cost of treatment and relative convenience and ease of administration;
- strength of sales, marketing and distribution support;
- the price of our medicines, both in absolute terms and relative to alternative treatments;
- impact of past and limitation of future medicine price increases;
- our ability to maintain a continuous supply of medicine for commercial sale;
- the effect of current and future healthcare laws;
- the performance of third-party distribution partners, over which we have limited control; and
- medicine labeling or medicine insert requirements of the U.S. Food and Drug Administration, or FDA, or other regulatory authorities.

With respect to DUEXIS and VIMOVO, studies indicate that physicians do not commonly co-prescribe gastrointestinal, or GI, protective agents to high-risk patients taking nonsteroidal anti-inflammatory drugs, or NSAIDs. We believe this is due in part to a lack of awareness among physicians prescribing NSAIDs regarding the risk of NSAID-induced upper GI ulcers, in addition to the inconvenience of prescribing two separate medications and patient compliance issues associated with multiple prescriptions. If physicians remain unaware of, or do not otherwise believe in, the benefits of combining GI protective agents with NSAIDs, our market opportunity for DUEXIS and VIMOVO will be limited. Some physicians may also be reluctant to prescribe DUEXIS or VIMOVO due to the inability to vary the dose of ibuprofen and naproxen, respectively, or if they believe treatment with NSAIDs or GI protective agents other than those contained in DUEXIS and VIMOVO, including those of its competitors, would be more effective for their patients. With respect to each of DUEXIS, PENNSAID 2% w/w, or PENNSAID 2%, RAYOS/LODOTRA, VIMOVO and BUPHENYL, their higher cost compared to the generic or branded forms of their active ingredients alone may limit adoption by physicians, patients and healthcare payers. With respect to ACTIMMUNE, while it is the only FDA-approved treatment for chronic granulomatous disease, or CGD, and severe, malignant osteopetrosis, or SMO, they are very rare conditions and, as a result, our ability to grow ACTIMMUNE sales will depend on our ability to further penetrate this limited market and obtain marketing approval for additional indications. With respect to RAVICTI, which is also approved to treat a very limited patient population, our ability to grow sales will depend in large part on our ability to transition urea cycle disorder, or UCD, patients from BUPHENYL or generic equivalents, which are comparatively much less expensive, to RAVICTI. With respect to KRYSTEXXA, our ability to grow sales will be affected by the success of our sales and marketing strategies and life cycle management, including studies designed to test reduction of immunogenicity in KRYSTEXXA which could expand the patient population and usage of KRYSTEXXA. With respect to MIGERGOT, our ability to sustain sales will depend on the management of inventory levels and the continued awareness of its benefits among physicians. With respect to PROCYSBI, which is approved to treat a very limited patient population, our ability to grow sales will depend in large part on our ability to transition patients from the first-generation immediate-release cysteamine therapy to PROCYSBI, to identify additional patients with nephropathic cystinosis, and expand commercialization in Europe. Unless QUINSAIR is approved for marketing in additional countries, our ability to drive growth of this medicine will largely depend on expanding its use in Europe and Canada. If our current medicines or any other medicine that we may seek approval for or acquire fail to attain market acceptance, we may not be able to generate significant revenue to achieve or sustain profitability, which would have a material adverse effect on our business, results of operations, financial condition and prospects (including, possibly, the value of our ordinary shares).

Our future prospects are highly dependent on our ability to successfully formulate and execute commercialization strategies for each of our medicines. Failure to do so would adversely impact our financial condition and prospects.

A substantial majority of our resources are focused on the commercialization of our current medicines. Our ability to generate significant medicine revenues and to achieve commercial success in the near-term will initially depend almost entirely on our ability to successfully commercialize these medicines in the United States.

With respect to our orphan business unit medicines, ACTIMMUNE, BUPHENYL, PROCYSBI, QUINSAIR and RAVICTI, and with respect to our rheumatology business unit medicine, KRYSTEXXA, our commercialization strategy includes efforts to increase awareness of the rare conditions that each medicine is designed to treat, enhancing efforts to identify target patients and in certain cases pursue opportunities for label expansion and more effective use through clinical trials. In addition, our strategy with respect to ACTIMMUNE includes pursuing label expansion for additional indications, such as for advanced urothelial carcinoma and renal cell carcinoma, and price increases but we cannot be certain that our pricing strategy will not result in downward pressure on sales or that we or others will be able to successfully complete clinical trials and obtain regulatory approvals in additional indications. With respect to PROCYSBI and RAVICTI, our strategy includes accelerating the transition of patients from first-generation therapies, and increasing the diagnosis of the associated rare conditions through patient and physician outreach. Part of our success in our strategy for RAVICTI will also depend on obtaining approval of RAVICTI for the treatment of UCD in patients less than two years of age. However, we cannot guarantee that on-going studies will be positive or that we will be able to expand the labeling for RAVICTI on our anticipated timeline or at all. Our strategy with respect to KRYSTEXXA includes the continued enhancement of the marketing campaign with improved immunogenicity data, continued volume growth and pricing optimization.

With respect to our primary care medicines DUEXIS, PENNSAID 2% and VIMOVO, our strategy has more recently included entering into rebate agreements with pharmacy benefit managers, or PBMs, for certain of our primary care medicines where we believe the rebates and costs justify expanded formulary access for patients. However, we cannot guarantee that we will be able to secure additional rebate agreements on commercially reasonable terms or that expected volume growth will sufficiently offset the rebates and fees paid to PBMs or that our existing agreements with PBMs will have the intended impact on formulary access. For each of our primary care medicines, we expect that our commercial success will depend on our sales and marketing efforts in the United States.

Our strategy for RAYOS in the United States is to focus on the rheumatology indications approved for RAYOS, including our collaboration with the Alliance for Lupus Research, or ALR, to study the effect of RAYOS on the fatigue experienced by systemic lupus erythematosus, or SLE, patients.

Our overall commercialization strategy also includes plans to expand sales in Europe and other countries outside the United States directly or through distributors for certain of our orphan and rheumatology medicines. In November 2015, we received approval of the Committee for Medicinal Products for Human Use of the European Medicines Agency, or EMA, for RAVICTI for use as an adjunctive therapy for chronic management of adult and pediatric UCD patients greater than two months of age. This authorizes us to market RAVICTI in all 28 Member States of the European Union, or EU, and will form the basis for recognition by the Member States of the European Economic Area, or EEA, namely Norway, Iceland and Liechtenstein, for the medicine to be placed on the market. In June 2016, we partnered with Clinigen Group plc's Idis managed access division to initiate a managed access program in selected European countries, which agreement will terminate on April 10, 2017 and after which we will partner with Swedish Orphan Biovitrum AB, or SOBI, to continue our managed access program in selected European countries. While we expect to commercially launch RAVICTI in Europe in 2017 through an exclusive distribution agreement with SOBI, we cannot guarantee we will be able to successfully implement our commercial plans for RAVICTI in Europe. With respect to PROCYSBI and QUINSAIR, which are approved for marketing in the EU, we intend to continue evaluating commercial launches in additional EU countries as well as pursuing early access programs. Although LODOTRA is approved for marketing in countries outside the United States, to date it has only been marketed in a limited number of countries.

If any of our commercial strategies are unsuccessful or we fail to successfully modify our strategies over time due to changing market conditions, our ability to increase market share for our medicines, grow revenues and sustain profitability will be harmed.

In order to increase adoption and sales of our medicines, we will need to continue developing our commercial organization as well as recruit and retain qualified sales representatives.

Part of our strategy is to continue to build a biopharmaceutical company to successfully execute the commercialization of our medicines in the U.S. market, and in selected markets outside the United States where we have commercial rights. We may not be able to successfully commercialize our medicines in the United States or in any other territories where we have commercial rights. In order to commercialize any approved medicines, we must continue to build our sales, marketing, distribution, managerial and other non-technical capabilities. Although we had expanded our sales force to approximately 480 sales representatives as of December 31, 2016, consisting of approximately 20 orphan disease sales representatives, 100 rheumatology sales specialists and 360 primary care sales representatives, we currently have limited resources compared to some of our competitors, and the continued development of our own commercial organization to market our medicines and any additional medicines we may acquire will be expensive and time-consuming. We also cannot be certain that we will be able to continue to successfully develop this capability.

As a result of the evolving role of various constituents in the prescription decision making process, we focus on hiring sales representatives for our primary care and rheumatology business units with successful business to business experience. For example, we have faced challenges due to pharmacists increasingly switching a patient's intended prescription from DUEXIS and VIMOVO to a generic or over-the-counter brand of their active ingredients. We have faced similar challenges for RAYOS, BUPHENYL and PENNSAID 2% with respect to generic brands. While we believe the profile of our representatives is better suited for this evolving environment, we cannot be certain that our representatives will be able to successfully protect our market for DUEXIS, PENNSAID 2%, RAYOS, BUPHENYL and VIMOVO or that we will be able to continue attracting and retaining sales representatives with our desired profile and skills. We will also have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train and retain commercial personnel. To the extent we rely on additional third parties to commercialize any approved medicines, we may receive less revenue than if we commercialized these medicines ourselves. In addition, we may have little or no control over the sales efforts of any third parties involved in our commercialization efforts. In the event we are unable to successfully develop and maintain our own commercial organization or collaborate with a third-party sales and marketing organization, we may not be able to commercialize our medicines and medicine candidates and execute on our business plan.

If we are unable to effectively train and equip our sales force, our ability to successfully commercialize our medicines will be harmed.

As we continue to acquire additional medicines through acquisition transactions, the members of our sales force may have limited experience promoting certain of our medicines. To the extent we employ an acquired entity's original sales forces to promote acquired medicines, we may not be successful in continuing to retain these employees and we otherwise will have limited experience marketing these medicines under our commercial organization. As a result, we are required to expend significant time and resources to train our sales force to be credible and persuasive in convincing physicians to prescribe and pharmacists to dispense our medicines. In addition, we must train our sales force to ensure that a consistent and appropriate message about our medicines is being delivered to our potential customers. Our sales representatives may also experience challenges promoting multiple medicines when we call on physicians and their office staff. We have experienced, and may continue to experience, turnover of the sales representatives that we hired or will hire, requiring us to train new sales representatives. If we are unable to effectively train our sales force and equip them with effective materials, including medical and sales literature to help them inform and educate physicians about the benefits of our medicines and their proper administration and label indication, as well as our patient access programs, our efforts to successfully commercialize our medicines could be put in jeopardy, which could have a material adverse effect on our financial condition, share price and operations.

If we cannot successfully implement our patient access programs or increase formulary access and reimbursement for our medicines in the face of increasing pressure to reduce the price of medications, the adoption of our medicines by physicians, patients and payers may decline.

There continues to be immense pressure from healthcare payers and PBMs to use less expensive generics or over-the-counter brands instead of branded medicines. For example, some of the largest PBMs previously placed DUEXIS and VIMOVO on their formulary exclusion lists. Additional healthcare plans, including those that contract with these PBMs but use different formularies, may also choose to exclude our medicines from their formularies or restrict coverage to situations where a generic or over-the-counter medicine has been tried first. Many payers and PBMs also require patients to make co-payments for branded medicines, including many of our medicines, in order to incentivize the use of generic or other lower-priced alternatives instead. Legislation enacted in most states in the United States allows, or in some instances mandates, that a pharmacist dispenses an available generic equivalent when filling a prescription for a branded medicine, in the absence of specific instructions from the prescribing physician. Because our medicines (other than BUPHENYL) do not currently have FDA-approved generic equivalents in the United States, we do not believe our medicines should be subject to mandatory generic substitution laws. However, we understand that some pharmacies may attempt to obtain physician authorization to switch prescriptions for DUEXIS or VIMOVO to prescriptions for multiple generic medicines with similar active pharmaceutical ingredients, or APIs, to ensure payment for the medicine if the physician's prescription for the branded medicine is not immediately covered by the payer, despite such substitution being off-label in the case of DUEXIS and VIMOVO. If these limitations in coverage and other incentives result in patients refusing to fill prescriptions or being dissatisfied with the out-of-pocket costs of their medications, or if pharmacies otherwise seek and receive physician authorization to switch prescriptions, not only would we lose sales on prescriptions that are ultimately not filled, but physicians may be dissuaded from writing prescriptions for our medicines in the first place in order to avoid potential patient non-compliance or dissatisfaction over medication costs, or to avoid spending the time and effort of responding to pharmacy requests to switch prescriptions.

Part of our commercial strategy to increase adoption and access to our medicines in the face of these incentives to use generic alternatives is to offer physicians the opportunity to have patients fill prescriptions through independent pharmacies participating in our HorizonCares patient access program. Through HorizonCares, financial assistance may be available to reduce eligible patients' out-of-pocket costs for prescriptions filled. Because of this assistance, eligible patients' out-of-pocket cost for our medicines when dispensed through HorizonCares may be significantly lower than such costs when our medicines are dispensed outside of the HorizonCares program. However, to the extent physicians do not direct prescriptions currently filled through traditional pharmacies, including those associated with or controlled by PBMs, to pharmacies participating in our HorizonCares program, we may experience a significant decline in DUEXIS, VIMOVO and PENNSAID 2% prescriptions as a result of formulary exclusions, co-payment requirements or other incentives to use lower-priced alternatives to our medicines. Our ability to increase utilization of our patient access programs will depend on physician and patient awareness and comfort with the programs, and we have limited ability to influence whether physicians use our patient access programs to prescribe our medicines or whether patients will agree to receive our medicines through our HorizonCares program. In addition, the HorizonCares program is not available to federal health care program (such as Medicare and Medicaid) beneficiaries. We have also contracted with certain PBMs and other payers to secure formulary status and reimbursement for certain of our primary care medicines, which generally require us to pay administrative fees and rebates to the PBMs and other payers for qualifying prescriptions. While we recently announced business relationships with two of the largest PBMs, Express Scripts, Inc., or Express Scripts, and CVS Caremark, that have resulted in DUEXIS and VIMOVO being removed from the Express Scripts and CVS Caremark 2017 exclusion lists, as well as a rebate agreement with another PBM, Prime Therapeutics LLC, and we believe these agreements will secure formulary status for certain of our medicines, we cannot guarantee that we will be able to agree to terms with other PBMs and other payers, or that such terms will be commercially reasonable to us. In addition, despite our agreements with PBMs, the extent of formulary status and reimbursement will ultimately depend to a large extent upon individual healthcare plan formulary decisions. If healthcare plans that contract with PBMs with which we have agreements do not adopt formulary changes recommended by the PBMs with respect to our medicines, we may not realize the expected access and reimbursement benefits from these agreements. If we are unable to increase adoption of HorizonCares for filling prescriptions of our medicines or to secure formulary status and reimbursement through arrangements with PBMs and other payers, our ability to maintain or increase prescriptions for our medicines could be impaired.

There has been negative publicity and inquiries from Congress and enforcement authorities regarding the use of specialty pharmacies and drug pricing. Our patient access programs are not involved in the prescribing of medicines and are solely to assist in ensuring that when a physician determines one of our medicines offers a potential clinical benefit to their patients and they prescribe one for an eligible patient, financial assistance may be available to reduce the patient's out-of-pocket costs. In addition, all pharmacies that fill prescriptions for our medicines are fully independent, including those that participate in HorizonCares. We do not own or possess any option to purchase an ownership stake in any pharmacy that distributes our medicines, and our relationship with each pharmacy is non-exclusive and arm's length. All of our sales are processed through pharmacies independent of us. Despite this, the negative publicity and interest from Congress and enforcement authorities regarding specialty pharmacies may result in physicians being less willing to participate in our patient access programs and thereby limit our ability to increase patient access and adoption of our medicines.

We may also encounter difficulty in forming and maintaining relationships with pharmacies that participate in our patient access programs. We currently depend on a limited number of pharmacies participating in HorizonCares to fulfill patient prescriptions under the HorizonCares program. If these HorizonCares participating pharmacies are unable to process and fulfill the volume of patient prescriptions directed to them under the HorizonCares program, our ability to maintain or increase prescriptions for our medicines will be impaired. The commercialization of our medicines and our operating results could be affected should any of the HorizonCares participating pharmacies choose not to continue participation in our HorizonCares program or by any adverse events at any of those HorizonCares participating pharmacies. For example, pharmacies that dispense our medicines could lose contracts that they currently maintain with managed care organizations, or MCOs, including PBMs. Pharmacies often enter into agreements with MCOs. They may be required to abide by certain terms and conditions to maintain access to MCO networks, including terms and conditions that could limit their ability to participate in patient access programs like ours. Failure to comply with the terms of their agreements with MCOs could result in a variety of penalties, including termination of their agreement, which could negatively impact the ability of those pharmacies to dispense our medicines and collect reimbursement from MCOs for such medicines.

The HorizonCares program may implicate certain state laws related to, among other things, unlawful schemes to defraud, excessive fees for services, tortious interference with patient contracts and statutory or common law fraud. We have a comprehensive compliance program in place to address adherence with various laws and regulations relating to the selling, marketing and manufacturing of our medicines, as well as certain third-party relationships, including pharmacies. Specifically with respect to pharmacies, the compliance program utilizes a variety of methods and tools to monitor and audit pharmacies, including those that participate in the HorizonCares program, to confirm their activities, adjudication and practices are consistent with our compliance policies and guidance. Despite our compliance efforts, to the extent the HorizonCares program is found to be inconsistent with applicable laws or the pharmacies that participate in our patient access programs do not comply with applicable laws, we may be required to restructure or discontinue such programs, terminate our relationship with certain pharmacies, or be subject to other significant penalties. In November 2015, we received a subpoena from the U.S. Attorney's Office for the Southern District of New York requesting documents and information related to our patient access programs and other aspects of our marketing and commercialization activities. We are unable to predict how long this investigation will continue or its outcome, but we have incurred and anticipate that we may continue to incur significant costs in connection with the investigation, regardless of the outcome. We may also become subject to similar investigations by other governmental agencies or Congress. The investigation by the U.S. Attorney's Office and any additional investigations of our patient access programs and sales and marketing activities may result in damages, fines, penalties, exclusion, additional reporting requirements and/or oversight or other administrative sanctions against us.

If the cost of maintaining our patient access programs increases relative to our sales revenues, we could be forced to reduce the amount of patient financial assistance that we offer or otherwise scale back or eliminate such programs, which could in turn have a negative impact on physicians' willingness to prescribe and patients' willingness to fill prescriptions of our medicines. While we believe that our recent arrangements with PBMs will result in broader inclusion of certain of our primary care medicines on healthcare plan formularies, and therefore increase payer reimbursement and lower our cost of providing patient access programs, these arrangements generally require us to pay administrative and rebate payments to the PBMs and/or other payers and their effectiveness will ultimately depend to a large extent upon individual healthcare plan formulary decisions that are beyond the control of the PBMs. If our arrangements with PBMs and other payers do not result in increased prescriptions and reductions in our costs to provide our patient access programs that are sufficient to offset the administrative fees and rebate payments to the PBMs and/or other payers, our financial results may be harmed.

If we are unable to successfully implement our commercial plans and facilitate adoption by patients and physicians of any approved medicines through our sales, marketing and commercialization efforts, then we will not be able to generate sustainable revenues from medicine sales which will have a material adverse effect on our business and prospects.

We are solely dependent on third parties to commercialize certain of our medicines outside the United States. Failure of these third parties or any other third parties to successfully commercialize our medicines and medicine candidates in the applicable jurisdictions could have a material adverse effect on our business.

Mundipharma International Corporation Limited, or Mundipharma, is our exclusive distributor for LODOTRA in Europe, Asia and Latin America. We rely on other third-party distributors for commercialization of BUPHENYL (known as AMMONAPS in certain European countries) in certain territories outside the United States for which we currently have rights. We have limited contractual rights to force these third parties to invest significantly in commercialization of these medicines in our markets. In the event that Mundipharma or our current ex-U.S. distributors for BUPHENYL or any other third-party with any future commercialization rights to any of our medicines or medicine candidates fail to adequately commercialize those medicines or medicine candidates because they lack adequate financial or other resources, decide to focus on other initiatives or otherwise, our ability to successfully commercialize our medicines or medicine candidates in the applicable jurisdictions would be limited, which would adversely affect our business, financial condition, results of operations and prospects. We have had disagreements with Mundipharma under our European agreements and may continue to have disagreements, which could harm commercialization of LODOTRA in Europe or result in the termination of our agreements with Mundipharma. In addition, our agreements with Mundipharma and our agreements with our current ex-U.S. distributors for BUPHENYL may be terminated by either party in the event of a bankruptcy of the other party or upon an uncured material breach by the other party. If these third parties terminated their agreements, we may not be able to secure an alternative distributor in the applicable territory on a timely basis or at all, in which case our ability to generate revenues from the sale of LODOTRA, QUINSAIR, RAVICTI or BUPHENYL outside the United States would be materially harmed.

Our medicines are subject to extensive regulation, and we may not obtain additional regulatory approvals for our medicines.

The clinical development, manufacturing, labeling, packaging, storage, recordkeeping, advertising, promotion, export, marketing and distribution and other possible activities relating to our medicines and our medicine candidates are, and will be, subject to extensive regulation by the FDA and other regulatory agencies. Failure to comply with FDA and other applicable regulatory requirements may, either before or after medicine approval, subject us to administrative or judicially imposed sanctions.

To market any drugs or biologics outside of the United States, we and current or future collaborators must comply with numerous and varying regulatory and compliance related requirements of other countries. Approval procedures vary among countries and can involve additional medicine testing and additional administrative review periods, including obtaining reimbursement and pricing approval in select markets. The time required to obtain approval in other countries might differ from that required to obtain FDA approval. The regulatory approval process in other countries may include all of the risks associated with FDA approval as well as additional, presently unanticipated, risks. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others.

Applications for regulatory approval, including a marketing authorization application, or MAA, for marketing new drugs in Europe, must be supported by extensive clinical and preclinical data, as well as extensive information regarding chemistry, manufacturing and controls, or CMC, to demonstrate the safety and effectiveness of the applicable medicine candidate. The number and types of preclinical studies and clinical trials that will be required for regulatory approval varies depending on the medicine candidate, the disease or the condition that the medicine candidate is designed to target and the regulations applicable to any particular medicine candidate. Despite the time and expense associated with preclinical and clinical studies, failure can occur at any stage, and we could encounter problems that cause us to repeat or perform additional preclinical studies, CMC studies or clinical trials. Regulatory authorities could delay, limit or deny approval of a medicine candidate for many reasons, including because they:

- may not deem a medicine candidate to be adequately safe and effective;
- may not find the data from preclinical studies, CMC studies and clinical trials to be sufficient to support a claim of safety and efficacy;
- may interpret data from preclinical studies, CMC studies and clinical trials significantly differently than we do;
- may not approve the manufacturing processes or facilities associated with our medicine candidates;
- may conclude that we have not sufficiently demonstrated long-term stability of the formulation for which we are seeking marketing approval;
- may change approval policies (including with respect to our medicine candidates' class of drugs) or adopt new regulations; or
- may not accept a submission due to, among other reasons, the content or formatting of the submission.

Even if we believe that data collected from our preclinical studies, CMC studies and clinical trials of our medicine candidates are promising and that our information and procedures regarding CMC are sufficient, our data may not be sufficient to support marketing approval by regulatory authorities, or regulatory interpretation of these data and procedures may be unfavorable. Even if approved, medicine candidates may not be approved for all indications requested and such approval may be subject to limitations on the indicated uses for which the medicine may be marketed, restricted distribution methods or other limitations. Our business and reputation may be harmed by any failure or significant delay in obtaining regulatory approval for the sale of any of our medicine candidates. We cannot predict when or whether regulatory approval will be obtained for any medicine candidate we develop.

If we are unable to obtain any further approvals for RAVICTI outside the United States, Canada and Europe, or determine that commercializing RAVICTI outside the United States, Canada and Europe is not economically viable, the market potential of RAVICTI may be limited.

On July 12, 2016, Raptor Pharmaceutical Corp., or Raptor, received a notice of deficiency, or NOD, from Health Canada, or HC, dated July 11, 2016 relating to the New Drug Submission, or NDS, Raptor submitted for PROCYSBI in January 2016. The NOD outlined specific deficiencies in the NDS that needed to be addressed for HC to complete its review. A complete response was submitted to HC to address the NOD on November 3, 2016. HC completed the screening process and accepted the NOD response for review on December 16, 2016. Based on a 180-day review for priority applications, we anticipate that HC will complete its review of the NDS and decide whether to grant marketing approval for PROCYSBI for the treatment of nephropathic cystinosis by June 14, 2017.

With respect to QUINSAIR, the FDA has indicated in previous written and verbal communications with Raptor and with the drug's previous sponsor that it believes the data submitted in connection with EMA's subsequent approval of QUINSAIR for the management of chronic pulmonary infections due to Pseudomonas aeruginosa in adults with cystic fibrosis does not provide substantial evidence of efficacy and safety to support FDA approval of QUINSAIR for treatment of patients with cystic fibrosis. On October 27, 2016, the FDA expressed its recommendation that an additional clinical trial should be conducted, and noted that if Raptor submits a new drug application, or NDA, without conducting an additional clinical trial, the FDA will review the submission to determine whether it is acceptable for filing. Based upon the FDA's feedback, we have made the decision not to pursue an NDA for U.S. approval of QUINSAIR as a treatment of Pseudomonas aeruginosa in adults with cystic fibrosis.

Prior to our acquisition of Raptor, Raptor planned to pursue the development of QUINSAIR for use in the indication of bronchiectasis, or BE, not associated with cystic fibrosis. On September 8, 2016, Raptor met the Medicines and Healthcare Products Regulatory Agency, or the MHRA, to discuss non-clinical and clinical development aspects of QUINSAIR for the treatment of BE. On September 29, 2016, Raptor received a written response from the MHRA, which included answers to questions on trial design, among other responses. Raptor submitted a protocol to FDA on August 18, 2016 for a Phase 2, placebo-controlled study of QUINSAIR in adults with BE. Feedback from FDA was received on October 17, 2016 requesting additional information and changes to the proposed study protocol. Raptor was also exploring further clinical development of QUINSAIR for the treatment of pulmonary nontuberculous mycobacteria, or NTM, infection, based on third-party data generated pertaining to the susceptibility of certain pathogens to treatment with levofloxacin and other fluoroquinolone molecules. No clinical data has been generated with QUINSAIR in patients with BE or with NTM infections, either by Raptor, by us or by other parties. This creates uncertainty regarding the potential efficacy of QUINSAIR in these indications.

We will evaluate all development opportunities, including all obligations to use commercial reasonable efforts to further develop QUINSAIR. However, we may determine not to pursue such further development.

The ultimate approval and commercial marketing of any of our medicines in additional indications or geographies is subject to substantial uncertainty. Failure to gain additional regulatory approvals would limit the potential revenues and value of our medicines and could cause our share price to decline.

The amount of our medicine sales in the EEA is dependent in part upon the pricing and reimbursement decisions adopted in each of the EEA countries, which may not be at acceptable levels to us.

One or more EEA countries may not support pricing within our target pricing and reimbursement range for our medicines due to budgetary decisions made by regional, national and local health authorities and third-party payers in the EEA, which would negatively affect our revenues. The pricing and reimbursement process in EEA countries can be lengthy, involved and difficult to predict. Failure to timely complete the pricing and reimbursement process in the EEA countries will delay our ability to market PROCYSBI, to bring QUINSAIR to market in the EEA and to derive revenues from those countries.

We may be subject to penalties and litigation and large incremental expenses if we fail to comply with regulatory requirements or experience problems with our medicines.

Even after we achieve regulatory approvals, we are subject to ongoing obligations and continued regulatory review with respect to many operational aspects including our manufacturing processes, labeling, packaging, distribution, storage, adverse event monitoring and reporting, dispensation, advertising, promotion and recordkeeping. These requirements include submissions of safety and other post-marketing information and reports, ongoing maintenance of medicine registration and continued compliance with current good manufacturing practices, or cGMPs, GCPs, good pharmacovigilance practice, good distribution practices and good laboratory practices, or GLPs. If we, our medicines or medicine candidates, or the third-party manufacturing facilities for our medicines or medicine candidates fail to comply with applicable regulatory requirements, a regulatory agency may:

- impose injunctions or restrictions on the marketing, manufacturing or distribution of a medicine, suspend or withdraw medicine approvals, revoke necessary licenses or suspend medicine reimbursement;
- issue warning letters, show cause notices or untitled letters describing alleged violations, which may be publicly available;
- suspend any ongoing clinical trials or delay or prevent the initiation of clinical trials;
- delay or refuse to approve pending applications or supplements to approved applications we have filed;
- refuse to permit drugs or precursor or intermediary chemicals to be imported or exported to or from the United States;
- suspend or impose restrictions or additional requirements on operations, including costly new manufacturing quality or pharmacovigilance requirements;
- seize or detain medicines or require us to initiate a medicine recall; and/or
- commence criminal investigations and prosecutions.

Moreover, existing regulatory approvals and any future regulatory approvals that we obtain will be subject to limitations on the approved indicated uses and patient populations for which our medicines may be marketed, the conditions of approval, requirements for potentially costly, post-market testing and requirements for surveillance to monitor the safety and efficacy of the medicines. In the EEA, the advertising and promotion of pharmaceuticals is strictly regulated. The direct-to-consumer promotion of prescription pharmaceuticals is not permitted, and some countries in the EEA require the notification and/or prior authorization of promotional or advertising materials directed at healthcare professionals. The FDA, EMA and other authorities in the EEA countries strictly regulate the promotional claims that may be made about prescription medicines, and our medicine labeling, advertising and promotion are subject to continuing regulatory review. Physicians nevertheless may prescribe our medicines to their patients in a manner that is inconsistent with the approved label or that is off-label. Positive clinical trial results in any of our medicine development programs increase the risk that approved pharmaceutical forms of the same APIs may be used off-label in those indications. Our investigational medicine candidate RP103 is comprised of the same API as PROCYSBI. If we are found to have improperly promoted off-label uses of approved medicines, we may be subject to significant sanctions, civil and criminal fines and injunctions prohibiting us from engaging in specified promotional conduct.

In addition, engaging in improper promotion of our medicines for off-label uses in the United States can subject us to false claims litigation under federal and state statutes. These false claims statutes in the United States include the federal False Claims Act, which allows any individual to bring a lawsuit against a pharmaceutical company on behalf of the federal government alleging submission of false or fraudulent claims or causing to present such false or fraudulent claims for payment by a federal program such as Medicare or Medicaid. Growth in false claims litigation has increased the risk that a pharmaceutical company will have to defend a false claim action, pay civil money penalties, settlement fines or restitution, agree to comply with burdensome reporting and compliance obligations and be excluded from Medicare, Medicaid and other federal and state healthcare programs.

The regulations, policies or guidance of regulatory agencies may change and new or additional statutes or government regulations may be enacted that could prevent or delay regulatory approval of our medicine candidates or further restrict or regulate post-approval activities. For example, the Food and Drug Administration Safety and Innovation Act requires the FDA to issue new guidance describing its policy regarding internet and social media promotion of regulated medical products, and the FDA may soon specify new restrictions on this type of promotion. In January 2014, the FDA released draft guidance on how drug companies can fulfill their regulatory requirements for post-marketing submission of interactive promotional media, and though the guidance provided insight into how the FDA views a company's responsibility for certain types of social media promotion, there remains a substantial amount of uncertainty. We cannot predict the likelihood, nature or extent of adverse government regulation that may arise from pending or future legislation or administrative action, either in the United States or abroad. If we are unable to achieve and maintain regulatory compliance, we will not be permitted to market our drugs, which would materially adversely affect our business, results of operations and financial condition.

Our limited history of commercial operations makes evaluating our business and future prospects difficult and may increase the risk of any investment in our ordinary shares.

We face considerable risks and difficulties as a company with limited commercial operating history, particularly as a global consolidated entity with operating subsidiaries that also have limited operating histories. If we do not successfully address these risks, our business, prospects, operating results and financial condition will be materially and adversely harmed. Our limited commercial operating history, including our limited history commercializing our current medicines, makes it particularly difficult for us to predict our future operating results and appropriately budget for our expenses. In the event that actual results differ from our estimates or we adjust our estimates in future periods, our operating results and financial position could be materially affected. For example, we may underestimate the resources we will require to successfully integrate recent or future medicine or company acquisitions, or to commercialize our medicines, or not realize the benefits we expect to derive from our recent or future acquisitions. In addition, we have a limited history implementing our commercialization strategy focused on patient access, and we cannot guarantee that we will be able to successfully implement this strategy or that it will represent a viable strategy over the long term.

We have rights to medicines in certain jurisdictions but have no control over third parties that have rights to commercialize those medicines in other jurisdictions, which could adversely affect our commercialization of these medicines.

Boehringer Ingelheim International GmbH, or Boehringer Ingelheim International, currently has certain rights to commercialize interferon gamma 1b, known as IMUKIN, outside the United States, Canada and Japan. On May 18, 2016, we entered into a definitive agreement with Boehringer Ingelheim International to acquire such rights to IMUKIN, or the IMUKIN Acquisition. The transaction is expected to close in 2017 and we are continuing to work with Boehringer Ingelheim International to enable the transfer of applicable marketing authorizations. AstraZeneca AB, or AstraZeneca, has retained its existing rights to VIMOVO in territories outside of the United States, including the right to use the VIMOVO name and related trademark. While we have the worldwide rights to BUPHENYL, the marketing and distribution rights are granted to SOBI. Similarly, Nuvo Research Inc., or Nuvo, has retained its rights to PENNSAID 2% in territories outside of the United States and has announced its intention to seek commercialization partners outside the United States. We have little or no control over Boehringer Ingelheim International's activities with respect to IMUKIN outside the United States, Canada and Japan, over AstraZeneca's activities with respect to VIMOVO outside of the United States, over SOBI's activities with respect to BUPHENYL in Europe, certain Asian, Latin American, Middle Eastern, North African and other countries or over Nuvo's or its future commercial partners' activities with respect to PENNSAID 2% outside of the United States, even though those activities could impact our ability to successfully commercialize these medicines. For example, AstraZeneca or its assignees or Nuvo or its assignees can make statements or use promotional materials with respect to VIMOVO or PENNSAID 2%, respectively, outside of the United States that are inconsistent with our positioning of the medicines in the United States, and could sell VIMOVO or PENNSAID 2%, respectively, in foreign countries, including Canada, at prices that are dramatically lower than the prices we charge in the United States. These activities and decisions, while occurring outside of the United States, could harm our commercialization strategy in the United States, in particular because AstraZeneca is continuing to market VIMOVO outside the United States under the same VIMOVO brand name that we are using in the United States. In addition, medicine recalls or safety issues with these medicines outside the United States, even if not related to the commercial medicine we sell in the United States, could result in serious damage to the brand in the United States and impair our ability to successfully market them. We also rely on Boehringer Ingelheim International, AstraZeneca, SOBI and Nuvo or their assignees to provide us with timely and accurate safety information regarding the use of these medicines outside of the United States (and outside of Canada and Japan with regards to Boehringer Ingelheim International), as we have or will have limited access to this information ourselves.

We rely on third parties to manufacture commercial supplies of all of our medicines, and we currently intend to rely on third parties to manufacture commercial supplies of any other approved medicines. The commercialization of any of our medicines could be stopped, delayed or made less profitable if those third parties fail to provide us with sufficient quantities of medicine or fail to do so at acceptable quality levels or prices or fail to maintain or achieve satisfactory regulatory compliance.

The facilities used by our third-party manufacturers to manufacture our medicines and medicine candidates must be approved by the applicable regulatory authorities. We do not control the manufacturing processes of third-party manufacturers and are currently completely dependent on our third-party manufacturing partners. In addition, we are required to obtain AstraZeneca's consent prior to engaging any third-party manufacturers for esomeprazole, one of the APIs in VIMOVO, other than the third-party manufacturer(s) used by AstraZeneca or its affiliates or licensees. To the extent such manufacturers are unwilling or unable to manufacture esomeprazole for us on commercially acceptable terms, we cannot guarantee that AstraZeneca would consent to our use of alternate sources of supply.

We rely on an exclusive supply agreement with Boehringer Ingelheim RCV GmbH & Co. KG, or Boehringer Ingelheim, for manufacturing and supply of ACTIMMUNE. However, Boehringer Ingelheim also currently manufactures interferon gamma-1b to supply its own commercial needs in its licensed territory, and this may lead to capacity allocation issues and supply constraints to our company. ACTIMMUNE is manufactured by starting with cells from working cell bank samples which are derived from a master cell bank. We and Boehringer Ingelheim separately store multiple vials of the master cell bank. In the event of catastrophic loss at our or Boehringer Ingelheim's storage facility, it is possible that we could lose multiple cell banks and have the manufacturing capacity of ACTIMMUNE severely impacted by the need to substitute or replace the cell banks. In addition, a key excipient used in PENNSAID 2% as a penetration enhancer is dimethyl sulfoxide, or DMSO. We and Nuvo, our exclusive supplier of PENNSAID 2%, rely on a sole proprietary form of DMSO for which we maintain a substantial safety stock. However, should this supply become inadequate, damaged, destroyed or unusable, we and Nuvo may not be able to qualify a second source. We rely on NOF Corporation, or NOF, as our exclusive supplier of the PEGylation agent that is a critical raw material in the manufacture of KRYSTEXXA. If NOF failed to supply such PEGylation agent, it may lead to KRYSTEXXA supply constraints.

If any of our third-party manufacturers cannot successfully manufacture material that conforms to our specifications and the applicable regulatory authorities' strict regulatory requirements, or pass regulatory inspection, they will not be able to secure or maintain regulatory approval for the manufacturing facilities. For example, Pharmaceutics International, Inc., or PII, our manufacturer of BUPHENYL, was found to be non-compliant for cGMPs by the MHRA, which could restrict PII from supplying BUPHENYL in the EU. However, BUPHENYL was considered to be critical to public health and as a result, the MHRA issued a certificate of cGMP compliance for PII which is valid until June 30, 2017. In addition, we have no control over the ability of third-party manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or any other applicable regulatory authorities do not approve these facilities for the manufacture of our medicines or if they withdraw any such approval in the future, or if our suppliers or third-party manufacturers decide they no longer want to supply our primary active ingredients or manufacture our medicines, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our medicines. To the extent any third-party manufacturers that we engage with respect to our medicines are different from those currently being used for commercial supply in the United States, the FDA will need to approve the facilities of those third-party manufacturers used in the manufacture of our medicines prior to our sale of any medicine using these facilities.

Although we have entered into supply agreements for the manufacture and packaging of our medicines, our manufacturers may not perform as agreed or may terminate their agreements with us. We currently rely on single source suppliers for certain of our medicines. If our manufacturers terminate their agreements with us, we may have to qualify new back-up manufacturers. We rely on safety stock to mitigate the risk of our current suppliers electing to cease producing bulk drug medicine or ceasing to do so at acceptable prices and quality. However, we can provide no assurance that such safety stocks would be sufficient to avoid supply shortfalls in the event we have to identify and qualify new contract manufacturers.

The manufacture of medicines requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of medicines often encounter difficulties in production, particularly in scaling up and validating initial production. These problems include difficulties with production costs and yields, quality control, including stability of the medicine, quality assurance testing, shortages of qualified personnel, as well as compliance with strictly enforced federal, state and foreign regulations. Furthermore, if microbial, viral or other contaminations are discovered in the medicines or in the manufacturing facilities in which our medicines are made, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the contamination. We cannot assure you that issues relating to the manufacture of any of our medicines will not occur in the future. Additionally, our manufacturers may experience manufacturing difficulties due to resource constraints or as a result of labor disputes or unstable political environments. If our manufacturers were to encounter any of these difficulties, or otherwise fail to comply with their contractual obligations, our ability to commercialize our medicines in the United States or provide any medicine candidates to patients in clinical trials would be jeopardized.

Any delay or interruption in our ability to meet commercial demand for our medicines will result in the loss of potential revenues and could adversely affect our ability to gain market acceptance for these medicines. In addition, any delay or interruption in the supply of clinical trial supplies could delay the completion of clinical trials, increase the costs associated with maintaining clinical trial programs and, depending upon the period of delay, require us to commence new clinical trials at additional expense or terminate clinical trials completely.

Failures or difficulties faced at any level of our supply chain could materially adversely affect our business and delay or impede the development and commercialization of any of our medicines or medicine candidates and could have a material adverse effect on our business, results of operations, financial condition and prospects.

We have experienced recent growth and expanded the size of our organization substantially in connection with our recent acquisition transactions, and we may experience difficulties in managing this growth as well as potential additional growth in connection with future medicine, development program or company acquisitions.

As of December 31, 2010 and prior to the commercial launch of DUEXIS, we employed approximately 40 full-time employees as a consolidated entity. As of December 31, 2016, we employed approximately 1,050 full-time employees, including approximately 480 sales representatives, representing a substantial change to the size of our organization. We have also experienced, and may continue to experience, turnover of the sales representatives that we hired or will hire in connection with the commercialization of our medicines, requiring us to hire and train new sales representatives. Our management, personnel, systems and facilities currently in place may not be adequate to support this recent and anticipated growth, and we may not be able to retain or recruit qualified personnel in the future due to competition for personnel among pharmaceutical businesses.

As our commercialization plans and strategies continue to develop, we will need to continue to recruit and train sales and marketing personnel and expect to need to expand the size of our employee base for managerial, operational, financial and other resources as a result of our recent acquisitions. Our ability to manage any future growth effectively may require us to, among other things:

- continue to manage and expand the sales and marketing efforts for our existing medicines;
- enhance our operational, financial and management controls, reporting systems and procedures;
- expand our international resources;
- successfully identify, recruit, hire, train, maintain, motivate and integrate additional employees;
- establish and increase our access to commercial supplies of our medicines and medicine candidates;
- expand our facilities and equipment; and
- manage our internal development efforts effectively while complying with our contractual obligations to licensors, licensees, contractors, collaborators, distributors and other third parties.

Our recent acquisitions have resulted in many changes, including significant changes in the corporate business and legal entity structure, the integration of other companies and their personnel with us, and changes in systems. We are currently undertaking numerous complex transition activities associated with our recent acquisitions, and we may encounter unexpected difficulties or incur unexpected costs, including:

- difficulties in achieving growth prospects from combining third-party businesses with our business;
- difficulties in the integration of operations and systems;
- difficulties in the assimilation of employees and corporate cultures;
- challenges in preparing financial statements and reporting timely results at both a statutory level for multiple entities and jurisdictions and at a consolidated level for public reporting;
- challenges in keeping existing physician prescribers and patients and increasing adoption of acquired medicines;
- difficulties in achieving anticipated cost savings, synergies, business opportunities and growth prospects from the combination;
- potential unknown liabilities, adverse consequences and unforeseen increased expenses associated with the transaction; and
- challenges in attracting and retaining key personnel.

If any of these factors impair our ability to continue to integrate our operations with those of any companies or businesses we acquire, we may not be able to realize the business opportunities, growth prospects and anticipated tax synergies from combining the businesses. In addition, we may be required to spend additional time or money on integration that otherwise would be spent on the development and expansion of our business.

As a result of our acquisition of Raptor and our plans to launch RAVICTI in Europe, we may continue expanding our operations and add commercial personnel in Europe. We may not be successful in integrating Raptor's existing European operations and personnel with our own or in otherwise growing our commercial operations outside the United States, and could encounter other challenges in growing our commercial presence in Europe, including due to risks associated with political and economic instability, operating under different legal requirements and tax complexities. If we are unable to manage our commercial growth outside of the Unites States, our opportunities to expand sales in other countries will be limited or we may experience greater costs with respect to our ex-U.S. commercial operations.

We are also broadening our acquisition strategy to potentially include development-stage assets or programs, which entails additional risk to us. For example, if we are unable to identify programs that ultimately result in approved medicines, we may spend material amounts of our capital and other resources evaluating, acquiring and developing medicines that ultimately do not provide a return on our investment. We have less experience evaluating development-stage assets and may be at a disadvantage compared to other entities pursuing similar opportunities. Regardless, development-stage programs generally have a high rate of failure and we cannot guarantee that any such programs will ultimately be successful. We will also need to enhance our clinical development and regulatory functions to properly evaluate and develop earlier-stage opportunities, which may include recruiting personnel that are knowledgeable in therapeutic areas we have not yet pursued. If we are unable to acquire promising development-stage assets or eventually obtain marketing approval for them, we may not be able to create a meaningful pipeline of new medicines and eventually realize a return on our investments.

Our management may also have to divert a disproportionate amount of its attention away from day-to-day activities and toward managing these growth and integration activities. Our future financial performance and our ability to execute on our business plan will depend, in part, on our ability to effectively manage any future growth and our failure to effectively manage growth could have a material adverse effect on our business, results of operations, financial condition and prospects.

We face significant competition from other biotechnology and pharmaceutical companies, including those marketing generic medicines and our operating results will suffer if we fail to compete effectively.

The biotechnology and pharmaceutical industries are intensely competitive. We have competitors both in the United States and international markets, including major multinational pharmaceutical companies, biotechnology companies and universities and other research institutions. Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff, experienced marketing and manufacturing organizations and well-established sales forces. Additional consolidations in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors and we will have to find new ways to compete and may have to potentially merge with or acquire other businesses to stay competitive. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or in-licensing on an exclusive basis, medicines that are more effective and/or less costly than our medicines.

DUEXIS and VIMOVO face competition from other NSAIDs, including Celebrex®, which was marketed by Pfizer Inc., and is also a generic medicine known as celecoxib and marketed by other pharmaceutical companies. DUEXIS and VIMOVO also face significant competition from the separate use of NSAIDs for pain relief and GI protective medications to reduce the risk of NSAID-induced upper GI ulcers. Both NSAIDs and GI protective medications are available in generic form and may be less expensive to use separately than DUEXIS or VIMOVO. PENNSAID 2% faces competition from generic versions of diclofenac sodium topical solutions that are priced significantly less than the price we charge for PENNSAID 2%, and Voltaren Gel, marketed by Endo Pharmaceuticals Solutions Inc., which is the market leader in the topical NSAID category. Legislation enacted in most states in the United States allows, or in some instances mandates, that a pharmacist dispense an available generic equivalent when filling a prescription for a branded medicine, in the absence of specific instructions from the prescribing physician. Because pharmacists often have economic and other incentives to prescribe lower-cost generics, if physicians prescribe DUEXIS, PENNSAID 2% or VIMOVO, those prescriptions may not result in sales. If physicians do not complete prescriptions through our HorizonCares program or otherwise provide prescribing instructions prohibiting the substitution of generic ibuprofen and famotidine separately as a substitution for DUEXIS or generic naproxen and branded Nexium® (esomeprazole) as a substitute for VIMOVO or generic diclofenac sodium topical solutions as a substitute for PENNSAID 2%, sales of DUEXIS, PENNSAID 2% and VIMOVO may suffer despite any success we may have in promoting DUEXIS, PENNSAID 2% or VIMOVO to physicians. In addition, other medicine candidates that contain ibuprofen and famotidine in combination or naproxen and esomeprazole in combination, while not currently known or FDA approved, may be developed and compete with DUEXIS or VIMOVO, respectively, in the future. While KRYSTEXXA faces limited direct competition, a number of competitors have drugs in Phase 1 or Phase 2 trials. On December 22, 2015, AstraZeneca secured approval from the FDA for ZURAMPIC (lesinurad) 200mg tablets in combination with a xanthine oxidase inhibitor, or XOI, for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid (sUA) levels with an XOI alone. In April 2016, the U.S. rights to ZURAMPIC were licensed to Ironwood Pharmaceuticals Inc. Although ZURAMPIC is not a direct competitor because it has not been approved for refractory gout, this therapy could be used prior to use of KRYSTEXXA and if effective, could reduce the target patient population for KRYSTEXXA. PROCYSBI faces competition from Cystagon (immediate-release cysteamine bitartrate capsules) for the treatment of cystinosis and Cystaran (cysteamine ophthalmic solution) for treatment of corneal crystal accumulation in patients with cystinosis. QUINSAIR faces competition from Tobramycin solution, which is available as a generic medicine for treatment of chronic Pseudomonas aeruginosa lung infections in patients with cystic fibrosis, TOBI Podhaler, Cayston and colistimethate.

We have also entered into settlement and license agreements that may allow certain of our competitors to sell generic versions of certain of our medicines in the United States, subject to the terms of such agreements. We granted a non-exclusive license (that is only royalty-bearing in some circumstances), to manufacture and commercialize a generic version of DUEXIS in the United States after January 1, 2023, or earlier under certain circumstances. We granted non-exclusive licenses to manufacture and commercialize generic versions of PENNSAID 2% in the United States after January 10, 2029, or earlier under certain circumstances. We granted a non-exclusive license to manufacture and commercialize a generic version of RAYOS tablets in the United States after December 23, 2022, or earlier under certain circumstances.

Patent litigation is currently pending in the United States District Court for the District of New Jersey against several companies intending to market a generic version of PENNSAID 2% prior to the expiration of certain of our patents listed in the FDA's Orange Book, or the Orange Book. These cases are collectively known as the PENNSAID 2% cases, and involve the following sets of defendants: (i) Actavis Laboratories UT, Inc., formerly known as Watson Laboratories, Inc., Actavis, Inc. and Actavis plc, or collectively Actavis; and (ii) Lupin Limited and Lupin Pharmaceuticals, Inc., or collectively Lupin. These cases arise from Paragraph IV Patent Certification notice letters from each of Actavis and Lupin advising each had filed an Abbreviated New Drug Application, or ANDA, with the FDA seeking approval to market a generic version of PENNSAID 2% before the expiration of the patents-in-suit. In Horizon Pharma Ireland Limited, et al v. Actavis Laboratories UT, Inc., C.A. No. 14-cv-7992-NLH-AMD, a bench trial is scheduled to begin on March 21, 2017. No trial date has been set in any other PENNSAID 2% case.

We received from Actavis a Paragraph IV Patent Certification Notice Letter dated September 27, 2016, against Orange Book listed U.S. Patent No. 9,415,029 advising that Actavis had filed an ANDA with the FDA for a generic version of PENNSAID 2%.

We received from Apotex Inc., or Apotex, three Paragraph IV Patent Certification Notice Letters dated April 1, 2016, June 30, 2016, and September 21, 2016 against Orange Book listed U.S. Patent Nos. 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164, 8,741,956, 8,871,809, 9,066,913, 9,101,591, 9,132,110, 9,168,304, 9,168,305, 9,220,784, 9,339,551, 9,339,552 and 9,415,029, advising that Apotex had filed an ANDA with the FDA for a generic version of PENNSAID 2%.

Patent litigation is currently pending in the United States District Court for the District of New Jersey against several companies intending to market a generic version of VIMOVO before the expiration of certain of our patents listed in the Orange Book. These cases are collectively known as the VIMOVO cases, and involve the following sets of defendants: (i) Dr. Reddy's Laboratories Inc. and Dr. Reddy's Laboratories Ltd., or collectively Dr. Reddy's; (ii) Lupin; and (iii) Mylan Pharmaceuticals Inc., Mylan Laboratories Limited, and Mylan Inc., or collectively Mylan. Patent litigation is currently pending before the Court of Appeals for the Federal Circuit against a fourth generic company, Actavis Laboratories FL., Inc. and Actavis Pharma, Inc., or collectively Actavis Pharma. The cases arise from Paragraph IV Patent Certification notice letters from each of Dr. Reddy's, Lupin and Mylan advising each had filed an ANDA with the FDA seeking approval to market generic versions of VIMOVO before the expiration of the patents-in-suit.

Patent litigation is currently pending in the United States District Court for the Eastern District of Texas against Par Pharmaceutical, Inc., or Par Pharmaceutical, and in the United States District Court for the District of New Jersey against Par Pharmaceutical and against Lupin, who are each intending to market generic versions of RAVICTI prior to the expiration of certain of our patents listed in the Orange Book. These cases are collectively known as the RAVICTI cases and arise from Paragraph IV Patent Certification notice letters from each of Par Pharmaceutical and Lupin advising each had filed an ANDA with the FDA seeking approval to market a generic version of RAVICTI before the expiration of the patents-in-suit.

If we are unsuccessful in any of the VIMOVO cases or PENNSAID 2% cases, we will likely face generic competition with respect to VIMOVO and/or PENNSAID 2% and sales of VIMOVO and/or PENNSAID 2% will be substantially harmed. If we are unsuccessful in any of the RAVICTI cases, RAVICTI would likely face generic competition in the United States when its orphan exclusivity expires (currently scheduled to occur in February 2020), and its sales would likely materially decline.

ACTIMMUNE is the only medicine currently approved by the FDA specifically for the treatment of CGD and SMO. While there are additional or alternative approaches used to treat patients with CGD and SMO, there are currently no medicines on the market that compete directly with ACTIMMUNE. A widely accepted protocol to treat CGD in the United States is the use of concomitant "triple prophylactic therapy" comprising ACTIMMUNE, an oral antibiotic agent and an oral antifungal agent. However, the FDA-approved labeling for ACTIMMUNE does not discuss this "triple prophylactic therapy," and physicians may choose to prescribe one or both of the other modalities in the absence of ACTIMMUNE. Because of the immediate and life-threatening nature of SMO, the preferred treatment option for SMO is often to have the patient undergo a bone marrow transplant which, if successful, will likely obviate the need for further use of ACTIMMUNE in that patient. Likewise, the use of bone marrow transplants in the treatment of patients with CGD is becoming more prevalent, which could have a material adverse effect on sales of ACTIMMUNE and its profitability. We are aware of a number of research programs investigating the potential of gene therapy as a possible cure for CGD. Additionally, other companies may be pursuing the development of medicines and treatments that target the same diseases and conditions which ACTIMMUNE is currently approved to treat. As a result, it is possible that our competitors may develop new medicines that manage CGD or SMO more effectively, cost less or possibly even cure CGD or SMO. In addition, U.S. healthcare legislation passed in March 2010 authorized the FDA to approve biological products, known as biosimilars, that are similar to or interchangeable with previously approved biological products, like ACTIMMUNE, based upon potentially abbreviated data packages. Biosimilars are likely to be sold at substantially lower prices than branded medicines because the biosimilar manufacturer would not have to recoup the research and development and marketing costs associated with the branded medicine. Though we are not currently aware of any biosimilar under development, the development and commercialization of any competing medicines or the discovery of any new alternative treatment for CGD or SMO could have a material adverse effect on sales of ACTIMMUNE and its profitability.

BUPHENYL's composition of matter patent protection and orphan drug exclusivity have expired. Because BUPHENYL has no regulatory exclusivity or listed patents, there is nothing to prevent a competitor from submitting an ANDA for a generic version of BUPHENYL and receiving FDA approval. In November 2011, Ampolgen Pharmaceuticals, LLC received FDA approval for a generic version of NaPBA tablets, which may compete with RAVICTI and BUPHENYL in treating UCD. In March 2013, SigmaPharm Laboratories, LLC received FDA approval for a generic version of NaPBA powder, which competes with BUPHENYL and may compete with RAVICTI in treating UCD. In July 2013, Lucane Pharma, or Lucane, received marketing approval from the EMA for taste-masked NaPBA and has announced a distribution partnership in Canada. In January 2015, Lucane announced it had received marketing approval for its taste-masked NaPBA in Canada. We believe Lucane is also seeking approval via an ANDA in the United States. If this ANDA is approved, this formulation may compete with RAVICTI and BUPHENYL in treating UCD in the United States. Generic versions of BUPHENYL to date have been priced at a discount relative to BUPHENYL or RAVICTI, and physicians, patients, or payers may decide that this less expensive alternative is preferable to BUPHENYL and RAVICTI. If this occurs, sales of BUPHENYL and/or RAVICTI could be materially reduced, but we would nevertheless be required to make royalty payments to Ucyclyd Pharma, Inc., or Ucyclyd, and another external party, at the same royalty rates. While Ucyclyd and its affiliates are generally contractually prohibited from developing or commercializing new medicines, anywhere in the world, for the treatment of UCD or hepatic encephalopathy, or HE, which are chemically similar to RAVICTI, they may still develop and commercialize medicines that compete with RAVICTI. For example, medicines approved for indications other than UCD and HE may still compete with RAVICTI if physicians prescribe such medicines off-label for UCD or HE. We are also aware that Orphan Europe SARL, or Orphan Europe, is conducting a clinical trial of carglumic acid to treat some of the UCD enzyme deficiencies for which RAVICTI was approved. Promethera Biosciences SA has successfully completed Phase I/II trials of its cell-based therapy for the treatment of UCD and plans to conduct a Phase IIb/III clinical trial. Carglumic acid is approved for maintenance therapy for chronic hyperammonemia and to treat hyperammonenic crises in Nacetylglutamate synthase deficiency, a rare UCD subtype, and is sold under the name Carbaglu. If the results of this trial are successful and Orphan Europe is able to complete development and obtain approval of Carbaglu to treat additional UCD enzyme deficiencies, RAVICTI would face additional competition from this compound.

The availability and price of our competitors' medicines could limit the demand, and the price we are able to charge, for our medicines. We will not successfully execute on our business objectives if the market acceptance of our medicines is inhibited by price competition, if physicians are reluctant to switch from existing medicines to our medicines, or if physicians switch to other new medicines or choose to reserve our medicines for use in limited patient populations.

In addition, established pharmaceutical companies may invest heavily to accelerate discovery and development of novel compounds or to acquire novel compounds that could make our medicines obsolete. Our ability to compete successfully with these companies and other potential competitors will depend largely on our ability to leverage our experience in clinical, regulatory and commercial development to:

- develop and acquire medicines that are superior to other medicines in the market;
- attract qualified clinical, regulatory, and sales and marketing personnel;
- obtain patent and/or other proprietary protection for our medicines and technologies;
- obtain required regulatory approvals; and
- successfully collaborate with pharmaceutical companies in the discovery, development and commercialization of new medicine candidates.

If we are unable to maintain or realize the benefits of orphan drug exclusivity, we may face increased competition with respect to certain of our medicines.

Under the Orphan Drug Act of 1983, the FDA may designate a medicine as an orphan drug if it is a drug intended to treat a rare disease or condition affecting fewer than 200,000 people in the United States. A company that first obtains FDA approval for a designated orphan drug for the specified rare disease or condition receives orphan drug marketing exclusivity for that drug for a period of seven years from the date of its approval. RAVICTI, KRYSTEXXA and PROCYSBI have been granted orphan drug exclusivity by the FDA, which we expect will provide orphan drug marketing exclusivity in the United States until February 2020, September 2017 and December 2020, respectively, with exclusivity for PROCYSBI extending to 2022 for patients ages two to six years. However, despite orphan drug exclusivity, the FDA can still approve another drug containing the same active ingredient and used for the same orphan indication if it determines that a subsequent drug is safer, more effective or makes a major contribution to patient care, and orphan exclusivity can be lost if the orphan drug manufacturer is unable to ensure that a sufficient quantity of the orphan drug is available to meet the needs of patients with the rare disease or condition. Orphan drug exclusivity may also be lost if the FDA later determines that the initial request for designation was materially defective. In addition, orphan drug exclusivity does not prevent the FDA from approving competing drugs for the same or similar indication containing a different active ingredient. If orphan drug exclusivity is lost and we were unable to successfully enforce any remaining patents covering RAVICTI, KRYSTEXXA or PROCYSBI, we could be subject to generic competition and revenues from RAVICTI, KRYSTEXXA or PROCYSBI could decrease materially. In addition, if a subsequent drug is approved for marketing for the same or a similar indication as RAVICTI, KRYSTEXXA or PROCYSBI despite orphan drug exclusivity, we may face increased competition and lose market share with respect to these medicines. KRYSTEXXA does not have orphan drug exclusivity in the EU or other regions of the world. RAVICTI will benefit from a period of 10 years of orphan market exclusivity in the EU, concurrently applied to each of the approved six sub-types of the UCDs. This will run concurrently with its marketing exclusivity status. PROCYSBI received marketing authorization in September 2013 from the European Commission for marketing in the EU as an orphan medicine for the management of proven nephropathic cystinosis. PROCYSBI received seven years of market exclusivity, through 2020 for patients six years and older as an orphan drug in the United States and ten years of market exclusivity, through 2023, as an orphan drug in Europe. QUINSAIR received 10 years of market exclusivity in the EU, beginning with its March 2015 marketing authorization. Orphan market exclusivity may be reduced to six years in the EU if the orphan drug designation criteria are no longer met after five years, including where it is shown that the medicine is sufficiently profitable. As in the United States, loss of orphan marketing exclusivity in the EU may result in early generic competition, which could substantially reduce our revenues from EU sales of these medicines.

Our business operations may subject us to numerous commercial disputes, claims and/or lawsuits and such litigation may be costly and time-consuming and could materially and adversely impact our financial position and results of operations.

Operating in the pharmaceutical industry, particularly the commercialization of medicines, involves numerous commercial relationships, complex contractual arrangements, uncertain intellectual property rights, potential product liability and other aspects that create heightened risks of disputes, claims and lawsuits. In particular, we may face claims related to the safety of our medicines, intellectual property matters, employment matters, tax matters, commercial disputes, competition, sales and marketing practices, environmental matters, personal injury, insurance coverage and acquisition or divestiture-related matters. For example, the active ingredient in QUINSAIR, levofloxacin, is currently subject to product liability claims. Any commercial dispute, claim or lawsuit may divert management's attention away from our business, we may incur significant expenses in addressing or defending any commercial dispute, claim or lawsuit, and we may be required to pay damage awards or settlements or become subject to equitable remedies that could adversely affect our operations and financial results.

We are currently in litigation with multiple generic drug manufacturers regarding intellectual property infringement. For example, we are currently involved in Hatch Waxman litigation with generic drug manufacturers related to VIMOVO, PENNSAID 2% and RAVICTI.

Similarly, from time to time we are involved in disputes with distributors, PBMs and licensing partners regarding our rights and performance of obligations under contractual arrangements. For example, we were previously in litigation with Express Scripts, related to alleged breach of contract claims and in which Express Scripts was seeking payment for rebates relating to DUEXIS, RAYOS and VIMOVO. We counterclaimed against Express Scripts, contesting the amount owed and contending Express Scripts had breached the rebate agreement. In September 2016, we entered into a settlement agreement and mutual release with Express Scripts pursuant to which we and Express Scripts were released from any and all claims relating to the litigation without admitting any fault or wrongdoing and we agreed to pay Express Scripts $65.0 million.

Litigation related to these disputes may be costly and time-consuming and could materially and adversely impact our financial position and results of operations if resolved against us.

A variety of risks associated with operating our business and marketing our medicines internationally could materially adversely affect our business.

In addition to our U.S. operations, we have operations in Ireland, Bermuda, the Grand Duchy of Luxembourg, or Luxembourg, the Netherlands, France, Switzerland, Germany, Canada, the Grand Cayman Islands and in Israel (through Andromeda Biotech Ltd). Moreover, Grünenthal S.A. is in the registration process for the commercialization of DUEXIS in Latin America. BUPHENYL is currently marketed in various territories outside the United States by third-party distributors. RAVICTI received marketing authorization from HC in March 2016 and marketing approval in the EU in November 2015. We launched RAVICTI in Canada in November 2016 and plan to begin commercializing RAVICTI in Europe in 2017. PROCYSBI received marketing authorization from the EMA in September 2013 and is marketed in various countries within the EEA. QUINSAIR received marketing authorization from the EMA in March 2015 and is also marketed in several countries within the EEA. QUINSAIR received marketing authorization from HC in June 2015 and we launched QUINSAIR in Canada in December 2016. We face risks associated with our international operations, including possible unfavorable regulatory, pricing and reimbursement, political, tax and labor conditions, which could harm our business. We are subject to numerous risks associated with international business activities, including:

- compliance with differing or unexpected regulatory requirements for our medicines;
- compliance with Irish laws and the maintenance of our Irish tax residency with respect to our overall corporate structure and administrative operations, including the need to generally hold meetings of our board of directors and make decisions in Ireland, which may make certain corporate actions more cumbersome, costly and time-consuming;
- difficulties in staffing and managing foreign operations;
- in certain circumstances, including with respect to the commercialization of LODOTRA in Europe and certain Asian, Latin American, Middle Eastern and African countries, commercialization of BUPHENYL in select countries throughout Europe, the Middle East, and the Asia-Pacific region, commercialization of RAVICTI in select countries throughout Europe and commercialization of DUEXIS in Latin America, increased dependence on the commercialization efforts and regulatory compliance of third-party distributors or strategic partners;

- compliance with German laws with respect to our Horizon Pharma GmbH subsidiary through which Horizon Pharma Switzerland GmbH conducts most of its European operations;
- foreign government taxes, regulations and permit requirements;
- U.S. and foreign government tariffs, trade restrictions, price and exchange controls and other regulatory requirements;
- anti-corruption laws, including the Foreign Corrupt Practices Act, or the FCPA;
- economic weakness, including inflation, natural disasters, war, events of terrorism or political instability in particular foreign countries;
- fluctuations in currency exchange rates, which could result in increased operating expenses and reduced revenues, and other obligations related to doing business in another country;
- compliance with tax, employment, immigration and labor laws, regulations and restrictions for employees living or traveling abroad;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad;
- changes in diplomatic and trade relationships; and
- challenges in enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States.

Our business activities outside of the United States are subject to the FCPA and similar anti-bribery or anti-corruption laws, regulations or rules of other countries in which we operate, including the United Kingdom's Bribery Act 2010, or the U.K. Bribery Act. The FCPA and similar anti-corruption laws generally prohibit offering, promising, giving, or authorizing others to give anything of value, either directly or indirectly, to non-U.S. government officials in order to improperly influence any act or decision, secure any other improper advantage, or obtain or retain business. The FCPA also requires public companies to make and keep books and records that accurately and fairly reflect the transactions of the company and to devise and maintain an adequate system of internal accounting controls. The U.K. Bribery Act prohibits giving, offering, or promising bribes to any person, including non-United Kingdom, or U.K., government officials and private persons, as well as requesting, agreeing to receive, or accepting bribes from any person. In addition, under the U.K. Bribery Act, companies which carry on a business or part of a business in the U.K. may be held liable for bribes given, offered or promised to any person, including non-U.K. government officials and private persons, by employees and persons associated with the company in order to obtain or retain business or a business advantage for the company. Liability is strict, with no element of a corrupt state of mind, but a defense of having in place adequate procedures designed to prevent bribery is available. Furthermore, under the U.K. Bribery Act there is no exception for facilitation payments. As described above, our business is heavily regulated and therefore involves significant interaction with public officials, including officials of non-U.S. governments. Additionally, in many other countries, the health care providers who prescribe pharmaceuticals are employed by their government, and the purchasers of pharmaceuticals are government entities; therefore, any dealings with these prescribers and purchasers may be subject to regulation under the FCPA. Recently the SEC and the U.S. Department of Justice have increased their FCPA enforcement activities with respect to pharmaceutical companies. In addition, under the Dodd–Frank Wall Street Reform and Consumer Protection Act, private individuals who report to the SEC original information that leads to successful enforcement actions may be eligible for a monetary award. We are engaged in ongoing efforts that are designed to ensure our compliance with these laws, including due diligence, training, policies, procedures and internal controls. However, there is no certainty that all employees and third-party business partners (including our distributors, wholesalers, agents, contractors, and other partners) will comply with anti-bribery laws. In particular, we do not control the actions of manufacturers and other third-party agents, although we may be liable for their actions. Violation of these laws may result in civil or criminal sanctions, which could include monetary fines, criminal penalties, and disgorgement of past profits, which could have a material adverse impact on our business and financial condition.

These and other risks associated with our international operations may materially adversely affect our business, financial condition and results of operations.

If we fail to develop or acquire other medicine candidates or medicines, our business and prospects would be limited.

A key element of our strategy is to develop or acquire and commercialize a portfolio of other medicines or medicine candidates in addition to our current medicines, through business or medicine acquisitions. Because we do not engage in proprietary drug discovery, the success of this strategy depends in large part upon the combination of our regulatory, development and commercial capabilities and expertise and our ability to identify, select and acquire approved or clinically enabled medicine candidates for therapeutic indications that complement or augment our current medicines, or that otherwise fit into our development or strategic plans on terms that are acceptable to us. Identifying, selecting and acquiring promising medicines or medicine candidates requires substantial technical, financial and human resources expertise. Efforts to do so may not result in the actual acquisition or license of a particular medicine or medicine candidate, potentially resulting in a diversion of our management's time and the expenditure of our resources with no resulting benefit. If we are unable to identify, select and acquire suitable medicines or medicine candidates from third parties or acquire businesses at valuations and on other terms acceptable to us, or if we are unable to raise capital required to acquire businesses or new medicines, our business and prospects will be limited.

Moreover, any medicine candidate we acquire may require additional, time-consuming development or regulatory efforts prior to commercial sale or prior to expansion into other indications, including preclinical studies if applicable, and extensive clinical testing and approval by the FDA and applicable foreign regulatory authorities. All medicine candidates are prone to the risk of failure that is inherent in pharmaceutical medicine development, including the possibility that the medicine candidate will not be shown to be sufficiently safe and/or effective for approval by regulatory authorities. In addition, we cannot assure you that any such medicines that are approved will be manufactured or produced economically, successfully commercialized or widely accepted in the marketplace or be more effective or desired than other commercially available alternatives.

In addition, if we fail to successfully commercialize and further develop our medicines, there is a greater likelihood that we will fail to successfully develop a pipeline of other medicine candidates to follow our existing medicines or be able to acquire other medicines to expand our existing portfolio, and our business and prospects would be harmed.

Our recent medicine and company acquisitions and any other strategic transactions that we may pursue in the future could have a variety of negative consequences, and we may not realize the benefits of such transactions or attempts to engage in such transactions.

We have recently completed multiple medicine and company acquisitions and our strategy is to engage in additional strategic transactions with third parties, such as acquisitions of companies or divisions of companies and asset purchases of medicines, medicine candidates or technologies that we believe will complement or augment our existing business. We may also consider a variety of other business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and other investments. Any such transaction may require us to incur non-recurring and other charges, increase our near and long-term expenditures, pose significant integration challenges, create additional tax, legal, accounting and operational complexities in our business, require additional expertise, result in dilution to our existing shareholders and disrupt our management and business, which could harm our operations and financial results. For example, in connection with our acquisition of the U.S. rights to VIMOVO, we assumed primary responsibility for the existing patent infringement litigation with respect to VIMOVO, and have also agreed to reimburse certain legal expenses of Pozen Inc., who subsequently entered into a business combination with Tribute Pharmaceuticals Canada Inc. to become known as Aralez Pharmaceuticals Inc., or Aralez, with respect to its continued involvement in such litigation. We also assumed responsibility for the existing patent infringement litigation with respect to RAVICTI upon the closing of our acquisition of Hyperion Therapeutics Inc., or Hyperion, and have assumed responsibility for completing post-marketing clinical trials of RAVICTI that are required by the FDA and are ongoing. We expect that the RAVICTI litigation will result in substantial on-going expenses and potential distractions to our management team.

In connection with our acquisition of Raptor, we assumed Raptor's post-marketing clinical study obligations in the MAA for QUINSAIR and contractual obligations under agreements with Tripex Pharmaceuticals, LLC, or Tripex, and PARI Pharma GmbH, or PARI, related to QUINSAIR. Under the agreement with Tripex, we are required to pursue commercially reasonable efforts to initiate, and subsequently to complete, an additional clinical trial of QUINSAIR in a non-cystic fibrosis patient population within a specified period of time and an obligation to progress toward submitting an NDA for approval of QUINSAIR in the United States for use in all or part of the cystic fibrosis patient population. These obligations are subject to certain exceptions due to, for example, manufacturing delays not under our control, or delays caused by the FDA. If we fail to properly exercise such efforts to initiate and complete an appropriate clinical trial, or fail to submit an NDA for U.S. approval in the cystic fibrosis patient population, during the time periods specified in the agreement, we may be subject to various claims by Tripex and parties affiliated with Tripex. In addition, if we do not spend a minimum amount on QUINSAIR development in each of the three years following our acquisition of Raptor, we may also be obligated to pre-pay a milestone payment related to initiating a clinical trial for QUINSAIR in a non-cystic fibrosis indication. Under the license agreement with PARI, we are required to comply with diligence milestones related to development and commercialization of QUINSAIR in the United States and to spend a specified minimum amount per year on development activities in the United States until submission of the NDA for QUINSAIR in the United States. If we do not comply with these obligations, our licenses to certain intellectual property related to QUINSAIR may become non-exclusive in the United States or could be terminated. We are also now subject to contractual obligations under license agreements with the Regents of the University of California, San Diego, or UCSD, with respect to PROCYSBI, including diligence obligations to develop PROCYSBI for the treatment of non-alcoholic steatohepatitis, or NASH, and Huntington's disease, with which we currently are not in compliance. To the extent that we fail to perform the diligence obligations under the agreement, UCSD may, with respect to such indication, terminate the license or otherwise cause the license to become non-exclusive. If one or more of these licenses was terminated, we would have no further right to use or exploit the related intellectual property, which would limit our ability to develop PROCYSBI or QUINSAIR in other indications, and could impact our ability to continue commercializing PROCYSBI or QUINSAIR in their approved indications.

We face significant competition in seeking appropriate strategic transaction opportunities and the negotiation process for any strategic transaction can be time-consuming and complex. In addition, we may not be successful in our efforts to engage in certain strategic transactions because our financial resources may be insufficient and/or third parties may not view our commercial and development capabilities as being adequate. We may not be able to expand our business or realize our strategic goals if we do not have sufficient funding or cannot borrow or raise additional capital. There is no assurance that following any of our recent acquisition transactions or any other strategic transaction, we will achieve the anticipated revenues, net income, tax or other benefits that we believe justify such transactions. In addition, any failures or delays in entering into strategic transactions anticipated by analysts or the investment community could seriously harm our consolidated business, financial condition, results of operations or cash flow.

Our parent company may not be able to successfully maintain its current advantageous tax status and resulting tax rates, which could adversely affect our business and financial condition, results of operations and growth prospects.

Our parent company is incorporated in Ireland and maintains subsidiaries in multiple jurisdictions, including Ireland, the U.K, the United States, Switzerland, Luxembourg, Germany, France, the Netherlands, Canada and Bermuda. Prior to our merger transaction with Vidara Therapeutics International Public Limited Company, or Vidara, and such transaction, the Vidara Merger, Vidara was able to achieve a favorable tax rate through the performance of certain functions and ownership of certain assets in tax-efficient jurisdictions, including Ireland and Bermuda, together with intra-group service and transfer pricing agreements, each on an arm's length basis. We are continuing a substantially similar structure and arrangements. Taxing authorities, such as the U.S. Internal Revenue Service, or IRS, actively audit and otherwise challenge these types of arrangements, and have done so in the pharmaceutical industry. We expect that these challenges will continue as a result of the recent increase in scrutiny and political attention on corporate tax structures. The IRS may challenge our structure and transfer pricing arrangements through an audit or lawsuit. Responding to or defending such a challenge could be expensive and consume time and other resources, and divert management's time and focus from operating our business. We cannot predict whether taxing authorities will conduct an audit or file a lawsuit challenging this structure, the cost involved in responding to any such audit or lawsuit, or the outcome. If we are unsuccessful in defending such a challenge, we may be required to pay taxes for prior periods, interest, fines or penalties, and may be obligated to pay increased taxes in the future, any of which could require us to reduce our operating expenses, decrease efforts in support of our medicines or seek to raise additional funds, all of which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

The IRS may not agree with our conclusion that our parent company should be treated as a foreign corporation for U.S. federal income tax purposes following the combination of the businesses of Horizon Pharma, Inc., or HPI, and Vidara.

Although our parent company is incorporated in Ireland, the IRS may assert that it should be treated as a U.S. corporation (and, therefore, a U.S. tax resident) for U.S. federal income tax purposes pursuant to Section 7874 of the Internal Revenue Code of 1986, as amended, or the Code. A corporation is generally considered a tax resident in the jurisdiction of its organization or incorporation for U.S. federal income tax purposes. Because our parent company is an Irish incorporated entity, it would generally be classified as a foreign corporation (and, therefore, a non-U.S. tax resident) under these rules. Section 7874 of the Code provides an exception pursuant to which a foreign incorporated entity may, in certain circumstances, be treated as a U.S. corporation for U.S. federal income tax purposes.

Under Section 7874 of the Code, a foreign corporation will be treated as a U.S. corporation for U.S. federal tax purposes if, due to an acquisition of a U.S. corporation, at least 80 percent of its stock (by vote or value) is held by former stockholders of the acquired U.S. corporation. We believe that we should be treated as a foreign corporation because the former stockholders of HPI owned (within the meaning of Section 7874 of the Code) less than 80 percent (by both vote and value) of the combined entity's stock immediately after the Vidara Merger. However, there can be no assurance that there will not exist in the future a subsequent change in the facts or in law which might cause our parent company to be treated as a domestic corporation for U.S. federal income tax purposes, including with retroactive effect.

Further, there can be no assurance that the IRS will agree with the position that the ownership test was satisfied. There is limited guidance regarding the application of Section 7874 of the Code, including with respect to the provisions regarding the application of the ownership test. If our parent company were unable to be treated as a foreign corporation for U.S. federal income tax purposes, one of our significant strategic reasons for completing the Vidara Merger would be nullified and we may not be able to recoup the significant investment in completing the transaction.

Future changes to U.S. and non-U.S. tax laws could materially adversely affect our company.

Under current law, we expect our parent company to be treated as a foreign corporation for U.S. federal income tax purposes. However, changes to the rules in Section 7874 of the Code or regulations promulgated thereunder or other guidance issued by the U.S. Department of the Treasury, or the U.S. Treasury, or the IRS could adversely affect our parent company's status as a foreign corporation for U.S. federal income tax purposes, and any such changes could have prospective or retroactive application. If our parent company is treated as a domestic corporation, more of our income will be taxed by the United States which may substantially increase our effective tax rate.

On April 4, 2016, the U.S. Treasury and the IRS issued temporary regulations that expand the scope of transactions subject to the rules designed to eliminate the U.S. tax benefits of inversions. Under the temporary regulations, the former stockholders of U.S. corporations acquired by a foreign corporation within 36 months of the signing date of the last such acquisition are aggregated for the purpose of determining whether the foreign corporation will be treated as a domestic corporation for U.S. federal tax purposes because at least 80 percent of the stock of the foreign corporation is held by former stockholders of a U.S. corporation. The requirement to aggregate the stockholders in such acquisitions for the purpose of determining whether the 80 percent threshold is met may limit our ability to use our stock to acquire U.S. corporations or their assets in the future.

The U.S. Treasury and the IRS also issued proposed regulations on April 4, 2016 that address whether an interest in a related corporation is debt or equity. The proposed regulations would treat certain inter-company debt issued on or after that date as equity including, subject to certain exceptions, inter-company debt issued in certain distributions, acquisitions of related party stock and asset reorganizations. As drafted, the proposed regulations would limit the ability of our U.S. group to deduct interest on such new inter-company debt. The proposed regulations could also result in recharacterization of inter-company debt to equity for inter-company debt incurred to provide funding for an acquisition by the U.S. group if, and to the extent of, certain cash or property transfers by our U.S. group to the foreign affiliates within 36 months before or after these inter-company borrowings. These limitations could result in more of our future income being taxed by the United States and thereby increase our effective tax rate.

In July 2015, the International Tax Bipartisan Tax Working Group of the United States Senate Committee on Finance, or the Finance Committee, issued its report on international tax reform. The Finance Committee's co-chairs concluded that it will be necessary to limit earnings stripping by foreign multinationals through interest deductions on inter-company debt in order to eliminate a competitive advantage that foreign multinationals would otherwise have over domestic multinational companies. The status of the recommendations from the International Tax Bipartisan Tax Working Group, including regulations aimed at curbing earnings stripping, as well as the status of United States tax reform in general, is subject to significant uncertainty as the White House and both houses of Congress are considering several material tax reform proposals. These proposals include, among other items, a significant reduction to the United States corporate tax rate and a possible "border adjustment tax" that would effectively increase the economic cost of imports. At this point in time it is not possible to determine all of the possible consequences to us of the various tax reform proposals that are under consideration. However, any tax reform could significantly impact our United States and worldwide tax liabilities.

In addition, the Organization for Economic Co-operation and Development released its Base Erosion and Profit Shifting project final report on October 5, 2015. This report provides the basis for international standards for corporate taxation that are designed to prevent, among other things, the artificial shifting of income to tax havens and low-tax jurisdictions, the erosion of the tax base through interest deductions on inter-company debt and the artificial avoidance of permanent establishments (i.e., tax nexus with a jurisdiction). Legislation to adopt these standards has been enacted or is currently under consideration in a number of jurisdictions. As a result, our income may be taxed in jurisdictions where it is not currently taxed and at higher rates of tax than it is currently taxed, which may substantially increase our effective tax rate.

The U.S. federal government has called for substantial changes to U.S. tax policy and laws. We do not currently have sufficient information that would allow us to predict what U.S. tax reform, if any, may be enacted in the future or what impact any such changes would have on our business. Changes to U.S. tax laws could significantly impact our business, financial condition, results of operations, or cash flows.

If we are not successful in attracting and retaining highly qualified personnel, we may not be able to successfully implement our business strategy.

Our ability to compete in the highly competitive biotechnology and pharmaceuticals industries depends upon our ability to attract and retain highly qualified managerial, scientific and medical personnel. We are highly dependent on our management, sales and marketing and scientific and medical personnel, including our executive committee composed of our Chairman, President and Chief Executive Officer, Timothy P. Walbert; our Executive Vice President, Chief Business Officer, Robert F. Carey; our Executive Vice President, Chief Financial Officer, Paul W. Hoelscher; our Executive Vice President, Chief Administrative Officer, Barry J. Moze; our Executive Vice President, Research and Development and Chief Medical Officer, Jeffrey W. Sherman, M.D., FACP; our Executive Vice President, General Counsel, Brian K. Beeler; our Executive Vice President, Primary Care Business Unit, George Hampton; our Executive Vice President, Orphan Business Unit, Dave Happel; our Executive Vice President, Technical Operations, Michael A. DesJardin and our Senior Vice President, Rheumatology Business Unit, Vikram Karnani. In order to retain valuable employees at our company, in addition to salary and cash incentives, we provide performance stock units, or PSUs, and stock options and restricted stock units that vest over time. The value to employees of PSUs, stock options and restricted stock units will be significantly affected by movements in our share price that are beyond our control, and may at any time be insufficient to counteract more lucrative offers from other companies.

Despite our efforts to retain valuable employees, members of our management, sales and marketing, regulatory affairs, clinical development, medical affairs and development teams may terminate their employment with us on short notice. Although we have written employment arrangements with all of our employees, these employment arrangements generally provide for at-will employment, which means that our employees can leave our employment at any time, with or without notice. The loss of the services of any of our executive officers or other key employees and our inability to find suitable replacements could potentially harm our business, financial condition and prospects. We do not maintain "key man" insurance policies on the lives of these individuals or the lives of any of our other employees. Our success also depends on our ability to continue to attract, retain and motivate highly skilled junior, mid-level, and senior managers as well as junior, mid-level, and senior sales and marketing and scientific and medical personnel.

Many of the other biotechnology and pharmaceutical companies with whom we compete for qualified personnel have greater financial and other resources, different risk profiles and longer histories in the industry than we do. They also may provide more diverse opportunities and better chances for career advancement. Some of these characteristics may be more appealing to high quality candidates than that which we have to offer. If we are unable to continue to attract and retain high quality personnel, the rate and success at which we can develop and commercialize medicines and medicine candidates will be limited.

We are, with respect to our current medicines, and will be, with respect to any other medicine or medicine candidate for which we obtain FDA or EMA approval or which we acquire, subject to ongoing FDA or the EMA obligations and continued regulatory review, which may result in significant additional expense. Additionally, any other medicine candidate, if approved by the FDA or the EMA, could be subject to labeling and other restrictions and market withdrawal, and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our medicines.

Any regulatory approvals that we obtain for our medicine candidates may also be subject to limitations on the approved indicated uses for which the medicine may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials and surveillance to monitor the safety and efficacy of the medicine candidate. In addition, with respect to our current FDA-approved medicines (and with respect to our medicine candidates, if approved), the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for the medicine are subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMPs, GCPs, international conference on harmonization regulations, or ICH regulations, and GLPs, which are regulations and guidelines enforced by the FDA for all of our medicines in clinical development, for any clinical trials that we conduct post-approval. With respect to RAVICTI, the FDA imposed several post-marketing requirements and a post-marketing commitment, which include remaining obligations to conduct studies in UCD patients during the first two months of life and from two months to two years of age, including a study of the pharmacokinetics in both age groups, and a randomized study to determine the safety and efficacy in UCD patients who are treatment naïve to phenylbutyrate treatment. Although we are committed to carrying out these commitments, there are challenges in conducting studies in pediatric patients including availability of study sites, patients, and obtaining parental informed consent. On June 29, 2016, we submitted a supplemental new drug application, or sNDA, to the FDA for RAVICTI to expand the age range for chronic management of UCDs from two years of age and older to two months of age and older. Subject to positive data from on-going studies, we have targeted an sNDA submission in the first quarter of 2018 in relation to UCD patients during the first two months of life. In connection with our acquisition of Crealta Holdings LLC, or Crealta, in January 2016, we assumed responsibility for an observational study related to KRYSTEXXA. Thus far in this study there have been no new safety signals and the reported safety results parallel those in the KRYSTEXXA product label. We are continuing to screen and enroll patients in the near term. With respect to QUINSAIR, we are required to conduct post-marketing clinical studies in cystic fibrosis patients pursuant to obligations in the MAA for QUINSAIR and submit data to the EMA regularly regarding observed clinical medicine profile and safety assessment.

In addition, the FDA closely regulates the marketing and promotion of drugs and biologics. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, restrict manufacturers' promotional communications. A significant number of pharmaceutical companies have been the target of inquiries and investigations by various U.S. federal and state regulatory, investigative, prosecutorial and administrative entities in connection with the promotion of medicines for off-label uses and other sales practices. These investigations have alleged violations of various U.S. federal and state laws and regulations, including claims asserting antitrust violations, violations of the Food, Drug and Cosmetic Act, false claims laws, the Prescription Drug Marketing Act, anti-kickback laws, and other alleged violations in connection with the promotion of medicines for unapproved uses, pricing and Medicare and/or Medicaid reimbursement.

Later discovery of previously unknown problems with a medicine, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on the marketing or manufacturing of the medicine, withdrawal of the medicine from the market, or voluntary or mandatory medicine recalls;
- fines, warning letters or holds on clinical trials;
- refusal by the FDA to approve pending applications or supplements to approved applications filed by us or our strategic partners, or suspension or revocation of medicine license approvals;

- medicine seizure or detention, or refusal to permit the import or export of medicines; and
- injunctions, the imposition of civil or criminal penalties, or exclusion, debarment or suspension from government healthcare programs.

If we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would have a material adverse effect on our business, results of operations, financial condition and prospects.

Coverage and reimbursement may not be available, or reimbursement may be available at only limited levels, for our medicines, which could make it difficult for us to sell our medicines profitably or to successfully execute planned medicine price increases.

Market acceptance and sales of our medicines will depend in large part on global coverage and reimbursement policies and may be affected by future healthcare reform measures, both in the United States and other key international markets. Successful commercialization of our medicines will depend in part on the availability of governmental and third-party payer reimbursement for the cost of our medicines. Government health administration authorities, private health insurers and other organizations generally provide reimbursement for healthcare. In particular, in the United States, private health insurers and other third-party payers often provide reimbursement for medicines and services based on the level at which the government (through the Medicare or Medicaid programs) provides reimbursement for such treatments. In the United States, the EU and other significant or potentially significant markets for our medicines and medicine candidates, government authorities and third-party payers are increasingly attempting to limit or regulate the price of medicines and services, particularly for new and innovative medicines and therapies, which has resulted in lower average selling prices. Further, the increased scrutiny of prescription drug pricing practices and emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the EU will put additional pressure on medicine pricing, reimbursement and usage, which may adversely affect our medicine sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical reimbursement policies and pricing in general. These pressures may create negative reactions to any medicine price increases, or limit the amount by which we may be able to increase our medicine prices, which may adversely affect our medicine sales and results of operations.

Patients are unlikely to use our medicines unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our medicines. Third-party payers may limit coverage to specific medicines on an approved list, also known as a formulary, which might not include all of the FDA-approved medicines for a particular indication. Moreover, a third-party payer's decision to provide coverage for a medicine does not imply that an adequate reimbursement rate will be approved. Additionally, one third-party payer's decision to cover a particular medicine does not ensure that other payers will also provide coverage for the medicine, or will provide coverage at an adequate reimbursement rate. Even though we have contracts with some PBMs in the United States, that does not guarantee that they will perform in accordance with the contracts, nor does that preclude them from taking adverse actions against us, which could materially adversely affect our operating results. In addition, the existence of such PBM contracts does not guarantee coverage by such PBM's contracted health plans or adequate reimbursement to their respective providers for our medicines. For example, two significant PBMs placed DUEXIS and VIMOVO on their exclusion lists beginning in 2015, which has resulted in a loss of coverage for patients whose healthcare plans have adopted these PBM lists. While DUEXIS and VIMOVO were removed from the Express Scripts and CVS Caremark 2017 exclusion lists, we cannot guarantee that Express Scripts or CVS Caremark will not later add these medicines back to their exclusion lists or that we will be able to otherwise expand formulary access for DUEXIS and VIMOVO under health plans that contract with Express Scripts and/or CVS Caremark. Additional healthcare plan formularies may also exclude our medicines from coverage due to the actions of certain PBMs, future price increases we may implement, our use of the HorizonCares program or any other co-pay programs, or other reasons. If our strategies to mitigate formulary exclusions are not effective, these events may reduce the likelihood that physicians prescribe our medicines and increase the likelihood that prescriptions for our medicines are not filled.

Outside of the United States, the success of our medicines, including BUPHENYL, LODOTRA, PROCYSBI, QUINSAIR, RAVICTI and, following the IMUKIN Acquisition, interferon gamma-1b (currently commercialized under the trade names IMUKIN, IMUKINE, IMMUKIN and IMMUKINE), will depend largely on obtaining and maintaining government coverage, because in many countries patients are unlikely to use prescription drugs that are not covered by their government healthcare programs. The majority of LODOTRA sales are in Germany and Italy where reimbursement has been approved. BUPHENYL is marketed in select countries throughout Europe, the Middle East and the Asia-Pacific region. We launched RAVICTI in Canada in November 2016 and we expect to begin commercializing RAVICTI in Europe in 2017. PROCYSBI is marketed in select countries in Europe and QUINSAIR was recently launched in certain countries in Europe and in Canada, but we cannot be certain that existing reimbursement in EU countries will be maintained or that we will be able to secure reimbursement in additional countries. Negotiating coverage and reimbursement with governmental authorities can delay commercialization by 12 months or more. Coverage and reimbursement policies may adversely affect our ability to sell our medicines on a profitable basis. In many international markets, governments control the prices of prescription pharmaceuticals, including through the implementation of reference pricing, price cuts, rebates, revenue-related taxes and profit control, and we expect prices of prescription pharmaceuticals to decline over the life of the medicine or as volumes increase. Many countries in the EU have increased the amount of discounts required on medicines, and we expect these discounts to continue as countries attempt to manage healthcare expenditures, especially in light of current economic conditions. As a result of these pricing practices, it may become difficult to achieve or sustain profitability or expected rates of growth in revenue or results of operations. Any shortfalls in revenue could adversely affect our business, financial condition and results of operations.

In light of such policies and the uncertainty surrounding proposed regulations and changes in the coverage and reimbursement policies of governments and third-party payers, we cannot be sure that coverage and reimbursement will be available for any of our medicines in any additional markets or for any other medicine candidates that we may develop. Also, we cannot be sure that reimbursement amounts will not reduce the demand for, or the price of, our medicines. If coverage and reimbursement are not available or are available only at limited levels, we may not be able to successfully commercialize our medicines.

We expect to experience pricing pressures in connection with the sale of our medicines due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative proposals relating to outcomes and quality. For example, the ACA increased the mandated Medicaid rebate from 15.1% to 23.1%, expanded the rebate to Medicaid managed care utilization and increased the types of entities eligible for the federal 340B drug discount program. On January 30, 2017, the White House Office of Management and Budget withdrew the draft August 2015 Omnibus Guidance document that was issued by the Department of Health and Human Services Health Resources and Services Administration, or HRSA, that addressed a broad range of topics including, among other items, the definition of a patient's eligibility for 340B drug pricing. However, as concerns over drug pricing have not abated, there remains the possibility that HRSA will propose a similar regulation or that Congress will explore changes to the program through legislation. Also, in March 2016, the Centers for Medicare & Medicaid Services, or CMS, announced a Proposed Rule that would test new payment models for Medicare Part B prescription drugs, and provider services incident to, or otherwise related to, such drugs. Generally, the Proposed Rule included payment models designed on quality and value propositions and incentives to drive utilization of efficient therapies and payments based on clinical outcomes. The Proposed Rule greatly differs from the current reimbursement methodology for Medicare Part B drugs and was subject to significant discussion among stakeholders including Congress, industry, payers, healthcare providers and other interested organizations. Although the Proposed Rule was withdrawn by CMS in December, we will continue to monitor for legislative developments and new regulatory proposals.

There may be additional pressure by payers, healthcare providers, and Congress, to use generic drugs that contain the active ingredients found in our medicines or any other medicine candidates that we may develop or acquire. If we fail to successfully secure and maintain coverage and adequate reimbursement for our medicines or are significantly delayed in doing so, we will have difficulty achieving market acceptance of our medicines and expected revenue and profitability which would have a material adverse effect on our business, results of operations, financial condition and prospects.

We may also experience pressure from payers concerning certain promotional approaches that we may implement such as our HorizonCares program or any other co-pay or free medicine programs whereby we assist qualified patients with certain out-of-pocket expenditures for our medicine. If we are unsuccessful with our HorizonCares program or any other co-pay initiatives or free medicine programs, or we alternatively are unable to secure expanded formulary access through additional arrangements with PBMs or other payers, we would be at a competitive disadvantage in terms of pricing versus preferred branded and generic competitors. We may also experience financial pressure in the future which would make it difficult to support investment levels in areas such as managed care contract rebates, HorizonCares and other access tools.

We are subject to federal, state and foreign healthcare laws and regulations and implementation or changes to such healthcare laws and regulations could adversely affect our business and results of operations.

The United States and some foreign jurisdictions are considering or have enacted a number of legislative and regulatory proposals to regulate and to change the healthcare system in ways that could affect our ability to sell our medicines profitably. In the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs (including a number of proposals pertaining to prescription drugs, specifically), improving quality and/or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives.

If we are found to be in violation of any of these laws or any other federal or state regulations, we may be subject to civil and/or criminal penalties, damages, fines, exclusion, additional reporting requirements and/or oversight from federal health care programs and the restructuring of our operations. Any of these could have a material adverse effect on our business and financial results. Since many of these laws have not been fully interpreted by the courts, there is an increased risk that we may be found in violation of one or more of their provisions. Any action against us for violation of these laws, even if we ultimately are successful in our defense, will cause us to incur significant legal expenses and divert our management's attention away from the operation of our business.

In January 2017, the United States House of Representatives and Senate passed legislation, the concurrent budget resolution for fiscal year 2017, which initiates actions that would repeal certain aspects of the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the ACA. Further, on January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA, to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. Congress also could consider subsequent legislation to replace elements of the ACA that are repealed.

Moreover, certain politicians, including President Trump, have called for federal legislation to regulate the prices of medicines. The majority of our medicines are purchased by private payers, and we do not believe that any such legislation, if enacted, would have a material effect on us or our business. However, we cannot know what form any such legislation may take, the likelihood it would be signed into law or the market's perception of how such legislation would affect us. Any reduction in reimbursement from government programs may result in a similar reduction in payments from private payers. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our current medicines and/or those for which we may receive regulatory approval in the future.

We are subject, directly or indirectly, to federal and state healthcare fraud and abuse and false claims laws and regulations. Prosecutions under such laws have increased in recent years and we may become subject to such litigation. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

In the United States, we are subject directly, or indirectly through our customers, to various state and federal fraud and abuse laws, including, without limitation, the federal Anti-Kickback Statute, the federal False Claims Act, civil monetary penalty statutes prohibiting beneficiary inducements, and similar state laws, federal and state privacy and security laws, sunshine laws, government price reporting laws, and other fraud laws. These laws may impact, among other things, our current and proposed sales, marketing and educational programs, as well as other possible relationships with customers, pharmacies, physicians, payers, and patients.

Compliance with these laws, including the development of a comprehensive compliance program, is difficult, costly and time consuming. Because of the breadth of these laws and the narrowness of available statutory and regulatory exemptions, it is possible that some of our business activities could be subject to challenge under one or more of such laws. These risks may be increased where there are evolving interpretations of applicable regulatory requirements, such as those applicable to manufacturer co-pay initiatives. Pharmaceutical manufacturer co-pay initiatives and free medicine programs are the subject of ongoing litigation (involving other manufacturers and to which we are not a party) and evolving interpretations of applicable regulatory requirements and certain state laws, and any change in the regulatory or enforcement environment regarding such programs could impact our ability to offer such programs. If we are unsuccessful with our HorizonCares programs, any other co-pay initiatives or free medicine programs, we would be at a competitive disadvantage in terms of pricing versus preferred branded and generic competitors, or be subject to significant penalties. We are engaged in various business arrangements with current and potential customers, and we can give no assurance that such arrangements would not be subject to scrutiny under such laws, despite our efforts to properly structure such arrangements. Even if we structure our programs with the intent of compliance with such laws, there can be no certainty that we would not need to defend our business activities against enforcement or litigation. Further, we cannot give any assurances that prior business activities or arrangements of other companies that we acquire will not be scrutinized or subject to enforcement or litigation.

There has also been a trend of increased federal and state regulation of payments made to physicians and other healthcare providers. The ACA, among other things, imposed reporting requirements on drug manufacturers for payments made by them to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit required information may result in significant civil monetary penalties.

We are unable to predict whether we could be subject to actions under any of these or other healthcare laws, or the impact of such actions. If we are found to be in violation of, or to encourage or assist the violation by third parties of any of the laws described above or other applicable state and federal fraud and abuse laws, we may be subject to penalties, including administrative, civil and criminal penalties, damages, fines, withdrawal of regulatory approval, imprisonment, exclusion from government healthcare reimbursement programs, contractual damages, reputational harm, diminished profits and future earnings, injunctions and other associated remedies, or private “qui tam” actions brought by individual whistleblowers in the name of the government, and the curtailment or restructuring of our operations, all of which could have a material adverse effect on our business and results of operations. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management’s attention from the operation of our business.

Our medicines or any other medicine candidate that we develop may cause undesirable side effects or have other properties that could delay or prevent regulatory approval or commercialization, result in medicine re-labeling or withdrawal from the market or have a significant impact on customer demand.

Undesirable side effects caused by any medicine candidate that we develop could result in the denial of regulatory approval by the FDA or other regulatory authorities for any or all targeted indications, or cause us to evaluate the future of our development programs. In our two Phase 3 clinical trials with DUEXIS, the most commonly reported treatment-emergent adverse events were nausea, dyspepsia, diarrhea, constipation and upper respiratory tract infection. In Phase 3 endoscopic registration clinical trials with VIMOVO, the most commonly reported treatment-emergent adverse events were erosive gastritis, dyspepsia, gastritis, diarrhea, gastric ulcer, upper abdominal pain, nausea and upper respiratory tract infection. The most common side effects observed in pivotal trials for ACTIMMUNE were "flu-like" or constitutional symptoms such as fever, headache, chills, myalgia and fatigue. The most commonly reported treatment-emergent adverse events in the Phase 3 clinical trials with RAYOS/LODOTRA included flare in rheumatoid arthritis related symptoms, abdominal pain, nasopharyngitis, headache, flushing, upper respiratory tract infection, back pain and weight gain. The most common adverse events reported in a Phase 2 clinical trial of PENNSAID 2% were application site reactions, such as dryness, exfoliation, erythema, pruritus, pain, induration, rash and scabbing. With respect to BUPHENYL, the most common side effects are change in the frequency of breathing, lack of or irregular menstruation, lower back, side, or stomach pain, mood or mental changes, muscle pain or twitching, nausea or vomiting, nervousness or restlessness, swelling of the feet or lower legs, unpleasant taste and unusual tiredness or weakness. With respect to RAVICTI, the most common side effects are diarrhea, nausea, decreased appetite, gas, vomiting, high blood levels of ammonia, headache, tiredness and dizziness. With respect to KRYSTEXXA, the most commonly reported serious adverse reactions in the pivotal trial were gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis, exacerbation of pre-existing congestive heart failure and vomiting. With respect to MIGERGOT, the most commonly reported adverse reactions are ischemia, cyanosis, absence of pulse, cold extremities, gangrene, precordial distress and pain, electrocardiogram change, muscle pain, nausea and vomiting, rectal or anal ulcer, parathesias, numbness weakness, vertigo, localized edemas and itching. With respect to PROCYSBI, the most common side effects include vomiting, nausea, abdominal pain, breath odor, diarrhea, skin odor, fatigue, rash and headache. With respect to QUINSAIR, the most common side effects include itching, wheezing, hives, rash, swelling, pale skin color, fast heartbeat and faintness.

The FDA or other regulatory authorities may also require, or we may undertake, additional clinical trials to support the safety profile of our medicines or medicine candidates.

In addition, if we or others identify undesirable side effects caused by our medicines or any other medicine candidate that we may develop that receives marketing approval, or if there is a perception that the medicine is associated with undesirable side effects:

- regulatory authorities may require the addition of labeling statements, such as a "black box" warning or a contraindication;
- regulatory authorities may withdraw their approval of the medicine or place restrictions on the way it is prescribed;
- we may be required to change the way the medicine is administered, conduct additional clinical trials or change the labeling of the medicine or implement a risk evaluation and mitigation strategy; and
- we may be subject to increased exposure to product liability and/or personal injury claims.

If any of these events occurred with respect to our medicines, our ability to generate significant revenues from the sale of these medicines would be significantly harmed.

We rely on third parties to conduct our preclinical and clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines or if they experience regulatory compliance issues, we may not be able to obtain regulatory approval for or commercialize our medicine candidates and our business could be substantially harmed.

We have agreements with third-party contract research organizations, or CROs, to conduct our clinical programs, including those required for post-marketing commitments, and we expect to continue to rely on CROs for the completion of on-going and planned clinical trials. We may also have the need to enter into other such agreements in the future if we were to develop other medicine candidates or conduct clinical trials in additional indications for our existing medicines. In connection with the investigator-initiated study to evaluate ACTIMMUNE in combination with PD-1/PD-L1 inhibitors in various forms of cancer including advanced urothelial carcinoma (bladder cancer) and renal cell carcinoma, we are collaborating with Fox Chase Cancer Center. In connection with our ongoing study to evaluate RAYOS/LODOTRA on the fatigue experienced by SLE patients, we are collaborating with the ALR. We rely heavily on these parties for the execution of our clinical studies and control only certain aspects of their activities. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol. We, our CROs and our academic research organizations are required to comply with current GCP or ICH regulations. The FDA enforces these GCP or ICH regulations through periodic inspections of trial sponsors, principal investigators and trial sites. If we or our CROs or collaborators fail to comply with applicable GCP or ICH regulations, the data generated in our clinical trials may be deemed unreliable and our submission of marketing applications may be delayed or the FDA may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that, upon inspection, the FDA will determine that any of our clinical trials comply or complied with GCP or ICH regulations. In addition, our clinical trials must be conducted with medicine produced under cGMP regulations, and may require a large number of test subjects. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. Moreover, our business may be implicated if any of our CROs or collaborators violates federal or state fraud and abuse or false claims laws and regulations or healthcare privacy and security laws. We must also obtain certain third-party institutional review board, or IRB, and ethics committee approvals in order to conduct our clinical trials. Delays by IRBs and ethics committees in providing such approvals may delay our clinical trials.

If any of our relationships with these third-party CROs or collaborators terminate, we may not be able to enter into similar arrangements on commercially reasonable terms, or at all. If CROs or collaborators do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our medicines and medicine candidates. As a result, our results of operations and the commercial prospects for our medicines and medicine candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed.

Switching or adding additional CROs or collaborators can involve substantial cost and require extensive management time and focus. In addition, there is a natural transition period when a new CRO or collaborator commences work. As a result, delays may occur, which can materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our CROs and collaborators, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition or prospects.

Clinical development of drugs and biologics involves a lengthy and expensive process with an uncertain outcome, and results of earlier studies and trials may not be predictive of future trial results.

Clinical testing is expensive and can take many years to complete, and its outcome is uncertain. Failure can occur at any time during the clinical trial process. The results of preclinical studies and early clinical trials of potential medicine candidates may not be predictive of the results of later-stage clinical trials. Medicine candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through preclinical studies and initial clinical testing. For example, Raptor announced in September 2015, based on information then available, that it would not advance its program for the treatment of pediatric NASH with PROCYSBI after a Phase 2b trial failed achieve its primary endpoints. Also, on December 8, 2016, we announced that the Phase 3 trial, Safety, Tolerability and Efficacy of ACTIMMUNE Dose Escalation in Friedreich's Ataxia study evaluating ACTIMMUNE for the treatment of Friedreich's ataxia, or FA, did not meet its primary endpoint of a statistically significant change from baseline in the modified Friedreich's Ataxia Rating Scale at twenty-six weeks versus treatment with placebo. In addition, the secondary endpoints did not meet statistical significance. We, in conjunction with the independent Data Safety Monitoring Board, the principal investigator and the Friedreich's Ataxia Research Alliance Collaborative Clinical Research Network in FA, determined that, based on the trial results, the STEADFAST program would be discontinued, including the twenty-six week extension study and the long-term safety study.

With respect to the investigator-initiated study to evaluate ACTIMMUNE in combination with OPDIVO® (nivolumab) in advanced solid tumors and to the extent that we are required to conduct additional clinical development of any of our existing or later acquired medicines or we conduct clinical development of earlier stage medicine candidates or for other additional indications for RAYOS/LODOTRA, we may experience delays in these clinical trials or investigator-initiated studies. We do not know whether any additional clinical trials will be initiated in the future, begin on time, need to be redesigned, enroll patients on time or be completed on schedule, if at all. Clinical trials can be delayed for a variety of reasons, including delays related to:

- obtaining regulatory approval to commence a trial;
- reaching agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- obtaining IRB or ethics committee approval at each site;
- recruiting suitable patients to participate in a trial;
- having patients complete a trial or return for post-treatment follow-up;
- clinical sites dropping out of a trial;
- adding new sites; or
- manufacturing sufficient quantities of medicine candidates for use in clinical trials.

Patient enrollment, a significant factor in the timing of clinical trials, is affected by many factors including the size and nature of the patient population, the proximity of patients to clinical sites, the eligibility criteria for the trial, the design of the clinical trial, competing clinical trials and clinicians' and patients' perceptions as to the potential advantages of the medicine candidate being studied in relation to other available therapies, including any new drugs or biologics that may be approved for the indications we are investigating. Furthermore, we rely and expect to rely on CROs and clinical trial sites to ensure the proper and timely conduct of our future clinical trials and while we have and intend to have agreements governing their committed activities, we will have limited influence over their actual performance.

We could encounter delays if prescribing physicians encounter unresolved ethical issues associated with enrolling patients in clinical trials of our medicine candidates in lieu of prescribing existing treatments that have established safety and efficacy profiles. Further, a clinical trial may be suspended or terminated by us, our collaborators, the FDA or other regulatory authorities due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a medicine candidate, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. If we experience delays in the completion of, or if we terminate, any clinical trial of our medicine candidates, the commercial prospects of our medicine candidates will be harmed, and our ability to generate medicine revenues from any of these medicine candidates will be delayed. In addition, any delays in completing our clinical trials will increase our costs, slow down our medicine development and approval process and jeopardize our ability to commence medicine sales and generate revenues.

Moreover, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and receive compensation in connection with such services. Under certain circumstances, we may be required to report some of these relationships to the FDA. The FDA may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected interpretation of the study. The FDA may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing applications by the FDA and may ultimately lead to the denial of marketing approval of one or more of our medicine candidates.

Any of these occurrences may harm our business, financial condition, results of operations and prospects significantly. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our medicine candidates.

Business interruptions could seriously harm our future revenue and financial condition and increase our costs and expenses.

Our operations could be subject to earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics and other natural or man-made disasters or business interruptions. While we carry insurance for certain of these events and have implemented disaster management plans and contingencies, the occurrence of any of these business interruptions could seriously harm our business and financial condition and increase our costs and expenses. We conduct significant management operations at both our global headquarters located in Dublin, Ireland and our U.S. office located in Lake Forest, Illinois. If our Dublin or Lake Forest offices were affected by a natural or man-made disaster or other business interruption, our ability to manage our domestic and foreign operations could be impaired, which could materially and adversely affect our results of operations and financial condition. We currently rely, and intend to rely in the future, on third-party manufacturers and suppliers to produce our medicines and third-party logistics partners to ship our medicines. Our ability to obtain commercial supplies of our medicines could be disrupted and our results of operations and financial condition could be materially and adversely affected if the operations of these third-party suppliers or logistics partners were affected by a man-made or natural disaster or other business interruption. The ultimate impact of such events on us, our significant suppliers and our general infrastructure is unknown.

We are dependent on information technology systems, infrastructure and data, which exposes us to data security risks.

We are dependent upon information technology systems, infrastructure and data, including mobile technologies, to operate our business. The multitude and complexity of our computer systems make them inherently vulnerable to service interruption or destruction, malicious intrusion and random attack. Likewise, data privacy or security breaches by employees or others may pose a risk that sensitive data, including our intellectual property, trade secrets or personal information of our employees, patients, customers or other business partners may be exposed to unauthorized persons or to the public. Cyber-attacks are increasing in their frequency, sophistication and intensity. Cyber-attacks could include the deployment of harmful malware, denial-of-service, social engineering and other means to affect service reliability and threaten data confidentiality, integrity and availability. Our business partners face similar risks and any security breach of their systems could adversely affect our security posture. A security breach or privacy violation that leads to disclosure or modification of or prevents access to patient information, including personally identifiable information or protected health information, could harm our reputation, compel us to comply with federal and/or state breach notification laws and foreign law equivalents, subject us to mandatory corrective action, require us to verify the correctness of database contents and otherwise subject us to liability under laws and regulations that protect personal data, any of which could disrupt our business and/or result in increased costs or loss of revenue. Moreover, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information, trade secrets or other intellectual property. While we have invested, and continue to invest, in the protection of our data and information technology infrastructure, there can be no assurance that our efforts will prevent service interruptions, or identify breaches in our systems, that could adversely affect our business and operations and/or result in the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm to us. In addition, our liability insurance may not be sufficient in type or amount to cover us against claims related to security breaches, cyber-attacks and other related breaches.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our medicines.

We face an inherent risk of product liability claims as a result of the commercial sales of our medicines and the clinical testing of our medicine candidates. For example, we may be sued if any of our medicines or medicine candidates allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the medicine, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our medicines and medicine candidates. Even a successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for our medicines or medicine candidates that we may develop;
- injury to our reputation;
- withdrawal of clinical trial participants;
- initiation of investigations by regulators;
- costs to defend the related litigation;
- a diversion of management's time and resources;
- substantial monetary awards to trial participants or patients;
- medicine recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- exhaustion of any available insurance and our capital resources; and
- the inability to commercialize our medicines or medicine candidates.

Our inability to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of medicines we develop. We currently carry product liability insurance covering our clinical studies and commercial medicine sales in the amount of $75 million in the aggregate. Although we maintain such insurance, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. If we determine that it is prudent to increase our product liability coverage due to the on-going commercialization of our current medicines in the United States, and/or the potential commercial launches of any of our medicines in additional markets or for additional indications, we may be unable to obtain such increased coverage on acceptable terms or at all. Our insurance policies also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We will have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts.

Our business involves the use of hazardous materials, and we and our third-party manufacturers must comply with environmental laws and regulations, which can be expensive and restrict how we do business.

Our third-party manufacturers' activities involve the controlled storage, use and disposal of hazardous materials owned by us, including the components of our medicine candidates and other hazardous compounds. We and our manufacturers are subject to federal, state and local as well as foreign laws and regulations governing the use, manufacture, storage, handling and disposal of these hazardous materials. Although we believe that the safety procedures utilized by our third-party manufacturers for handling and disposing of these materials comply with the standards prescribed by these laws and regulations, we cannot eliminate the risk of accidental contamination or injury from these materials. In the event of an accident, state, federal or foreign authorities may curtail the use of these materials and interrupt our business operations. We do not currently maintain hazardous materials insurance coverage. If we are subject to any liability as a result of our third-party manufacturers' activities involving hazardous materials, our business and financial condition may be adversely affected. In the future we may seek to establish longer-term third-party manufacturing arrangements, pursuant to which we would seek to obtain contractual indemnification protection from such third-party manufacturers potentially limiting this liability exposure.

Our employees, independent contractors, principal investigators, consultants, vendors, distributors and CROs may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk that our employees, independent contractors, principal investigators, consultants, vendors, distributors and CROs may engage in fraudulent or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct or unauthorized activities that violate FDA regulations, including those laws that require the reporting of true, complete and accurate information to the FDA, manufacturing standards, federal and state healthcare fraud and abuse laws and regulations, and laws that require the true, complete and accurate reporting of financial information or data. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Misconduct by our employees and other third parties may also include the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. We have adopted a Code of Business Conduct and Ethics, but it is not always possible to identify and deter misconduct by our employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs and imprisonment.

Risks Related to our Financial Position and Capital Requirements

In the past we have incurred significant operating losses.

We have a limited operating history and even less history operating as a combined organization following the acquisitions of Vidara, Hyperion, Crealta and Raptor. We have financed our operations primarily through equity and debt financings and have incurred significant operating losses in the past. We had an operating loss of $147.2 million for the year ended December 31, 2016, operating income of $55.4 million for the year ended December 31, 2015 and an operating loss of $8.5 million for the year ended December 31, 2014. We had a net loss of $166.8 million and a net income of $39.5 million for the years ended December 31, 2016 and 2015, respectively, and a net loss of $263.6 million for the year ended December 31, 2014. As of December 31, 2016, we had an accumulated deficit of $848.0 million. Our prior losses have resulted principally from costs incurred in our development activities for our medicines and medicine candidates, commercialization activities related to our medicines, costs associated with our acquisition transactions and costs associated with derivative liability accounting. Our prior losses, combined with possible future losses, have had and will continue to have an adverse effect on our shareholders' deficit and working capital. While we anticipate that we will continue to generate operating profits in the future, whether we can sustain this will depend on the revenues we generate from the sale of our medicines being sufficient to cover our operating expenses.

We have limited sources of revenues and significant expenses. We cannot be certain that we will sustain profitability, which would depress the market price of our ordinary shares and could cause our investors to lose all or a part of their investment.

Our ability to sustain profitability depends upon our ability to generate sales of our medicines. We have a limited history of commercializing our medicines as a company, and commercialization has been primarily in the United States. We may never be able to successfully commercialize our medicines or develop or commercialize other medicines in the United States or in the EU, which we believe represents our most significant commercial opportunity. Our ability to generate future revenues depends heavily on our success in:

- continued commercialization of our existing medicines and any other medicine candidates for which we obtain approval;
- obtaining FDA approvals for additional indications for ACTIMMUNE and RAVICTI;
- securing additional foreign regulatory approvals for our medicines in territories where we have commercial rights; and
- developing, acquiring and commercializing a portfolio of other medicines or medicine candidates in addition to our current medicines.

Even if we do generate additional medicine sales, we may not be able to sustain profitability on a quarterly or annual basis. Our failure to remain profitable would depress the market price of our ordinary shares and could impair our ability to raise capital, expand our business, diversify our medicine offerings or continue our operations.

We may need to obtain additional financing to fund additional acquisitions.

Our operations have consumed substantial amounts of cash since inception. We expect to continue to spend substantial amounts to:

- commercialize our existing medicines in the United States, including the substantial expansion of our sales force in recent years;
- complete the regulatory approval process, and any future required clinical development related thereto, for our medicines and medicine candidates;
- potentially acquire other businesses or additional complementary medicines or medicines that augment our current medicine portfolio, including costs associated with refinancing debt of acquired companies; and
- conduct clinical trials with respect to potential additional indications, as well as conduct post-marketing requirements and commitments, with respect to our medicines and medicines we acquire.

While we believe that our existing cash and cash equivalents will be sufficient to fund our operations based on our current expectations of continued revenue growth, we may need to raise additional funds if we choose to expand our commercialization or development efforts more rapidly than presently anticipated, if we develop or acquire additional medicines or acquire companies, or if our revenue does not meet expectations.

We cannot be certain that additional funding will be available on acceptable terms, or at all. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of one or more of our medicines or medicine candidates or one or more of our other research and development initiatives, or delay, cut back or abandon our plans to grow the business through acquisition. We also could be required to:

- seek collaborators for one or more of our current or future medicine candidates at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available; or
- relinquish or license on unfavorable terms our rights to technologies or medicine candidates that we would otherwise seek to develop or commercialize ourselves.

In addition, if we are unable to secure financing to support future acquisitions, our ability to execute on a key aspect of our overall growth strategy would be impaired.

Any of the above events could significantly harm our business, financial condition and prospects.

We have incurred a substantial amount of debt, which could adversely affect our business, including by restricting our ability to engage in additional transactions or incur additional indebtedness, and prevent us from meeting our debt obligations.

As of December 31, 2016, we had $1,807.5 million book value, or $1,944.0 million principal amount, of indebtedness, including $769.0 million in secured indebtedness. In connection with the acquisition of Hyperion, we issued $475.0 million aggregate principal amount of 6.625% Senior Notes due 2023, or the 2023 Senior Notes, in April 2015 and borrowed $400.0 million in principal amount of secured loans pursuant to a credit agreement we entered into in May 2015 with Citibank, N.A., as administrative and collateral agent, and the lenders from time to time party thereto providing for (i) the six-year $400.0 million term loan facility; (ii) an uncommitted accordion facility subject to the satisfaction of certain financial and other conditions; and (iii) one or more uncommitted refinancing loan facilities with respect to loans thereunder, or the 2015 Senior Secured Credit Facility. We repaid $1.0 million in principal amount from this facility quarterly from the third quarter of 2015 to the fourth quarter of 2016. In connection with the acquisition of Raptor, we issued $300.0 million aggregate principal amount of 8.75% Senior Notes due 2024, or the 2024 Senior Notes, in October 2016 and borrowed $375.0 million in principal amount of secured loans, or the 2016 Incremental Loan Facility, pursuant to an amendment to our credit agreement, or as amended, the credit agreement. Accordingly, we have a significant amount of debt outstanding on a consolidated basis.

This substantial level of debt could have important consequences to our business, including, but not limited to:

- reducing the benefits we expect to receive from our recent and any future acquisition transactions;
- making it more difficult for us to satisfy our obligations;
- requiring a substantial portion of our cash flows from operations to be dedicated to the payment of principal and interest on our indebtedness, therefore reducing our ability to use our cash flows to fund acquisitions, capital expenditures, and future business opportunities;
- exposing us to the risk of increased interest rates to the extent of any future borrowings, including borrowings under our credit agreement, at variable rates of interest;
- making it more difficult for us to satisfy our obligations with respect to our indebtedness, including our outstanding notes, our credit agreement, and any failure to comply with the obligations of any of our debt instruments, including restrictive covenants and borrowing conditions, could result in an event of default under the agreements governing such indebtedness;
- increasing our vulnerability to, and reducing our flexibility to respond to, changes in our business or general adverse economic and industry conditions;

- limiting our ability to obtain additional financing for working capital, capital expenditures, debt service requirements, acquisitions, and general corporate or other purposes and increasing the cost of any such financing;
- limiting our flexibility in planning for, or reacting to, changes in our business and the industry in which we operate; and placing us at a competitive disadvantage as compared to our competitors, to the extent they are not as highly leveraged and who, therefore, may be able to take advantage of opportunities that our leverage may prevent us from exploiting; and
- restricting us from pursuing certain business opportunities.

The credit agreement and the indentures governing the 2024 Senior Notes and the 2023 Senior Notes impose, and the terms of any future indebtedness may impose, various covenants that limit our ability and/or the ability of our restricted subsidiaries' (as designated under such agreements) to, among other things, pay dividends or distributions, repurchase equity, prepay junior debt and make certain investments, incur additional debt and issue certain preferred stock, incur liens on assets, engage in certain asset sales, consolidate with or merge or sell all or substantially all of our assets, enter into transactions with affiliates, designate subsidiaries as unrestricted subsidiaries, and allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to us.

Our ability to obtain future financing and engage in other transactions may be restricted by these covenants. In addition, any credit ratings will impact the cost and availability of future borrowings and our cost of capital. Our ratings at any time will reflect each rating organization's then opinion of our financial strength, operating performance and ability to meet our debt obligations. There can be no assurance that we will achieve a particular rating or maintain a particular rating in the future. A reduction in our credit ratings may limit our ability to borrow at acceptable interest rates. If our credit ratings were downgraded or put on watch for a potential downgrade, we may not be able to sell additional debt securities or borrow money in the amounts, at the times or interest rates or upon the more favorable terms and conditions that might otherwise be available. Any impairment of our ability to obtain future financing on favorable terms could have an adverse effect on our ability to refinance any of our then-existing debt and may severely restrict our ability to execute on our business strategy, which includes the continued acquisition of additional medicines or businesses.

We may not be able to generate sufficient cash to service all of our indebtedness and may be forced to take other actions to satisfy our obligations under our indebtedness, which may not be successful.

Our ability to make scheduled payments under or to refinance our debt obligations depends on our financial condition and operating performance, which is subject to prevailing economic, industry and competitive conditions and to certain financial, business and other factors beyond our control. Our ability to generate cash flow to meet our payment obligations under our debt may also depend on the successful implementation of our operating and growth strategies. Any refinancing of our debt could be at higher interest rates and may require us to comply with more onerous covenants, which could further restrict our business operations. We cannot assure you that we will maintain a level of cash flows from operating activities sufficient to pay the principal, premium, if any, and interest on our indebtedness.

If our cash flows and capital resources are insufficient to fund our debt service obligations, we may be forced to reduce or delay capital expenditures, sell assets or business operations, seek additional capital or restructure or refinance our indebtedness. We cannot ensure that we would be able to take any of these actions, that these actions would be successful and permit us to meet our scheduled debt service obligations or that these actions would be permitted under the terms of existing or future debt agreements, including the indentures that govern the 2024 Senior Notes and the 2023 Senior Notes and the credit agreement. In addition, any failure to make payments of interest and principal on our outstanding indebtedness on a timely basis would likely result in a reduction of our credit rating, which could harm our ability to incur additional indebtedness.

If we cannot make scheduled payments on our debt, we will be in default and, as a result:

- our debt holders could declare all outstanding principal and interest to be due and payable;
- the administrative agent and/or the lenders under the credit agreement could foreclose against the assets securing the borrowings then outstanding; and
- we could be forced into bankruptcy or liquidation, which could result in you losing your investment.

We generally have broad discretion in the use of our cash and may not use it effectively.

Our management has broad discretion in the application of our cash, and investors will be relying on the judgment of our management regarding the use of our cash. Our management may not apply our cash in ways that ultimately increase the value of any investment in our securities. We expect to use our existing cash to fund commercialization activities for our medicines, to potentially fund additional medicine or business acquisitions, to potentially fund additional regulatory approvals of certain of our medicines, to potentially fund development, life cycle management or manufacturing activities of our medicines for other indications, to potentially fund share repurchases, and for working capital, capital expenditures and general corporate purposes. We may also invest our cash in short-term, investment-grade, interest-bearing securities. These investments may not yield a favorable return to our shareholders. If we do not invest or apply our cash in ways that enhance shareholder value, we may fail to achieve expected financial results, which could cause the price of our ordinary shares to decline.

Our ability to use net operating loss carryforwards and certain other tax attributes may be limited.

Under Sections 382 and 383 of the Code, if a corporation undergoes an "ownership change" (generally defined as a greater than 50 percent change (by value) in its equity ownership over a three-year period), the corporation's ability to use pre-change net operating loss carryforwards and other pre-change tax attributes to offset post-change income may be limited. We continue to carry forward our annual limitation resulting from an ownership change date of August 2, 2012. The limitation on pre-change net operating losses incurred prior to the August 2, 2012 change date is approximately $14.7 million for 2017 and $7.7 million for 2018 through 2028. During the third quarter of 2016, we also recognized additional net operating losses and federal and state tax credits as a result of our acquisition of Raptor on October 25, 2016 in the amount of approximately $97.3 million of federal net operating losses, state operating losses of approximately $177.5 million and approximately $22.4 million of federal and state tax credits. We continue to carry forward the annual limitation related to Hyperion of $50 million resulting from the last ownership change date in 2014. The net operating loss carryforward limitation is cumulative such that any use of the carryforwards below the limitations in one year will result in a corresponding increase in the limitations for the subsequent tax year.

Following certain acquisitions of a U.S. corporation by a foreign corporation, Section 7874 of the Code limits the ability of the acquired U.S. corporation and its U.S. affiliates to utilize U.S. tax attributes such as net operating losses to offset U.S. taxable income resulting from certain transactions. Based on the limited guidance available, we expect this limitation is applicable following the Vidara Merger. As a result, it is not currently expected that we or our other U.S. affiliates will be able to utilize their U.S. tax attributes to offset their U.S. taxable income, if any, resulting from certain taxable transactions following the Vidara Merger. Notwithstanding this limitation, we expect that we will be able to fully use our U.S. net operating losses prior to their expiration. As a result of this limitation, however, it may take HPI longer to use its net operating losses. Moreover, contrary to these expectations, it is possible that the limitation under Section 7874 of the Code on the utilization of U.S. tax attributes could prevent us from fully utilizing our U.S. tax attributes prior to their expiration if we do not generate sufficient taxable income.

Any limitation on our ability to use our net operating loss and tax credit carryforwards, including the carryforwards of companies that we acquire, will likely increase the taxes we would otherwise pay in future years if we were not subject to such limitations.

Unstable market and economic conditions may have serious adverse consequences on our business, financial condition and share price.

As widely reported, global credit and financial markets have experienced extreme disruptions in the past several years, including severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates, and uncertainty about economic stability. While there has been some recent improvement in some of these financial metrics, there can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions will not occur. Our general business strategy may be adversely affected by any such economic downturn, volatile business environment and continued unpredictable and unstable market conditions. If the current equity and credit markets deteriorate again, or do not improve, it may make any necessary debt or equity financing more difficult to complete, more costly, and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and share price and could require us to delay or abandon commercialization or development plans. There is a risk that one or more of our current service providers, manufacturers and other partners may not survive these difficult economic times, which could directly affect our ability to attain our operating goals on schedule and on budget.

The U.K.'s referendum to leave the EU or "Brexit," has and may continue to cause disruptions to capital and currency markets worldwide. The full impact of the Brexit decision, however, remains uncertain. A process of negotiation will determine the future terms of the U.K.'s relationship with the EU. During this period of negotiation, our results of operations and access to capital may be negatively affected by interest rate, exchange rate and other market and economic volatility, as well as regulatory and political uncertainty. Brexit may also have a detrimental effect on our customers, distributors and suppliers, which would, in turn, adversely affect our revenues and financial condition.

At December 31, 2016, we had $509.1 million of cash and cash equivalents consisting of cash and money market funds. While we are not aware of any downgrades, material losses, or other significant deterioration in the fair value of our cash equivalents since December 31, 2016, no assurance can be given that further deterioration in conditions of the global credit and financial markets would not negatively impact our current portfolio of cash equivalents or our ability to meet our financing objectives. Further dislocations in the credit market may adversely impact the value and/or liquidity of marketable securities owned by us.

Changes in accounting rules or policies may affect our financial position and results of operations.

Accounting principles generally accepted in the United States, or GAAP, and related implementation guidelines and interpretations can be highly complex and involve subjective judgments. Changes in these rules or their interpretation, the adoption of new guidance or the application of existing guidance to changes in our business could significantly affect our financial position and results of operations. In addition, our operation as an Irish company with multiple subsidiaries in different jurisdictions adds additional complexity to the application of GAAP and this complexity will be exacerbated further if we complete additional strategic transactions. Changes in the application of existing rules or guidance applicable to us or our wholly owned subsidiaries could significantly affect our consolidated financial position and results of operations.

Covenants under the indentures governing our 2024 Senior Notes and 2023 Senior Notes and the credit agreement may restrict our business and operations in many ways, and if we do not effectively manage our covenants, our financial conditions and results of operations could be adversely affected.

The indentures governing the 2024 Senior Notes and the 2023 Senior Notes and the credit agreement impose various covenants that limit our ability and/or our restricted subsidiaries' ability to, among other things:

- pay dividends or distributions, repurchase equity, prepay, redeem or repurchase certain debt and make certain investments;
- incur additional debt and issue certain preferred stock;
- provide guarantees in respect of obligations of other persons;
- incur liens on assets;
- engage in certain asset sales;
- merge, consolidate with or sell all or substantially all of our assets to another person;
- enter into transactions with affiliates;
- sell assets and capital stock of our subsidiaries;
- enter into agreements that restrict distributions from our subsidiaries;
- designate subsidiaries as unrestricted subsidiaries; and
- allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to us.

These covenants may:

- limit our ability to borrow additional funds for working capital, capital expenditures, acquisitions or other general business purposes;
- limit our ability to use our cash flow or obtain additional financing for future working capital, capital expenditures, acquisitions or other general business purposes;
- require us to use a substantial portion of our cash flow from operations to make debt service payments;

- limit our flexibility to plan for, or react to, changes in our business and industry;
- place us at a competitive disadvantage compared to less leveraged competitors; and
- increase our vulnerability to the impact of adverse economic and industry conditions.

If we are unable to successfully manage the limitations and decreased flexibility on our business due to our significant debt obligations, we may not be able to capitalize on strategic opportunities or grow our business to the extent we would be able to without these limitations.

Our failure to comply with any of the covenants could result in a default under the credit agreement or the indentures governing the 2024 Senior Notes or the 2023 Senior Notes, which could permit the administrative agent or the trustee, as applicable, or permit the lenders or the holders of the 2024 Senior Notes or the 2023 Senior Notes to cause the administrative agent or the trustee, as applicable, to declare all or part of any outstanding senior secured term loans, the 2023 Senior Notes or the 2024 Senior Notes to be immediately due and payable or to exercise any remedies provided to the administrative agent or the trustee, including, in the case of the credit agreement proceeding against the collateral granted to secure our obligations under the credit agreement. An event of default under the credit agreement or the indentures governing the 2024 Senior Notes or the 2023 Senior Notes could also lead to an event of default under the terms of the other agreements and the indenture governing our 2.50% Exchangeable Senior Notes due 2022, or the Exchangeable Senior Notes. Any such event of default or any exercise of rights and remedies by our creditors could seriously harm our business.

If intangible assets that we have recorded in connection with our acquisition transactions become impaired, we could have to take significant charges against earnings.

In connection with the accounting for our various acquisition transactions, we have recorded significant amounts of intangible assets. Under GAAP, we must assess, at least annually and potentially more frequently, whether the value of goodwill and other indefinite-lived intangible assets has been impaired. Amortizing intangible assets will be assessed for impairment in the event of an impairment indicator. Any reduction or impairment of the value of goodwill or other intangible assets will result in a charge against earnings, which could materially adversely affect our results of operations and shareholders' equity in future periods.

Risks Related to Our Intellectual Property

If we are unable to obtain or protect intellectual property rights related to our medicines and medicine candidates, we may not be able to compete effectively in our markets.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our medicines and medicine candidates. The strength of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions and can be uncertain. The patent applications that we own may fail to result in issued patents with claims that cover our medicines in the United States or in other foreign countries. If this were to occur, early generic competition could be expected against our current medicines and other medicine candidates in development. There is no assurance that all potentially relevant prior art relating to our patents and patent applications has been found, which prior art can invalidate a patent or prevent a patent from issuing based on a pending patent application. In particular, because the APIs in DUEXIS, VIMOVO and RAYOS/LODOTRA have been on the market as separate medicines for many years, it is possible that these medicines have previously been used off-label in such a manner that such prior usage would affect the validity of our patents or our ability to obtain patents based on our patent applications. In addition, claims directed to dosing and dose adjustment may be substantially less likely to issue in light of the Supreme Court decision in Mayo Collaborative Services v. Prometheus Laboratories, Inc., where the court held that claims directed to methods of determining whether to adjust drug dosing levels based on drug metabolite levels in the red blood cells were not patent eligible because they were directed to a law of nature. This decision may have wide-ranging implications on the validity and scope of pharmaceutical method claims.

Even if patents do successfully issue, third parties may challenge their validity, enforceability or scope, which may result in such patents being narrowed or invalidated.

Patent litigation is currently pending in the United States District Court for the District of New Jersey against several companies intending to market a generic version of VIMOVO before the expiration of certain of our patents listed in the Orange Book. These cases are collectively known as the VIMOVO cases, and involve the following sets of defendants: (i) Dr. Reddy's; (ii) Lupin; and (iii) Mylan. Patent litigation against a fourth generic company, Actavis, is currently pending in the Court of Appeals for the Federal Circuit. Patent litigation against a fourth generic company, Actavis, is currently pending in the Court of Appeals for the Federal Circuit. The cases arise from Paragraph IV Patent Certification notice letters from each of Dr. Reddy's, Lupin, Mylan and Actavis advising each had filed an ANDA with the FDA seeking approval to market generic versions of VIMOVO before the expiration of the patents-in-suit.

On January 12, 2017, a six-day bench trial commenced against defendants Dr. Reddy's and Mylan before the Honorable Judge Mary Cooper in the District of New Jersey. The patents at issue in this trial included two Orange Book listed patents: U.S. Patent Nos. 6,926,907 and 8,557,285. Defendant Lupin formerly entered into a stay pending entry of judgment in this consolidated action. Currently, closing arguments and post-trial filings are not scheduled.

On August 19, 2015, Lupin filed Petitions for inter partes review, or IPR, of U.S. Patent No. 8,858,996, or the '996 patent, and U.S. Patent Nos. 8,852,636 and 8,865,190, or the '190 patent, all patents in litigation in the above referenced VIMOVO cases. On March 1, 2016, the Patent Trial and Appeal Board, or the PTAB, issued decisions to institute the IPRs for the '996 patent and the '190 patent. The PTAB must issue a final written decision on the IPRs of the '996 patent and the '190 patent no later than March 1, 2017. Also on March 1, 2016, the PTAB denied the Petition for IPR for U.S. Patent No. 8,852,636. The PTAB hearings for the '996 and '190 patents were both held on November 29, 2016. The PTAB must issue final written decision on the IPRs of the '996 and '190 patents no later than March 1, 2017.

Patent litigation is currently pending in the United States District Court for the District of New Jersey against several companies intending to market a generic version of PENNSAID 2% prior to the expiration of certain of our patents listed in the Orange Book. These cases are collectively known as the PENNSAID 2% cases, and involve the following sets of defendants: (i) Actavis and (ii) Lupin. These cases arise from Paragraph IV Patent Certification notice letters from each of Actavis and Lupin advising each had filed an ANDA with the FDA seeking approval to market a generic version of PENNSAID 2% before the expiration of the patents-in-suit. The status of these cases is as set forth below.

We received from Actavis a Paragraph IV Patent Certification Notice Letter dated September 27, 2016, against Orange Book listed U.S. Patent No. 9,415,029, advising that Actavis had filed an ANDA with the FDA for a generic version of PENNSAID 2%.

We have received from Apotex three Paragraph IV Patent Certification Notice Letters dated April 1, 2016, June 30, 2016, and September 21, 2016 against Orange Book listed U.S. Patent Nos. 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164, 8,741,956, 8,871,809, 9,066,913, 9,101,591, 9,132,110, 9,168,304, 9,168,305, 9,220,784, 9,339,551, 9,339,552 and 9,415,029, advising that Apotex had filed an ANDA with the FDA for a generic version of PENNSAID 2%.

Patent litigation is currently pending in the United States District Court for the Eastern District of Texas against Par Pharmaceutical and in the United States District Court for the District of New Jersey against Lupin and against Par Pharmaceutical, who are each intending to market generic versions of RAVICTI prior to the expiration of certain of our patents listed in the Orange Book. These cases are collectively known as the RAVICTI cases, and arise from Paragraph IV Patent Certification notice letters from each of Par Pharmaceutical and Lupin advising each had filed an ANDA with the FDA seeking approval to market a generic version of RAVICTI before the expiration of the patents-in-suit.

On April 29, 2015, Par Pharmaceutical filed Petitions for IPR of U.S. Patent No. 8,404,215 and U.S. Patent No. 8,642,012, two of the patents involved in the above mentioned RAVICTI cases. On November 4, 2015, the PTAB issued decisions instituting such IPRs and on December 14, 2015, the District Court Judge Roy Payne issued a stay pending a final written decision from the PTAB with respect to such IPRs. On September 29, 2016, the PTAB found all of the claims in U.S. Patent No. 8,404,215 to be unpatentable. Horizon has not appealed the PTAB's final written decision with respect to U.S. Patent No. 8,404,215. On November 3, 2016, the PTAB issued a final written decision holding all of the claims of U.S. Patent No. 8,642,012 patentable. On December 29, 2016, Par filed a notice of appeal with the Federal Circuit to appeal the final written decision of the PTAB concerning the patentability of U.S. Patent No. 8,642,012.

On April 1, 2016, Lupin filed a Petition for IPR of U.S. Patent No. 9,095,559, a patent currently at issue in the Lupin RAVICTI case. On September 30, 2016, the PTAB issued a decision instituting the IPR. The PTAB must issue a final written decision on the IPR no later than September 30, 2017.

We intend to vigorously defend our intellectual property rights relating to our medicines, but we cannot predict the outcome of the VIMOVO cases, the PENNSAID 2% cases, the RAVICTI cases or the IPRs. Any adverse outcome in these matters or any new generic challenges that may arise could result in one or more generic versions of our medicines being launched before the expiration of the listed patents, which could adversely affect our ability to successfully execute our business strategy to increase sales of our medicines, and would negatively impact our financial condition and results of operations, including causing a significant decrease in our revenues and cash flows.

Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property or prevent others from designing around our claims. If the patent applications we hold with respect to our medicines fail to issue or if their breadth or strength of protection is threatened, it could dissuade companies from collaborating with us to develop them and threaten our ability to commercialize our medicines. We cannot offer any assurances about which, if any, patents will issue or whether any issued patents will be found not invalid and not unenforceable or will go unthreatened by third parties. Since patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we were the first to file any patent application related to our medicines or any other medicine candidates. Furthermore, if third parties have filed such patent applications, an interference proceeding in the United States can be provoked by a third-party or instituted by us to determine which party was the first to invent any of the subject matter covered by the patent claims of our applications.

With respect to RAVICTI, the composition of matter patent we hold would have expired in the United States in February 2015 without term extension. However, Hyperion applied for a term extension for this patent under the Drug Price Competition and Patent Term Restoration Act and received notice that the United States Patent and Trademark Office, or the U.S. PTO, extended the expiration date of the patent to July 28, 2018. We cannot guarantee that pending patent applications related to RAVICTI will result in additional patents or that other existing and future patents related to RAVICTI will be held valid and enforceable or will be sufficient to deter generic competition in the United States. Therefore, it is possible that upon expiration of the RAVICTI composition of matter patent, we would need to rely on forms of regulatory exclusivity, to the extent available, to protect against generic competition.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable, processes for which patents are difficult to enforce and any other elements of our drug discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. Although we expect all of our employees to assign their inventions to us, and all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques.

Our ability to obtain patents is highly uncertain because, to date, some legal principles remain unresolved, there has not been a consistent policy regarding the breadth or interpretation of claims allowed in patents in the United States and the specific content of patents and patent applications that are necessary to support and interpret patent claims is highly uncertain due to the complex nature of the relevant legal, scientific and factual issues. Changes in either patent laws or interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property or narrow the scope of our patent protection. For example, on September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. The U.S. PTO has developed new and untested regulations and procedures to govern the full implementation of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, only became effective in March 2013. The Leahy-Smith Act has also introduced procedures making it easier for third-parties to challenge issued patents, as well as to intervene in the prosecution of patent applications. Finally, the Leahy-Smith Act contains new statutory provisions that still require the U.S. PTO to issue new regulations for their implementation and it may take the courts years to interpret the provisions of the new statute. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. In addition, the ACA allows applicants seeking approval of biosimilar or interchangeable versions of biological products such as ACTIMMUNE to initiate a process for challenging some or all of the patents covering the innovator biological product used as the reference product. This process is complicated and could result in the limitation or loss of certain patent rights. An inability to obtain, enforce and defend patents covering our proprietary technologies would materially and adversely affect our business prospects and financial condition.

Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. For example, if the issuance, in a given country, of a patent to us, covering an invention, is not followed by the issuance, in other countries, of patents covering the same invention, or if any judicial interpretation of the validity, enforceability, or scope of the claims in, or the written description or enablement in, a patent issued in one country is not similar to the interpretation given to the corresponding patent issued in another country, our ability to protect our intellectual property in those countries may be limited. Changes in either patent laws or in interpretations of patent laws in the United States and other countries may materially diminish the value of our intellectual property or narrow the scope of our patent protection. If we are unable to prevent material disclosure of the non-patented intellectual property related to our technologies to third parties, and there is no guarantee that we will have any such enforceable trade secret protection, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, results of operations and financial condition.

Third-party claims of intellectual property infringement may prevent or delay our development and commercialization efforts.

Our commercial success depends in part on us avoiding infringement of the patents and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions and inter party reexamination proceedings before the U.S. PTO. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which our collaborators are developing medicine candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our medicine candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our medicines and/or any other medicine candidates. Because patent applications can take many years to issue, there may be currently pending patent applications, which may later result in issued patents that our medicine candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our medicine candidates, any molecules formed during the manufacturing process or any final medicine itself, the holders of any such patents may be able to block our ability to commercialize such medicine candidate unless we obtained a license under the applicable patents, or until such patents expire. Similarly, if any third-party patent were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or methods of use, including combination therapy, the holders of any such patent may be able to block our ability to develop and commercialize the applicable medicine candidate unless we obtained a license or until such patent expires. In either case, such a license may not be available on commercially reasonable terms or at all.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our medicine candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties or redesign our infringing medicines, which may be impossible or require substantial time and monetary expenditure. We cannot predict whether any such license would be available at all or whether it would be available on commercially reasonable terms. Furthermore, even in the absence of litigation, we may need to obtain licenses from third parties to advance our research or allow commercialization of our medicine candidates, and we have done so from time to time. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. In that event, we would be unable to further develop and commercialize one or more of our medicine candidates, which could harm our business significantly. We cannot provide any assurances that third-party patents do not exist which might be enforced against our medicines, resulting in either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties.

If we fail to comply with our obligations in the agreements under which we license rights to technology from third parties, we could lose license rights that are important to our business.

We are party to a number of technology licenses that are important to our business and expect to enter into additional licenses in the future. For example, we hold an exclusive license to Vectura Group plc's, or Vectura, proprietary technology and know-how covering the delayed-release of corticosteroids relating to RAYOS/LODOTRA. If we fail to comply with our obligations under our agreement with Vectura or our other license agreements, or if we are subject to a bankruptcy, the licensor may have the right to terminate the license, in which event we would not be able to market medicines covered by the license, including RAYOS/ LODOTRA.

In connection with our November 2013 acquisition of the U.S. rights to VIMOVO, we (i) received the benefit of a covenant not to sue under AstraZeneca's patent portfolio with respect to Nexium (which shall automatically become a license under such patent portfolio if and when AstraZeneca reacquires control of such patent portfolio from Merck Sharp & Dohme Corp. and certain of its affiliates), (ii) were assigned AstraZeneca's amended and restated collaboration and license agreement for the United States with Aralez, under which AstraZeneca has in-licensed exclusive rights under certain of Aralez's patents with respect to VIMOVO, and (iii) acquired AstraZeneca's co-ownership rights with Aralez with respect to certain joint patents covering VIMOVO, all for the commercialization of VIMOVO in the United States. If we fail to comply with our obligations under our agreements with AstraZeneca or if we fail to comply with our obligations under our agreements with Aralez, our rights to commercialize VIMOVO in the United States may be adversely affected or terminated by AstraZeneca or Aralez.

We also license rights to patents, know-how and trademarks for ACTIMMUNE from Genentech Inc., or Genentech, under an agreement that remains in effect for so long as we continue to commercialize and sell ACTIMMUNE. However, Genentech may terminate the agreement upon our material default, if not cured within a specified period of time. Genentech may also terminate the agreement in the event of our bankruptcy or insolvency. Upon such a termination of the agreement, all intellectual property rights conveyed to us under the agreement, including the rights to the ACTIMMUNE trademark, revert to Genentech. If we fail to comply with our obligations under this agreement, we could lose the ability to market and distribute ACTIMMUNE, which would have a material adverse effect on our business, financial condition and results of operations.

We rely on a license from Ucyclyd with respect to technology developed by Ucyclyd in connection with the manufacturing of RAVICTI. The purchase agreement under which Hyperion purchased the worldwide rights to RAVICTI contains obligations to pay Ucyclyd regulatory and sales milestone payments relating to RAVICTI, as well as royalties on the net sales of RAVICTI. On May 31, 2013, when Hyperion acquired BUPHENYL under a restated collaboration agreement with Ucyclyd, Hyperion received a license to use some of the manufacturing technology developed by Ucyclyd in connection with the manufacturing of BUPHENYL. The restated collaboration agreement also contains obligations to pay Ucyclyd regulatory and sales milestone payments, as well as royalties on net sales of BUPHENYL. If we fail to make a required payment to Ucyclyd and do not cure the failure within the required time period, Ucyclyd may be able to terminate the license to use its manufacturing technology for RAVICTI and BUPHENYL. If we lose access to the Ucyclyd manufacturing technology, we cannot guarantee that an acceptable alternative method of manufacture could be developed or acquired. Even if alternative technology could be developed or acquired, the loss of the Ucyclyd technology could still result in substantial costs and potential periods where we would not be able to market and sell RAVICTI and/or BUPHENYL. We also license intellectual property necessary for commercialization of RAVICTI from an external party. This party may be entitled to terminate the license if we breach the agreement, including failure to pay required royalties on net sales of RAVICTI, or we do not meet specified diligence obligations in our development and commercialization of RAVICTI, and we do not cure the failure within the required time period. If the license is terminated, it may be difficult or impossible for us to continue to commercialize RAVICTI, which would have a material adverse effect on our business, financial condition and results of operations.

We also hold an exclusive license to patents and technology from Duke University, or Duke, and Mountain View Pharmaceuticals, Inc., or MVP, covering KRYSTEXXA. Duke and MVP may terminate the license if we commit fraud or for our willful misconduct or illegal conduct. Duke and MVP may also terminate the license upon our material breach of the agreement, if not cured within a specified period of time, or upon written notice if we have committed two or more material breaches under the agreement. Duke and MVP may also terminate the license in the event of our bankruptcy or insolvency. If the license is terminated, it may be impossible for us to continue to commercialize KRYSTEXXA, which would have a material adverse effect on our business, financial condition and results of operations.

In addition, we are subject to contractual obligations under our agreements with Tripex and PARI related to QUINSAIR. Under the agreement with Tripex, we are required to pursue commercially reasonable efforts to initiate, and subsequently to complete, an additional clinical trial of QUINSAIR in a non-cystic fibrosis patient population within a specified period of time and an obligation to progress toward submitting an NDA for approval of QUINSAIR in the United States for use in all or part of the cystic fibrosis patient population. These obligations are subject to certain exceptions due to, for example, manufacturing delays not under our control, or delays caused by the FDA. If we fail to properly exercise such efforts to initiate and complete an appropriate clinical trial, or fail to submit an NDA for U.S. approval in the cystic fibrosis patient population, during the time periods specified in the agreement, we may be subject to various claims by Tripex and parties affiliated with Tripex. In addition, if we do not spend a minimum amount on QUINSAIR development in each of the three years following our acquisition of Raptor, we may also be obligated to pre-pay a milestone payment related to initiating a clinical trial for QUINSAIR in a non-cystic fibrosis indication. Under the license agreement with PARI, we are required to comply with diligence milestones related to development and commercialization of QUINSAIR in the United States and to spend a specified minimum amount per year on development activities in the United States until submission of the NDA for QUINSAIR in the United States. If we do not comply with these obligations, our licenses to certain intellectual property related to QUINSAIR may become non-exclusive in the United States or could be terminated. We are also subject to contractual obligations under our license agreements with the UCSD with respect to PROCYSBI, including diligence obligations to develop PROCYSBI for the treatment of NASH and Huntington's disease, with which we currently are not in compliance. To the extent that we fail to perform the diligence obligations under the agreement, UCSD may, with respect to such indication, terminate the license or otherwise cause the license to become non-exclusive. If one or more of these licenses was terminated, we would have no further right to use or exploit the related intellectual property, which would limit our ability to develop PROCYSBI or QUINSAIR in other indications, and could impact our ability to continue commercializing PROCYSBI or QUINSAIR in their approved indications.

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our patents or the patents of our licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that one of our patents, or a patent of one of our licensors, is not valid or is unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing.

There are numerous post grant review proceedings available at the U.S. PTO (including IPR, post-grant review and ex-parte reexamination) and similar proceedings in other countries of the world that could be initiated by a third-party that could potentially negatively impact our issued patents.

Interference proceedings provoked by third parties or brought by us may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our collaborators or licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our ordinary shares.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees on any issued patent are due to be paid to the U.S. PTO and foreign patent agencies in several stages over the lifetime of the patent. The U.S. PTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we or licensors that control the prosecution and maintenance of our licensed patents fail to maintain the patents and patent applications covering our medicine candidates, our competitors might be able to enter the market, which would have a material adverse effect on our business.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties.

We employ individuals who were previously employed at other biotechnology or pharmaceutical companies. We may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed confidential information of our employees' former employers or other third parties. We may also be subject to claims that former employers or other third parties have an ownership interest in our patents. Litigation may be necessary to defend against these claims. There is no guarantee of success in defending these claims, and even if we are successful, litigation could result in substantial cost and be a distraction to our management and other employees.

Risks Related to Ownership of Our Ordinary Shares

The market price of our ordinary shares historically has been volatile and is likely to continue to be volatile, and you could lose all or part of any investment in our ordinary shares.

The trading price of our ordinary shares has been volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. In addition to the factors discussed in this "Risk Factors" section and elsewhere in this report, these factors include:

- our failure to successfully execute our commercialization strategy with respect to our approved medicines, particularly our commercialization of our medicines in the United States;
- actions or announcements by third-party or government payers with respect to coverage and reimbursement of our medicines;
- disputes or other developments relating to intellectual property and other proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our medicines and medicine candidates;
- unanticipated serious safety concerns related to the use of our medicines;
- adverse regulatory decisions;
- changes in laws or regulations applicable to our business, medicines or medicine candidates, including but not limited to clinical trial requirements for approvals or tax laws;
- inability to comply with our debt covenants and to make payments as they become due;
- inability to obtain adequate commercial supply for any approved medicine or inability to do so at acceptable prices;
- developments concerning our commercial partners, including but not limited to those with our sources of manufacturing supply;
- our decision to initiate a clinical trial, not to initiate a clinical trial or to terminate an existing clinical trial;
- adverse results or delays in clinical trials;

- our failure to successfully develop and/or acquire additional medicine candidates or obtain approvals for additional indications for our existing medicine candidates;
- introduction of new medicines or services offered by us or our competitors;
- overall performance of the equity markets, including the pharmaceutical sector, and general political and economic conditions;
- failure to meet or exceed revenue and financial projections that we may provide to the public;
- actual or anticipated variations in quarterly operating results;
- failure to meet or exceed the estimates and projections of the investment community;
- inaccurate or significant adverse media coverage;
- publication of research reports about us or our industry or positive or negative recommendations or withdrawal of research coverage by securities analysts;
- our inability to successfully enter new markets;
- the termination of a collaboration or the inability to establish additional collaborations;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us or our competitors;
- our inability to maintain an adequate rate of growth;
- ineffectiveness of our internal controls or our inability to otherwise comply with financial reporting requirements;
- adverse U.S. and foreign tax exposure;
- additions or departures of key management, commercial or regulatory personnel;
- issuances of debt or equity securities;
- significant lawsuits, including patent or shareholder litigation;
- changes in the market valuations of similar companies to us;
- sales of our ordinary shares by us or our shareholders in the future;
- trading volume of our ordinary shares;
- effects of natural or man-made catastrophic events or other business interruptions; and
- other events or factors, many of which are beyond our control.

In addition, the stock market in general, and The NASDAQ Global Select Market and the stock of biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may adversely affect the market price of our ordinary shares, regardless of our actual operating performance.

We have never declared or paid dividends on our share capital and we do not anticipate paying dividends in the foreseeable future.

We have never declared or paid any cash dividends on our ordinary shares. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future, including due to limitations that are currently imposed by the 2015 Senior Secured Credit Facility, the 2016 Incremental Loan Facility, the 2024 Senior Notes and the 2023 Senior Notes. Any return to shareholders will therefore be limited to the increase, if any, of our ordinary share price.

We have incurred and will continue to incur significant increased costs as a result of operating as a public company and our management will be required to devote substantial time to compliance initiatives.

As a public company, we have incurred and will continue to incur significant legal, accounting and other expenses that we did not incur as a private company. In particular, the Sarbanes-Oxley Act of 2000, or the Sarbanes-Oxley Act, as well as rules subsequently implemented by the SEC and the NASDAQ Stock Market, Inc., or NASDAQ, impose significant requirements on public companies, including requiring establishment and maintenance of effective disclosure and financial controls and changes in corporate governance practices. These rules and regulations have substantially increased our legal and financial compliance costs and have made some activities more time-consuming and costly. These effects are exacerbated by our transition to an Irish company and the integration of numerous acquired businesses and operations into our historical business and operating structure. If these requirements divert the attention of our management and personnel from other business concerns, they could have a material adverse effect on our business, financial condition and results of operations. The increased costs will continue to decrease our net income or increase our net loss, and may require us to reduce costs in other areas of our business or increase the prices of our medicines or services. For example, these rules and regulations make it more difficult and more expensive for us to obtain and maintain director and officer liability insurance. We cannot predict or estimate the amount or timing of additional costs that we may incur to respond to these requirements. The impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers. If we fail to comply with the continued listing requirements of NASDAQ, our ordinary shares could be delisted from The NASDAQ Global Select Market, which would adversely affect the liquidity of our ordinary shares and our ability to obtain future financing.

The Sarbanes-Oxley Act requires, among other things, that we maintain effective internal controls for financial reporting and disclosure controls and procedures. In particular, we are required to perform annual system and process evaluation and testing of our internal controls over financial reporting to allow management to report on the effectiveness of our internal controls over financial reporting, as required by Section 404 of the Sarbanes-Oxley Act, or Section 404. Our independent registered public accounting firm is also required to deliver a report on the effectiveness of our internal control over financial reporting. Our testing, or the testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses. Our compliance with Section 404 requires that we incur substantial expense and expend significant management efforts, particularly because of our Irish parent company structure and international operations. If we are not able to comply with the requirements of Section 404 or if we or our independent registered public accounting firm identify deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses, the market price of our ordinary shares could decline and we could be subject to sanctions or investigations by NASDAQ, the SEC or other regulatory authorities, which would require additional financial and management resources.

New laws and regulations as well as changes to existing laws and regulations affecting public companies, including the provisions of the Sarbanes-Oxley Act and rules adopted by the SEC and by NASDAQ, would likely result in increased costs as we respond to their requirements.

Sales of a substantial number of our ordinary shares in the public market could cause our share price to decline.

If our existing shareholders sell, or indicate an intention to sell, substantial amounts of our ordinary shares in the public market, the trading price of such ordinary shares could decline. In addition, our ordinary shares that are either subject to outstanding options or reserved for future issuance under our employee benefit plans are or may become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules and Rule 144 and Rule 701 under the Securities Act of 1933, as amended, or the Securities Act. If these additional ordinary shares are sold, or if it is perceived that they will be sold, in the public market, the trading price of our ordinary shares could decline.

Certain holders of our ordinary shares are entitled to rights with respect to the registration of their shares under the Securities Act. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act, except for shares purchased by our affiliates. For example, we are subject to a registration rights agreement with certain former Vidara shareholders that acquired our ordinary shares in connection with our acquisition of Vidara. Pursuant to this agreement, we filed and are required to maintain a registration statement covering the resale of ordinary shares held by these shareholders and in certain circumstances, these holders can require us to participate in an underwritten public offering of their ordinary shares. Any sales of securities by these shareholders or a public announcement of such sales could have a material adverse effect on the trading price of our ordinary shares.

In addition, any conversion or exchange of our Exchangeable Senior Notes, whether pursuant to their terms or pursuant to privately negotiated transactions between the issuer and/or us and a holder of such securities, could depress the market price for our ordinary shares.

Future sales and issuances of our ordinary shares, securities convertible into our ordinary shares or rights to purchase ordinary shares or convertible securities could result in additional dilution of the percentage ownership of our shareholders and could cause our share price to decline.

Additional capital may be needed in the future to continue our planned operations. To the extent we raise additional capital by issuing equity securities or securities convertible into or exchangeable for ordinary shares, our shareholders may experience substantial dilution. We may sell ordinary shares, and we may sell convertible or exchangeable securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell such ordinary shares, convertible or exchangeable securities or other equity securities in subsequent transactions, existing shareholders may be materially diluted. New investors in such subsequent transactions could gain rights, preferences and privileges senior to those of holders of ordinary shares. We also maintain equity incentive plans, including our Amended and Restated 2014 Equity Incentive Plan, 2014 Non-Employee Equity Plan and 2014 Employee Share Purchase Plan, and intend to grant additional ordinary share awards under these and future plans, which will result in additional dilution to our existing shareholders.

Irish law differs from the laws in effect in the United States and may afford less protection to holders of our securities.

It may not be possible to enforce court judgments obtained in the United States against us in Ireland based on the civil liability provisions of the U.S. federal or state securities laws. In addition, there is some uncertainty as to whether the courts of Ireland would recognize or enforce judgments of U.S. courts obtained against us or our directors or officers based on the civil liabilities provisions of the U.S. federal or state securities laws or hear actions against us or those persons based on those laws. We have been advised that the U.S. currently does not have a treaty with Ireland providing for the reciprocal recognition and enforcement of judgments in civil and commercial matters. Therefore, a final judgment for the payment of money rendered by any U.S. federal or state court based on civil liability, whether or not based solely on U.S. federal or state securities laws, would not automatically be enforceable in Ireland.

As an Irish company, we are governed by the Irish Companies Acts, which differ in some material respects from laws generally applicable to U.S. corporations and shareholders, including, among others, differences relating to interested director and officer transactions and shareholder lawsuits. Likewise, the duties of directors and officers of an Irish company generally are owed to the company only. Shareholders of Irish companies generally do not have a personal right of action against directors or officers of the company and may exercise such rights of action on behalf of the company only in limited circumstances. Accordingly, holders of our securities may have more difficulty protecting their interests than would holders of securities of a corporation incorporated in a jurisdiction of the United States.

Provisions of our articles of association could delay or prevent a takeover of us by a third-party.

Our articles of association could delay, defer or prevent a third-party from acquiring us, despite the possible benefit to our shareholders, or otherwise adversely affect the price of our ordinary shares. For example, our articles of association:

- impose advance notice requirements for shareholder proposals and nominations of directors to be considered at shareholder meetings;
- stagger the terms of our board of directors into three classes; and
- require the approval of a supermajority of the voting power of the shares of our share capital entitled to vote generally at a meeting of shareholders to amend or repeal our articles of association.

In addition, several mandatory provisions of Irish law could prevent or delay an acquisition of us. For example, Irish law does not permit shareholders of an Irish public limited company to take action by written consent with less than unanimous consent. We are also subject to various provisions of Irish law relating to mandatory bids, voluntary bids, requirements to make a cash offer and minimum price requirements, as well as substantial acquisition rules and rules requiring the disclosure of interests in our ordinary shares in certain circumstances.

These provisions may discourage potential takeover attempts, discourage bids for our ordinary shares at a premium over the market price or adversely affect the market price of, and the voting and other rights of the holders of, our ordinary shares. These provisions could also discourage proxy contests and make it more difficult for you and our other shareholders to elect directors other than the candidates nominated by our board of directors, and could depress the market price of our ordinary shares.

A transfer of our ordinary shares may be subject to Irish stamp duty.

In certain circumstances, the transfer of shares in an Irish incorporated company will be subject to Irish stamp duty, which is a legal obligation of the buyer. This duty is currently charged at the rate of 1.0 percent of the price paid or the market value of the shares acquired, if higher. Because our ordinary shares are traded on a recognized stock exchange in the United States, an exemption from this stamp duty is available to transfers by shareholders who hold ordinary shares beneficially through brokers which in turn hold those shares through the Depositary Trust Company, or DTC, to holders who also hold through DTC. However, a transfer by or to a record holder who holds ordinary shares directly in his, her or its own name could be subject to this stamp duty. We, in our absolute discretion and insofar as the Companies Acts or any other applicable law permit, may, or may provide that one of our subsidiaries will pay Irish stamp duty arising on a transfer of our ordinary shares on behalf of the transferee of such ordinary shares. If stamp duty resulting from the transfer of ordinary shares which would otherwise be payable by the transferee is paid by us or any of our subsidiaries on behalf of the transferee, then in those circumstances, we will, on our behalf or on behalf of such subsidiary (as the case may be), be entitled to (i) seek reimbursement of the stamp duty from the transferee, (ii) set-off the stamp duty against any dividends payable to the transferee of those ordinary shares and (iii) claim a first and permanent lien on the ordinary shares on which stamp duty has been paid by us or such subsidiary for the amount of stamp duty paid. Our lien shall extend to all dividends paid on those ordinary shares.

Dividends paid by us may be subject to Irish dividend withholding tax.

In certain circumstances, as an Irish tax resident company, we will be required to deduct Irish dividend withholding tax (currently at the rate of 20%) from dividends paid to our shareholders. Shareholders that are resident in the United States, EU countries (other than Ireland) or other countries with which Ireland has signed a tax treaty (whether the treaty has been ratified or not) generally should not be subject to Irish withholding tax so long as the shareholder has provided its broker, for onward transmission to our qualifying intermediary or other designated agent (in the case of shares held beneficially), or our or its transfer agent (in the case of shares held directly), with all the necessary documentation by the appropriate due date prior to payment of the dividend. However, some shareholders may be subject to withholding tax, which could adversely affect the price of our ordinary shares.

If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, our share price and trading volume could decline.

The trading market for our ordinary shares will depend in part on the research and reports that securities or industry analysts publish about us or our business. If one or more of the analysts who cover us downgrade our rating or publish inaccurate or unfavorable research about our business, our share price could decline. If one or more of these analysts cease coverage of our company or fail to publish reports on our company regularly, demand for our ordinary shares could decrease, which might cause our share price and trading volume to decline.

Securities class action litigation could divert our management's attention and harm our business and could subject us to significant liabilities.

The stock markets have from time to time experienced significant price and volume fluctuations that have affected the market prices for the equity securities of pharmaceutical companies. These broad market fluctuations may cause the market price of our ordinary shares to decline. In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology and biopharmaceutical companies have experienced significant stock price volatility in recent years. For example, following declines in our stock price, two federal securities class action lawsuits were filed in March 2016 against us and certain of our current and former officers alleging violations of the Securities Exchange Act of 1934, as amended. Subsequently, the two actions were consolidated, and plaintiff added claims under the Securities Act and named additional defendants. This consolidated class action (captioned Schaffer v. Horizon Pharma plc, et al., Case No. 1:16-cv-01763) is currently pending in the United States District Court for the Southern District of New York. In November 2016, defendants filed motions to dismiss plaintiffs' consolidated amended complaint, which are fully briefed but have not yet been decided by the court. Even if we are successful in defending against this action or any similar claims that may be brought in the future, such litigation could result in substantial costs and may be a distraction to our management, and may lead to an unfavorable outcome that could adversely impact our financial condition and prospects.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Location	Approximate Square Footage	Lease Expiry Date
Dublin, Ireland	18,900	November 3, 2029
Lake Forest, Illinois	160,000	March 31, 2024
Novato, California	61,000	August 31, 2021
Deerfield, Illinois (1)	53,500	June 30, 2018
Brisbane, California	20,100	November 30, 2019
Mannheim, Germany	14,300	December 31, 2018
Chicago, Illinois	6,500	December 31, 2018
Utrecht, the Netherlands	5,400	October 31, 2019
Reinach, Switzerland	3,500	May 31, 2020

(1) We vacated the premises in Deerfield, Illinois, and began occupying the premises in Lake Forest, Illinois, in January 2016.

Item 3. Legal Proceedings

For a description of our legal proceedings, see Note 16 of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K.

Item 4. Mine Safety Disclosures

None.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Information

Our ordinary shares trade on The NASDAQ Global Select Market under the trading symbol "HZNP".

The following table sets forth the high and low sales prices per share of our ordinary shares as reported on The NASDAQ Global Select Market for the periods indicated.

	High	Low
2016		
First quarter	$ 22.02	$ 13.36
Second quarter	19.45	13.05
Third quarter	23.44	16.18
Fourth quarter	21.98	14.16

	High	Low
2015		
First quarter	$ 26.46	$ 12.64
Second quarter	34.99	25.26
Third quarter	39.49	16.22
Fourth quarter	23.70	12.86

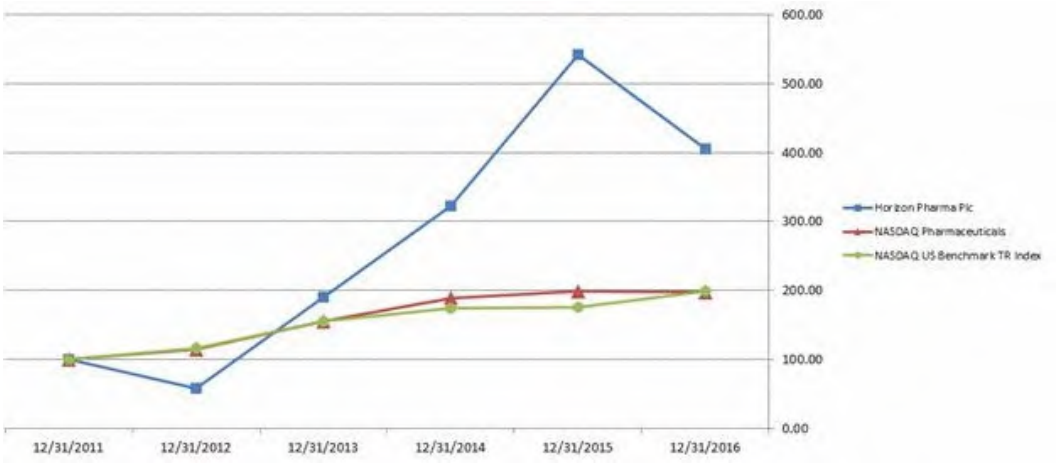
Holders of Record

The closing price of our ordinary shares on February 22, 2017 was $17.04. As of February 22, 2017, there were approximately thirteen holders of record of our ordinary shares.

Performance Graph

The following graph shows a comparison from December 31, 2011 through December 31, 2016 of the cumulative total return for (i) our ordinary shares, (ii) the NASDAQ U.S. Benchmark TR Index and (iii) NASDAQ Pharmaceuticals.

Information set forth in the graph below represents the performance of the Horizon Pharma, Inc. common stock from December 31, 2011 until September 18, 2014, the day before the consummation of the Vidara Merger, and the performance of our ordinary shares from September 19, 2014 through December 31, 2016. Our ordinary shares trade on the same exchange, the NASDAQ Global Select Market, and under the same trading symbol, "HZNP", as the Horizon Pharma, Inc. common stock prior to the Vidara Merger. The graph assumes an initial investment of $100 on December 31, 2011. The comparisons in the graph are required by the Securities and Exchange Commission and are not intended to forecast or be indicative of possible future performance of our ordinary shares.



	12/31/2011	12/31/2012	12/31/2013	12/31/2014	12/31/2015	12/31/2016
Cumulative Returns						
Horizon Pharma plc	$ 100.00	$ 58.25	$ 190.50	$ 322.25	$ 541.75	$ 404.50
NASDAQ Pharmaceuticals	100.00	114.32	155.11	188.95	199.22	197.05
NASDAQ U.S. Benchmark TR Index	100.00	116.43	155.41	174.78	175.62	198.47

The foregoing graph and table are furnished solely with this report, and are not filed with this report, and shall not be deemed incorporated by reference into any other filing under the Securities Act of 1933, as amended, or the Securities Act, or the Securities Exchange Act of 1934, as amended, whether made by us before or after the date hereof, regardless of any general incorporation language in any such filing, except to the extent we specifically incorporate this material by reference into any such filing.

Dividend Policy

We have never declared or paid cash dividends on our common equity. We currently intend to retain all available funds and any future earnings to support operations and finance the growth and development of our business and do not intend to pay cash dividends on our ordinary shares for the foreseeable future. Under Irish law, dividends may only be paid, and share repurchases and redemptions must generally be funded only out of, "distributable reserves." In addition, our ability to pay cash dividends is currently prohibited by the terms of our credit agreement we entered into in May 2015 with Citibank, N.A., as administrative and collateral agent, as amended, $475.0 million aggregate principal amount of 6.625% Senior Notes due 2023 and the $300.0 million aggregate principal amount of 8.75% Senior Notes due 2024, subject to customary exceptions. Any future determination as to the payment of dividends will, subject to Irish legal requirements, be at the sole discretion of our board of directors and will depend on our financial condition, results of operations, capital requirements and other factors our board of directors deems relevant.

Securities Authorized for Issuance under Equity Compensation Plans

See Item 12 of Part III of this Annual Report on Form 10-K regarding information about securities authorized for issuance under our equity compensation plans.

Recent Sales of Unregistered Securities

We completed the following issuances of unregistered securities during the year ended December 31, 2016 which were not previously reported in a Quarterly Report on Form 10-Q or in a Current Report on Form 8-K:

- In December 2016, we issued an aggregate of 500 ordinary shares to Peter Orlando upon the cash exercise of warrants and we received proceeds of $2,285 representing the aggregate exercise price of such warrants.
- In December 2016, we issued an aggregate of 500 ordinary shares to Troon Capital upon the cash exercise of warrants and we received proceeds of $2,285 representing the aggregate exercise price of such warrants.
- In December 2016, we issued an aggregate of 750 ordinary shares to Foster Equities LP upon the cash exercise of warrants and we received proceeds of $3,428 representing the aggregate exercise price of such warrants.

The offers, sales and issuances of the securities described above were deemed to be exempt from registration under the Securities Act of 1933, as amended, in reliance on Rule 506 of Regulation D in that each issuance of securities was to an accredited investor under Rule 501 of Regulation D and did not involve a public offering. The recipients of securities in each of these transactions acquired the securities for investment only and not with a view to or for sale in connection with any distribution thereof and where appropriate, legends were affixed to the securities issued in these transactions.

Issuer Repurchases of Equity Securities

None.

Irish Law Matters

See *Irish Law Matters* included in Item 1 of Part I of this Annual Report on Form 10-K.

Item 6. Selected Financial Data

The selected statement of comprehensive (loss) income data and selected statement of cash flows data for the years ended December 31, 2016, 2015 and 2014, and the balance sheet data as of December 31, 2016 and 2015 have been derived from our audited financial statements included elsewhere in this Annual Report on Form 10-K. The selected statements of comprehensive loss data and selected statement of cash flows data for the years ended December 31, 2013 and 2012, and the balance sheet data as of December 31, 2014, 2013 and 2012 have been derived from audited financial statements which are not included in this Annual Report on Form 10-K.

Our historical results are not necessarily indicative of future results. The selected financial data should be read in conjunction with "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our financial statements and related notes included elsewhere in this Annual Report on Form 10-K. The selected financial data for periods prior to the year ended December 31, 2014 is that of Horizon Pharma, Inc., our predecessor, while the selected financial data for the years ended December 31, 2016, 2015 and 2014 is that of Horizon Pharma plc.

	As of December 31,				
	2016	2015	2014	2013	2012
	(in thousands)				
Selected Balance Sheet Data					
Cash and cash equivalents	$ 509,055	$ 859,616	$ 218,807	$ 80,480	$ 104,087
Working capital	440,430	748,595	106,024	67,455	79,983
Total assets (1)	4,292,059	3,058,588	1,102,842	246,328	190,789
Total debt, net (1)	1,807,493	1,136,756	334,012	104,494	45,606
Accumulated deficit	(848,021)	(681,187)	(720,719)	(457,116)	(308,111)
Total shareholders' equity (deficit)	1,263,779	1,313,145	540,204	(49,082)	105,978

	For the Years Ended December 31,				
	2016	2015	2014	2013	2012
	(in thousands, except per share data)				
Selected Statement of Comprehensive (Loss) Income Data					
Net sales	$ 981,120	$ 757,044	$ 296,955	$ 74,016	$ 18,844
Cost of goods sold	393,272	219,502	78,753	14,625	11,875
Gross profit	587,848	537,542	218,202	59,391	6,969
Loss before benefit for income taxes	(228,085)	(132,712)	(269,687)	(150,126)	(92,965)
Net (loss) income	(166,834)	39,532	(263,603)	(149,005)	(87,794)
Net (loss) income per ordinary share - basic	(1.04)	0.27	(3.15)	(2.34)	(2.26)
Net (loss) income per ordinary share - diluted	(1.04)	0.25	(3.15)	(2.34)	(2.26)
Selected Statement of Cash Flows Data					
Net cash provided by (used in) operating activities	$ 369,456	$ 194,166	$ 27,549	$ (54,287)	$ (76,641)
Net cash used in investing activities	(1,375,881)	(995,048)	(227,720)	(36,135)	(1,386)
Net cash provided by financing activities	657,074	1,442,481	338,285	66,716	164,308
Payments for acquisitions, net of cash acquired	(1,356,271)	(1,022,361)	(224,220)	(35,000)	—
Net proceeds from the issuance of common stock	4,884	500,454	41,934	6,637	128,518
Net proceeds from the issuance of debt	656,190	1,241,027	286,966	143,598	55,578
Repayment of debt	(4,000)	(299,000)	—	(64,884)	(19,788)

(1) In 2016, we retrospectively adopted Accounting Standards Update No. 2015-03, *Interest-Imputation of Interest (Subtopic 835-30): Simplifying the Presentation of Debt Issuance Costs*, simplifying the presentation of debt issuance costs. As a result, deferred financing costs of $11.5 million, $6.3 million and $3.2 million that were classified within "total assets" at December 31, 2014, December 31, 2013 and December 31, 2012, respectively, were reclassified to "total debt, net" in the above table to conform prior-period classifications as a result of the new guidance.

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and the related notes appearing at the end of this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. You should read the "Risk Factors" section of this Annual Report on Form 10-K for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

The discussion below contains "forward-looking statements," as defined in Section 21E of the Securities Exchange Act of 1934, as amended, that reflect our current expectations regarding our future growth, results of operations, cash flows, performance and business prospects and opportunities, as well as assumptions made by, and information currently available to, our management. We have tried to identify forward-looking statements by using words such as "anticipate," "believe," "plan," "expect," "intend," "will," and similar expressions, but these words are not the exclusive means of identifying forward-looking statements. These statements are based on information currently available to us and are subject to various risks, uncertainties, and other factors, including, but not limited to, those matters discussed in Item 1A. "Risk Factors" in Part I of this Annual Report on Form 10-K, that could cause our actual growth, results of operations, cash flows, performance and business prospects and opportunities to differ materially from those expressed in, or implied by, these statements. Except as expressly required by the federal securities laws, we undertake no obligation to update such factors or to publicly announce the results of any of the forward-looking statements contained herein to reflect future events, developments, or changed circumstances, or for any other reason.

OVERVIEW

Unless otherwise indicated or the context otherwise requires, references to the "Company", "we", "us" and "our" refer to Horizon Pharma plc and its consolidated subsidiaries, including its predecessor, Horizon Pharma, Inc., or HPI. All references to "Vidara" are references to Horizon Pharma plc (formerly known as Vidara Therapeutics International Public Limited Company) and its consolidated subsidiaries prior to the effective time of the merger of the businesses of HPI and Vidara on September 19, 2014, or the Vidara Merger. The disclosures in this report relating to the pre-Vidara Merger business of Horizon Pharma plc, unless noted as being the business of Vidara prior to the Vidara Merger, pertain to the business of HPI prior to the Vidara Merger.

Our Business

We are a biopharmaceutical company focused on improving patients' lives by identifying, developing, acquiring and commercializing differentiated and accessible medicines that address unmet medical needs. We market eleven medicines through our orphan, rheumatology and primary care business units. Our marketed medicines are ACTIMMUNE® (interferon gamma-1b), BUPHENYL® (sodium phenylbutyrate) Tablets and Powder, DUEXIS® (ibuprofen/famotidine), KRYSTEXXA® (pegloticase), MIGERGOT® (ergotamine tartrate & caffeine suppositories), PENNSAID® (diclofenac sodium topical solution) 2% w/w, or PENNSAID 2%, PROCYSBI® (cysteamine bitartrate) delayed-release capsules, QUINSAIR™ (aerosolized form of levofloxacin), RAVICTI® (glycerol phenylbutyrate) Oral Liquid, RAYOS® (prednisone) delayed-release tablets and VIMOVO® (naproxen/esomeprazole magnesium).

We developed DUEXIS and RAYOS, known as LODOTRA® outside the United States, acquired the U.S. rights to VIMOVO from AstraZeneca AB, or AstraZeneca, in November 2013, acquired certain rights to ACTIMMUNE as a result of the Vidara Merger in September 2014, acquired the U.S. rights to PENNSAID 2% from Nuvo Research Inc., or Nuvo, in October 2014, acquired RAVICTI and BUPHENYL, known as AMMONAPS® in certain European countries, as a result of our acquisition of Hyperion Therapeutics Inc., or Hyperion, in May 2015, acquired KRYSTEXXA and the U.S. rights to MIGERGOT as a result of our acquisition of Crealta Holdings LLC., or Crealta, in January 2016 and acquired PROCYSBI and QUINSAIR as a result of our acquisition of Raptor Pharmaceutical Corp., or Raptor, in October 2016.

On January 13, 2016, we completed our acquisition of Crealta for approximately $539.7 million, including cash acquired of $24.9 million. Following completion of the acquisition, Crealta became our wholly owned subsidiary and was renamed Horizon Pharma Rheumatology LLC.

On May 18, 2016, we entered into a definitive agreement with Boehringer Ingelheim International GmbH, or Boehringer Ingelheim International, to acquire certain rights to interferon gamma-1b, which Boehringer Ingelheim International currently commercializes under the trade names IMUKIN®, IMUKINE®, IMMUKIN® and IMMUKINE® in an estimated thirty countries primarily in Europe and the Middle East. Under the terms of the agreement, we paid Boehringer Ingelheim International €5.0 million ($5.6 million when converted using a Euro-to-Dollar exchange rate at date of payment of 1.1132) upon signing and will pay €20.0 million upon closing, for certain rights for interferon gamma-1b in all territories outside of the United States, Canada and Japan, as we currently hold marketing rights to interferon gamma-1b in these territories. We currently market interferon gamma-1b as ACTIMMUNE in the United States. The transaction is expected to close in 2017 and we are continuing to work with Boehringer Ingelheim International to enable the transfer of applicable marketing authorizations. We recorded an impairment charge of €5.0 million ($5.3 million when converted using a Euro-to-Dollar exchange rate at date of impairment of 1.052) during the three months ended December 31, 2016 to fully write off the value of the initial payment on our consolidated balance sheet, and upon closing we expect to record the additional €20.0 million payment as an expense in our consolidated statement of comprehensive (loss) income. See “Results from Phase 3 Study of ACTIMMUNE (interferon gamma-1b) in Friedreich's Ataxia” section below for further details.

On October 25, 2016, we completed our acquisition of Raptor in which we acquired all of the issued and outstanding shares of Raptor’s common stock for $9.00 per share in cash. The total consideration was $860.8 million, including cash acquired of $24.9 million and $56.0 million to repay Raptor’s outstanding debt. Following completion of the acquisition, Raptor became our wholly owned subsidiary and converted to a limited liability company, changing its name to Horizon Pharmaceutical LLC. We financed the transaction through $300.0 million aggregate principal amount of 8.75% Senior Notes due 2024, or the 2024 Senior Notes, $375.0 million aggregate principal amount of loans pursuant to an amendment to our existing credit agreement and cash on hand.

Part of our commercial strategy for RAYOS and our primary care medicines is to offer physicians the opportunity to have their patients fill prescriptions through pharmacies participating in our HorizonCares patient access program. For commercial patients who are prescribed our primary care medicines or RAYOS, the HorizonCares program offers co-pay assistance when a third-party commercial payer covers a prescription but requires an eligible patient to pay a co-pay or deductible, and offers full subsidization when a third-party commercial payer rejects coverage for an eligible patient. During 2016, we entered into business arrangements with pharmacy benefit managers, or PBMs, and other payers to secure formulary status and reimbursement of our medicines, such as our arrangements with Express Scripts, Inc., or Express Scripts, CVS Caremark and Prime Therapeutics LLC. While we believe that this strategy will result in broader inclusion of certain of our primary care medicines on healthcare plan formularies, and therefore increase payer reimbursement and lower our cost of providing patient access programs, these arrangements generally require us to pay administrative and rebate payments to the PBMs and/or other payers.

We market our medicines in the United States through our field sales force, which numbered approximately 480 representatives as of December 31, 2016. Our strategy is to continue to build a well-balanced, diversified, high-growth biopharmaceutical company. We are executing this through the successful commercialization of our existing medicines, a strong commitment to patient access and support and business development efforts focused on transformative acquisitions to accelerate our rare disease leadership as well as on-market and development-stage medicines to fill out our pipeline.

We are building a sustainable biopharmaceutical company by helping ensure that patients have access to their medicines and support services, and by investing in the further development of medicines for patients with rare or underserved diseases. Our growing business is diversified across three business units: orphan, rheumatology and primary care, and is driven by a successful commercial model that focuses on differentiated, long-life medicines, innovative patient access programs and a disciplined business development strategy.

Results from Phase 3 Study of ACTIMMUNE (interferon gamma-1b) in Friedreich's Ataxia

On December 8, 2016, we announced that the Phase 3 trial, Safety, Tolerability and Efficacy of ACTIMMUNE Dose Escalation in Friedreich's Ataxia study, or STEADFAST, evaluating ACTIMMUNE for the treatment of Friedreich's ataxia, or FA, did not meet its primary endpoint of a statistically significant change from baseline in the modified Friedreich's Ataxia Rating Scale, or FARS-mNeuro, at twenty-six weeks versus treatment with placebo and that the secondary endpoints did not meet statistical significance, or the FA announcement. No new safety findings were identified on initial review of data other than those already noted in the ACTIMMUNE prescribing information for approved indications. We, in conjunction with the independent Data Safety Monitoring Board, the principal investigator and the Friedreich's Ataxia Research Alliance, or FARA, Collaborative Clinical Research Network in FA, determined that, based on the trial results, the STEADFAST program would be discontinued, including the twenty-six week extension study and the long-term safety study.

Following the FA announcement, we recorded the following amounts in our consolidated statement of comprehensive loss during the year ended December 31, 2016 (in thousands):

Description	Financial Statement Line Item	Amount Loss/(Gain)	Note
Impairment of in-process research and development	Impairment of in-process research and development	$ 66,000	1
Impairment of non-current asset	General and administrative expenses	5,260	2
Loss on inventory purchase commitments	Cost of goods sold	14,287	3
Remeasurement of contingent royalty liabilities	Cost of goods sold	(2,480)	4
Clinical trial wind-down costs	Research and development expenses	3,966	5
Total		$ 87,033	

Note 1 In-process research and development, or IPR&D, related to the research and development project to evaluate ACTIMMUNE in the treatment of FA, which we acquired in the Vidara Merger. At the time of the Vidara Merger, IPR&D was considered separable from the business as the project could be sold to a third party, and we assigned a fair value of $66.0 million to the intangible asset using an income approach in our purchase accounting. Following the FA announcement, we determined that the IPR&D has no alternative use or economic value, and we recorded an impairment charge during the three months ended December 31, 2016 to fully write off the value of the asset on our consolidated balance sheet.

Note 2 As described above, on May 18, 2016, we entered into a definitive agreement with Boehringer Ingelheim International to acquire certain rights to interferon gamma-1b, and we paid Boehringer Ingelheim International €5.0 million upon signing. The purchase price was determined with the expectation that the STEADFAST study would be successful. Following the FA announcement, we determined that this payment, which was recorded in "other assets" on our consolidated balance sheet was impaired, and we recorded an impairment charge during the three months ended December 31, 2016 to fully write off the value of the asset ($5.3 million when converted using a Euro-to-Dollar exchange rate at date of impairment of 1.052). Upon closing, we will pay Boehringer Ingelheim International an additional €20.0 million and we expect to record this payment as an expense in our consolidated statement of comprehensive (loss) income.

Note 3 During the year ended December 31, 2016, we committed to purchase additional units of ACTIMMUNE from Boehringer Ingelheim RCV GmbH & Co KG, or Boehringer Ingelheim. These additional units of ACTIMMUNE were intended to cover anticipated demand if the results of the STEADFAST study of ACTIMMUNE for the treatment of FA had been successful. Following the FA announcement, we recorded a loss of $14.3 million for firm, non-cancellable and unconditional purchase commitments for quantities in excess of our current forecasts for future demand. During the year ended December 31, 2016, we also committed to incur an additional $14.9 million for the harmonization of the drug substance manufacturing process with Boehringer Ingelheim. These additional costs have not been included in our consolidated statement of comprehensive loss or our consolidated balance sheet at December 31, 2016.

Note 4 At the time of the Vidara Merger, we assigned a fair value to a contingent liability for royalties potentially payable under previously existing royalty and licensing agreements related to ACTIMMUNE, which included an amount of $2.5 million for estimated future sales of ACTIMMUNE for FA. Following the FA announcement, we recorded an adjustment to reduce the contingent royalty liability for ACTIMMUNE by $2.5 million as we do not anticipate future sales of ACTIMMUNE for FA.

Note 5 Following the FA announcement, we recorded an amount of $4.0 million at December 31, 2016 related to costs anticipated to be incurred to discontinue the STEADFAST study. These costs will be incurred without economic benefit to us, and represent costs to us to wind down the study under U.S. Food and Drug Administration, or FDA, protocol.

RESULTS OF OPERATIONS

Year Ended December 31, 2016 Compared to Year Ended December 31, 2015

	For the Years Ended December 31,		Increase / (Decrease)	Change %
	2016	2015		
	(in thousands)			
Net sales	$ 981,120	$ 757,044	$ 224,076	30%
Cost of goods sold	393,272	219,502	173,770	79%
Gross profit	587,848	537,542	50,306	9%
Operating expenses				
Research and development	60,707	41,865	18,842	45%
Sales and marketing	320,366	220,444	99,922	45%
General and administrative	287,942	219,861	68,081	31%
Impairment of in-process research and development	66,000	—	66,000	*
Total operating expenses	735,015	482,170	252,845	52%
Operating (loss) income	(147,167)	55,372	(202,539)	(366)%
Other income (expense), net:				
Interest expense, net	(86,610)	(69,900)	(16,710)	24%
Foreign exchange loss	(1,005)	(1,237)	232	(19)%
Loss on induced conversion of debt and debt extinguishment	—	(77,624)	77,624	*
Loss on sale of long-term investments	—	(29,032)	29,032	*
Other income (expense), net	6,697	(10,291)	16,988	(165)%
Total other expense, net	(80,918)	(188,084)	107,166	(57)%
Loss before benefit for income taxes	(228,085)	(132,712)	(95,373)	72%
Benefit for income taxes	(61,251)	(172,244)	110,993	(64)%
Net (loss) income	$ (166,834)	$ 39,532	$ (206,366)	(522)%

* Percentage change is not meaningful.

Net sales. Net sales increased $224.1 million, or 30%, to $981.1 million during the year ended December 31, 2016, from $757.0 million during the year ended December 31, 2015.

The following table presents a summary of total net sales attributed to geographic sources for the years ended December 31, 2016 and 2015 (in thousands):

	Year Ended December 31, 2016		Year Ended December 31, 2015	
	Amount	% of Total Net Sales	Amount	% of Total Net Sales
United States	$ 964,041	98%	$ 744,036	98%
Rest of world	17,079	2%	13,008	2%
Total net sales	$ 981,120		$ 757,044	

The following table reflects the components of net sales for the years ended December 31, 2016 and 2015 (in thousands):

	Year Ended December 31,		Change	Change
	2016	2015	$	%
PENNSAID 2%	$ 304,433	$ 147,010	$ 157,423	107%
DUEXIS	173,728	190,357	(16,629)	-9%
RAVICTI	151,532	86,875	64,657	74%
VIMOVO	121,315	166,672	(45,357)	-27%
ACTIMMUNE	104,624	107,444	(2,820)	-3%
KRYSTEXXA	91,102	—	91,102	*
RAYOS	47,356	40,329	7,027	17%
PROCYSBI	25,268	—	25,268	*
BUPHENYL	16,879	13,458	3,421	25%
MIGERGOT	4,651	—	4,651	*
LODOTRA	4,193	4,899	(706)	-14%
QUINSAIR	1,039	—	1,039	*
Litigation settlement	(65,000)	—	(65,000)	*
Total net sales	$ 981,120	$ 757,044	$ 224,076	30%

* Percentage change is not meaningful.

The increase in net sales during the year ended December 31, 2016 was primarily due to the growth in net sales of PENNSAID 2%, the full-period recognition of RAVICTI sales in 2016, compared to a partial period recognition in 2015 following the acquisition of Hyperion in May 2015, the recognition of KRYSTEXXA sales following the acquisition of Crealta in January 2016 and the recognition of PROCYSBI sales following the acquisition of Raptor in October 2016, offset by the $65.0 million litigation settlement with Express Scripts along with lower net sales of VIMOVO and DUEXIS.

PENNSAID 2%. Net sales increased $157.4 million, or 107%, to $304.4 million during the year ended December 31, 2016, from $147.0 million during the year ended December 31, 2015. Net sales increased by approximately $87.5 million due to higher net pricing and $69.9 million resulting from prescription volume growth.

DUEXIS. Net sales decreased $16.6 million, or 9%, to $173.7 million during the year ended December 31, 2016, from $190.3 million during the year ended December 31, 2015. Net sales decreased by approximately $50.4 million due to lower net pricing resulting from higher co-pay and other patient assistance, offset by an increase of approximately $33.8 million resulting from prescription volume growth.

RAVICTI. Net sales increased $64.7 million, or 74%, to $151.5 million during the year ended December 31, 2016, from $86.8 million during the year ended December 31, 2015. Net sales increased by approximately $55.7 million resulting from prescription volume growth and $9.0 million due to higher net pricing. We began recognizing RAVICTI sales following the acquisition of Hyperion in May 2015, therefore only a partial period of RAVICTI sales were recognized during the year ended December 31, 2015, compared with full-period recognition of sales during the year ended December 31, 2016.

VIMOVO. Net sales decreased $45.4 million, or 27%, to $121.3 million during the year ended December 31, 2016, from $166.7 million during the year ended December 31, 2015. Net sales decreased by approximately $35.9 million due to lower net pricing resulting from higher co-pay and other patient assistance and approximately $9.5 million resulting from lower prescription volumes.

ACTIMMUNE. Net sales decreased $2.8 million, or 3%, to $104.6 million during the year ended December 31, 2016, from $107.4 million during the year ended December 31, 2015. Net sales decreased by approximately $8.8 million resulting from prescription volume decreases, offset by an increase of approximately $6.0 million due to higher net pricing.

KRYSTEXXA. Net sales were $91.1 million during the year ended December 31, 2016. We began recognizing KRYSTEXXA sales following the acquisition of Crealta in January 2016.

RAYOS. Net sales increased $7.0 million, or 17%, to $47.4 million during the year ended December 31, 2016, from $40.4 million during the year ended December 31, 2015. Net sales increased by approximately $8.4 million resulting from prescription volume growth, offset by a decrease of approximately $1.4 million due to lower net pricing.

PROCYSBI. Net sales were $25.3 million during the year ended December 31, 2016. We began recognizing PROCYSBI sales following the acquisition of Raptor in October 2016.

BUPHENYL. Net sales increased $3.4 million, or 25%, to $16.9 million during the year ended December 31, 2016, from $13.5 million during the year ended December 31, 2015. We began recognizing BUPHENYL sales following the acquisition of Hyperion in May 2015, therefore only a partial period of BUPHENYL sales were recognized during the year ended December 31, 2015, compared with full-period recognition of sales during the year ended December 31, 2016.

MIGERGOT. Net sales were $4.7 million during the year ended December 31, 2016. We began recognizing MIGERGOT sales following the acquisition of Crealta in January 2016.

LODOTRA. Net sales decreased $0.7 million, or 14%, to $4.2 million during the year ended December 31, 2016, from $4.9 million during the year ended December 31, 2015. The decrease was due to fewer shipments to our European distribution partner, Mundipharma International Corporation Limited, or Mundipharma. LODOTRA sales to Mundipharma occur at the time we ship, based on Mundipharma's estimated requirements. Accordingly, LODOTRA sales are not linear or directly tied to Mundipharma's in-market sales and can therefore fluctuate significantly.

QUINSAIR. Net sales were $1.0 million during the year ended December 31, 2016. We began recognizing QUINSAIR sales following the acquisition of Raptor in October 2016.

In September 2016, we entered into a settlement agreement and mutual release with Express Scripts pursuant to which we and Express Scripts were released from any and all claims relating to our then ongoing litigation without admitting any fault or wrongdoing and we agreed to pay Express Scripts $65.0 million. This settlement has been accounted for as a reduction of "net sales" in the consolidated statement of comprehensive loss for the year ended December 31, 2016.

The table below reconciles our gross sales to net sales for the years ended December 31, 2016 and 2015 (in millions):

	Year Ended December 31, 2016		Year Ended December 31, 2015	
	Amount	% of Gross Sales	Amount	% of Gross Sales
Gross sales	$ 3,234.2	100.0%	$ 2,057.3	100.0%
Adjustments to gross sales:				
Prompt pay discounts	(64.0)	(2.0)%	(41.3)	(2.0)%
Medicine returns	(17.1)	(0.5)%	(14.4)	(0.7)%
Co-pay and other patient assistance	(1,701.3)	(52.6)%	(1,020.2)	(49.6)%
Wholesaler fees and commercial rebates	(133.7)	(4.2)%	(66.1)	(3.2)%
Government rebates and chargebacks	(272.0)	(8.4)%	(158.3)	(7.7)%
Litigation settlement	(65.0)	(2.0)%	—	—
Total adjustments	(2,253.1)	(69.7)%	(1,300.3)	(63.2)%
Net sales	$ 981.1	30.3%	$ 757.0	36.8%

During the year ended December 31, 2016, co-pay and other patient assistance, as a percentage of gross sales, increased to 52.6% from 49.6% during the year ended December 31, 2015. The increase was primarily due to the expansion of our HorizonCares program during 2016.

On a quarter-to-quarter basis, our net sales have traditionally been lower in first half of the year, particularly in the first quarter, with the second half of the year representing a greater share of overall net sales each year. This is due to annual managed care plan changes and the re-setting of patient deductibles at the beginning of each year, resulting in higher co-pay and other patient assistance costs as patients meet their annual deductibles during the first and second quarters, and higher net sales in the second half of the year after patients meet their deductibles and healthcare plans reimburse a greater portion of the total cost of our medicines.

Cost of Goods Sold. Cost of goods sold increased $173.8 million to $393.3 million during the year ended December 31, 2016, from $219.5 million during the year ended December 31, 2015. As a percentage of net sales, cost of goods sold was 40.0% during the year ended December 31, 2016, compared to 29.0% during the year ended December 31, 2015. The large increase in costs of goods sold as a percentage of net sales was due to the one-time reduction in net sales in the year ended December 31, 2016 as a result of the litigation settlement with Express Scripts and an increase in cost of goods sold in the year ended December 31, 2016. The increase in cost of goods sold was primarily a result of higher intangible amortization expense of $84.0 million and increased inventory step-up expense of $59.6 million. Other factors that caused cost of goods sold to increase during the year included a $14.3 million expense related to a loss on inventory purchase commitments, higher royalty accretion expense of $20.5 million and a $16.2 million increase in direct and indirect costs associated with higher sales, offset by a $20.8 million decrease in charges relating to the remeasurement of contingent royalty liabilities.

The increase in intangible amortization of $84.0 million during the year ended December 31, 2016 compared to the prior year was due to a $33.9 million increase in amortization expense related to RAVICTI and BUPHENYL intangible assets (acquired in May 2015), $35.9 million amortization of developed technology related to KRYSTEXXA and MIGERGOT (acquired in January 2016), $14.0 million amortization of developed technology related to PROCYSBI (acquired in October 2016) and $0.2 million increase in amortization related to ACTIMMUNE.

Because inventory step-up expense is acquisition-related, will not continue indefinitely and has a significant effect on our gross profit, gross margin percentage and net income (loss) for all affected periods, we disclose balance sheet and income statement amounts related to inventory step-up within the notes to the consolidated financial statements. The increase in inventory step-up expense of $59.6 million during the year ended December 31, 2016 compared to the prior year was due to $48.8 million recorded during the year ended December 31, 2016 related to KRYSTEXXA and MIGERGOT inventory step-up (acquired in January 2016) and $22.4 million related to PROCYSBI and QUINSAIR inventory step-up (acquired in October 2016), compared to $8.4 million recorded during the year ended December 31, 2015 related to RAVICTI and BUPHENYL inventory step-up (acquired in May 2015) and $3.2 million related to ACTIMMUNE inventory step-up (acquired in September 2014).

Research and Development Expenses. Research and development expenses increased $18.8 million to $60.7 million during the year ended December 31, 2016, from $41.9 million during the year ended December 31, 2015. The increase in research and development expenses during the year ended December 31, 2016 was primarily attributable to $2.8 million of higher share-based compensation, an increase of $5.5 million in other employee costs resulting from growth in our headcount following the Hyperion, Crealta and Raptor acquisitions, $4.0 million related to costs to be incurred in the winding down of the STEADFAST study, an increase of $3.0 million in general research and development costs, a $2.0 million upfront fee paid for a license of a patent and an increase of $1.5 million in regulatory submission fees.

Sales and Marketing Expenses. Sales and marketing expenses increased $99.9 million to $320.4 million during the year ended December 31, 2016, from $220.5 million during the year ended December 31, 2015. The increase in sales and marketing expenses was in line with the significant growth in gross sales and an increase in the number of sales representatives over the same period, which primarily contributed to an increase of $52.2 million in employee costs resulting from increased staffing of our field sales force and an increase of $47.7 million in marketing and commercialization expenses following the Hyperion, Crealta and Raptor acquisitions.

General and Administrative Expenses. General and administrative expenses increased $68.1 million to $287.9 million during the year ended December 31, 2016, from $219.8 million during the year ended December 31, 2015. The increase was attributable to $22.4 million of higher share-based compensation, $10.2 million in other employee costs resulting from growth in our headcount following the Hyperion, Crealta and Raptor acquisitions, an increase of $36.8 million in costs following the Hyperion, Crealta and Raptor acquisitions and $5.3 million due to the impairment of the initial amount paid to Boehringer Ingelheim International for certain rights to interferon gamma-1b, offset by a decrease of $6.6 million in acquisition-related general and administrative expenses.

Impairment of In-Process Research and Development. At the time of the Vidara Merger, IPR&D was considered separable from the business as the project could be sold to a third party, and we assigned a fair value of $66.0 million to the intangible asset. Following the FA announcement, we determined that the IPR&D has no alternative use or economic value, and we recorded an impairment charge during the three months ended December 31, 2016 to fully write off the value of the asset on our consolidated balance sheet.

Interest Expense, Net. Interest expense, net, increased $16.7 million to $86.6 million during the year ended December 31, 2016, from $69.9 million during the year ended December 31, 2015. The increased interest expense, net, was primarily due to full-period recognition during the year ended December 31, 2016 of the interest on higher borrowings to fund the acquisition of Hyperion in May 2015, including our $475.0 million aggregate principal amount of 6.625% Senior Notes due 2023, or the 2023 Senior Notes, six-year $400.0 million term loan facility, or the 2015 Term Loan Facility, and $400.0 million aggregate principal amount of 2.50% Exchangeable Senior Notes due 2022, or the Exchangeable Senior Notes, as compared to partial period recognition of the interest on these borrowings during the year ended December 31, 2015 and our lower prior year borrowings under our prior five-year $300.0 million term loan facility, or 2014 Term Loan Facility. We also incurred additional interest expense following our borrowings to fund the acquisition of Raptor in October 2016, including our additional $375.0 million additional borrowings under the 2015 Term Loan Facility, or the 2016 Incremental Loan Facility, and the 2024 Senior Notes.

Foreign Exchange Loss. During the year ended December 31, 2016, we reported a foreign exchange loss of $1.0 million.

Loss on Induced Conversion of Debt and Debt Extinguishment. The loss on induced conversion of debt and debt extinguishment during the year ended December 31, 2015 of $77.6 million was composed of $20.7 million related to the induced conversions of our 5.00% Convertible Senior Notes due 2018, or Convertible Senior Notes, including $10.0 million for cash inducement payments, a $10.1 million charge for the extinguishment of debt and $0.6 million of expenses, and $56.9 million related to the extinguishment of the 2014 Term Loan Facility, consisting of a $45.4 million early redemption premium and a $11.5 million charge for the extinguishment of debt. The number of shares issued equaled the number of shares based on the underlying conversion option. The aggregate cash payments to the holders for additional exchange consideration were recorded as part of the extinguishment loss. There were no induced conversions in 2016.

Loss on Sale of Long-Term Investments. The loss on sale of long-term investments during the year ended December 31, 2015 was $29.0 million. During the third quarter of 2015, we purchased 2,250,000 shares of common stock of Depomed, Inc., or Depomed, representing 3.75% of Depomed's then outstanding common stock. The shares were acquired at a cost of $71.8 million. During the fourth quarter of 2015, following our decision to withdraw our offer to acquire Depomed, we sold all of our shares in Depomed, receiving sales proceeds of $42.8 million and recognized a realized loss of $29.0 million. There were no sales of long-term investments in 2016.

Other Income (Expense) net. Other income, net during the year ended December 31, 2016 was primarily related to the release of a contingent liability of $6.9 million which was assumed as part of the Crealta acquisition. In December 2015, Crealta considered it probable that the manufacture of the active pharmaceutical ingredient, or API, for KRYSTEXXA would be moved out of Israel based on a notice of termination provided by its contract manufacturer, therefore triggering a repayment obligation to Israel's Office of the Chief Scientist. As a result, Crealta established a $6.9 million contingent liability reserve in its December 31, 2015 financial statements. As of the date of our acquisition of Crealta, the $6.9 million repayment obligation was still probable. Therefore, it was recorded as an assumed liability in "other long-term liabilities" as part of the acquisition accounting for Crealta. During the third quarter of 2016, Horizon management negotiated a new amendment to the manufacturing agreement and it was determined that the manufacture of the KRYSTEXXA API would not be moved outside of Israel and thus the repayment of the $6.9 million would not be triggered. The contingent liability was released to "other income (expense)" during the year ended December 31, 2016 as it was a reversal of an assumed liability and therefore did not represent income from operations. Other expense, net, during the year ended December 31, 2015 totaled $10.3 million, which primarily included the fees related to the Hyperion acquisition financing commitment.

Benefit for Income Taxes. During the year ended December 31, 2016, we recorded an income tax benefit of $61.3 million compared to $172.2 million during the year ended December 31, 2015. The recognition of income tax benefit during the year ended December 31, 2016 was primarily attributable to the mix of income and losses amongst jurisdictions, a notional interest deduction and the change in our U.S. state effective tax rate. The recognition of an income tax benefit during the year ended December 31, 2015 was primarily attributable to the release of $103.1 million in valuation allowances in the U.S. tax consolidation group due to the recognition of significant deferred tax liabilities as a result of the Hyperion acquisition as well as the ability to recognize a tax benefit on losses incurred in the United States.

Year Ended December 31, 2015 Compared to Year Ended December 31, 2014

	For the Years Ended December 31, 2015	2014	Increase / (Decrease)	Change %
	(in thousands)			
Net sales	$ 757,044	$ 296,955	$ 460,089	155%
Cost of goods sold	219,502	78,753	140,749	179%
Gross profit	537,542	218,202	319,340	146%
Operating expenses				
Research and development	41,865	17,460	24,405	140%
Sales and marketing	220,444	120,276	100,168	83%
General and administrative	219,861	88,957	130,904	147%
Total operating expenses	482,170	226,693	255,477	113%
Operating income (loss)	55,372	(8,491)	63,863	752%
Other income (expense), net:				
Interest expense, net	(69,900)	(23,826)	46,074	193%
Foreign exchange loss	(1,237)	(3,905)	(2,668)	(68)%
Loss on derivative fair value	—	(214,995)	(214,995)	(100)%
Loss on induced conversion and debt extinguishment	(77,624)	(29,390)	48,234	164%
Loss on sale of long-term investments	(29,032)	—	29,032	100%
Bargain purchase gain	—	22,171	22,171	100%
Other expense	(10,291)	(11,251)	(960)	(9)%
Total other expense, net	(188,084)	(261,196)	(73,112)	28%
Loss before benefit for income taxes	(132,712)	(269,687)	(136,975)	(51)%
Benefit for income taxes	(172,244)	(6,084)	166,160	2,731%
Net income (loss)	$ 39,532	$ (263,603)	$ 303,135	115%

Net sales. Net sales increased $460.1 million, or 155%, to $757.0 million during the year ended December 31, 2015, from $296.9 million during the year ended December 31, 2014.

The following table presents a summary of total net sales attributed to geographic sources for the years ended December 31, 2015 and 2014 (in thousands):

	Year Ended December 31, 2015		Year Ended December 31, 2014	
	Amount	% of Total Net Sales	Amount	% of Total Net Sales
United States	$ 744,036	98%	$ 290,396	98%
Rest of world	13,008	2%	6,559	2%
Total net sales	$ 757,044		$ 296,955	

The following table reflects the components of net sales for the years ended December 31, 2015 and 2014:

	Year Ended December 31, 2015	2014	Change $	Change %
	(in thousands)			
DUEXIS	$ 190,357	$ 83,243	$ 107,114	129%
VIMOVO	166,672	162,954	3,718	2%
PENNSAID 2%	147,010	-	147,010	*
ACTIMMUNE	107,444	25,251	82,193	326%
RAVICTI	86,875	-	86,875	*
RAYOS	40,329	19,020	21,309	112%
BUPHENYL	13,458	-	13,458	*
LODOTRA	4,899	6,487	(1,588)	(25%)
Total net sales	$ 757,044	$ 296,955	$ 460,089	155%

* Percentage change is not meaningful.

The increase in net sales during the year ended December 31, 2015 was primarily due to the recognition of PENNSAID 2% sales beginning in January 2015 following our acquisition of the U.S. rights to PENNSAID 2% from Nuvo in October 2014, the growth in sales of DUEXIS, the recognition of RAVICTI and BUPHENYL sales following the acquisition of Hyperion in May 2015, full-period recognition of ACTIMMUNE sales during the year ended December 31, 2015 compared with partial-period recognition during the year ended December 31, 2014, following the Vidara Merger on September 19, 2014, and the growth of RAYOS sales.

DUEXIS. Net sales increased $107.1 million, or 129%, to $190.4 million during the year ended December 31, 2015, from $83.3 million during the year ended December 31, 2014. DUEXIS net sales increased $58.0 million as a result of prescription volume growth driven by the expansion of our field sales force and increased $49.1 million due to higher net pricing resulting from wholesale acquisition cost, or WAC, price increases partially offset by additional patient co-pay reimbursements.

VIMOVO. Net sales increased $3.7 million, or 2%, to $166.7 million during the year ended December 31, 2015, from $163.0 million during the year ended December 31, 2014. VIMOVO net sales increased by $23.5 million resulting from prescription volume growth, offset by a decrease of $19.8 million due to lower net pricing. While we have increased the WAC price for VIMOVO over the last 12 months, the increases were more than offset by additional patient co-pay reimbursements.

PENNSAID 2%. Net sales were $147.0 million during the year ended December 31, 2015. We began recognizing PENNSAID 2% sales in January 2015 following our acquisition of the U.S. rights to PENNSAID 2% from Nuvo in October 2014.

ACTIMMUNE. Net sales increased $82.2 million, or 326%, to $107.5 million during the year ended December 31, 2015, from $25.3 million during the year ended December 31, 2014. Net sales increased by approximately $47.1 million resulting from prescription volume growth and $35.1 million due to higher net pricing. We began recognizing ACTIMMUNE sales following the closing of the Vidara Merger on September 19, 2014, therefore only a partial period of ACTIMMUNE sales were recognized during the year ended December 31, 2014, compared with full-period recognition of sales during the year ended December 31, 2015.

RAVICTI. Net sales were $86.9 million during the year ended December 31, 2015. We began recognizing RAVICTI sales following the acquisition of Hyperion in May 2015.

RAYOS. Net sales increased $21.3 million, or 112%, to $40.3 million during the year ended December 31, 2015, from $19.0 million during the year ended December 31, 2014. The increase was primarily due to prescription growth and net price increases resulting in higher net sales of approximately $20.2 million and $1.1 million, respectively.

BUPHENYL. Net sales were $13.5 million during the year ended December 31, 2015. We began recognizing BUPHENYL sales following the acquisition of Hyperion in May 2015.

LODOTRA. Net sales decreased $1.6 million, or 25%, to $4.9 million during the year ended December 31, 2015, from $6.5 million during the year ended December 31, 2014. The decrease was due to fewer shipments to our European distribution partner, Mundipharma. LODOTRA sales to Mundipharma occur at the time we ship, based on Mundipharma's estimated requirements. Accordingly, LODOTRA sales are not linear or directly tied to Mundipharma's in-market sales and can therefore fluctuate significantly.

The table below reconciles our gross sales to net sales for the years ended December 31, 2015 and 2014 (in millions):

	Year Ended December 31, 2015		Year Ended December 31, 2014	
	Amount	% of Gross Sales	Amount	% of Gross Sales
Gross sales	$ 2,057.3	100.0%	$ 600.8	100.0%
Adjustments to gross sales:				
Prompt pay discounts	(41.3)	(2.0)%	(11.0)	(1.8)%
Medicine returns	(14.4)	(0.7)%	(7.2)	(1.2)%
Co-pay and other patient assistance	(1,020.2)	(49.6)%	(138.3)	(23.1)%
Wholesaler fees and commercial rebates	(66.1)	(3.2)%	(102.0)	(17.0)%
Government rebates and chargebacks	(158.3)	(7.7)%	(45.3)	(7.5)%
Total adjustments	(1,300.3)	(63.2)%	(303.8)	(50.6)%
Net sales	$ 757.0	36.8%	$ 297.0	49.4%

During the year ended December 31, 2015, co-pay and other patient assistance, as a percentage of gross sales, increased to 49.6% from 23.1% during the year ended December 31, 2014. The increase was primarily due to the rollout of our HorizonCares program to all sales territories during 2015 which helped ensure patient access to our medicines in the face of exclusionary actions by certain PBMs. During the year ended December 31, 2015, wholesaler fees and commercial rebates, as a percentage of gross sales, decreased to 3.2% from 17.0% during the year ended December 31, 2014, primarily due to a decrease in our managed care rebates following the termination of our agreements with CVS Caremark and Express Scripts in 2014.

Effective January 1, 2015, two significant PBMs placed DUEXIS and VIMOVO on their exclusion lists, which resulted in a loss of reimbursement for patients whose healthcare plans have adopted these PBM exclusion lists. However, this action did not negatively impact sales volume for either medicine. In fact, with successful adoption of our HorizonCares program by physicians, we saw increases in sales volume for both medicines. During the year ended December 31, 2015, DUEXIS sales volumes increased by 70% and VIMOVO sales volumes increased by 14%, each, when compared to the year ended December 31, 2014.

Cost of Goods Sold. Cost of goods sold increased $140.7 million to $219.5 million during the year ended December 31, 2015, from $78.8 million during the year ended December 31, 2014. As a percentage of net sales, cost of goods sold was 29.0% during the year ended December 31, 2015 compared to 26.5% during the year ended December 31, 2014. The increase in cost of goods sold was primarily attributable to an increase in intangible amortization expense of $100.0 million, a $19.1 million increase in medicine costs associated with higher sales, higher royalty accretion expense of $11.1 million and a $10.5 million increase in charges relating to the remeasurement of contingent royalty liabilities.

The increase in intangible amortization of $100.0 million during the year ended December 31, 2015 compared to the prior year was primarily due to increases in intangible amortization expense of $62.2 million in relation to RAVICTI and BUPHENYL (acquired on May 7, 2015), $31.1 million relating to ACTIMMUNE developed technology (acquired on September 19, 2014) and $7.3 million relating to PENNSAID 2% (U.S. rights acquired in October 2014).

Research and Development Expenses. Research and development expenses increased $24.4 million to $41.9 million during the year ended December 31, 2015, from $17.5 million during the year ended December 31, 2014. The increase in research and development expenses during the year ended December 31, 2015 was primarily associated with $17.1 million in research and development expenses for ACTIMMUNE, RAVICTI and BUPHENYL, which included $4.0 million related to the STEADFAST study. We also recorded an increase of $5.1 million in share-based compensation expense during the year ended December 31, 2015 compared to the year ended December 31, 2014 as a result of the increase in the number of employees involved in research and development activities following the Vidara Merger and Hyperion acquisition.

Sales and Marketing Expenses. Sales and marketing expenses increased $100.1 million to $220.4 million during the year ended December 31, 2015, from $120.3 million during the year ended December 31, 2014. The increase in sales and marketing expenses reflects the growth in revenue and increase in the number of sales representatives over the same period, and was primarily attributable to an increase of $58.5 million in employee costs, including $18.9 million related to share-based compensation, resulting from the increased staffing of our field sales force and the expansion of our HorizonCares support team. We also recorded an increase of $22.0 million in marketing and commercialization expenses and an increase of $6.8 million in medicine samples distributed.

General and Administrative Expenses. General and administrative expenses increased $130.9 million to $219.9 million during the year ended December 31, 2015, from $89.0 million during the year ended December 31, 2014. The increase in general and administrative expenses was primarily attributable to an increase of $48.6 million in share-based compensation expense, $18.4 million in acquisition-related general and administrative expenses, and $63.9 million related to our growth in headcount, facilities, finance fees, legal fees and information technology expenses following the Vidara Merger and Hyperion acquisition.

Interest Expense, Net. Interest expense, net, increased $46.1 million to $69.9 million during the year ended December 31, 2015, from $23.8 million during the year ended December 31, 2014. The increased interest expense, net, was due to a full year of interest expense in 2015 on borrowings to fund the Vidara Merger in September 2014 and interest on additional borrowings to partially fund the acquisition of Hyperion in May 2015, including the 2023 Senior Notes, the 2015 Term Loan Facility, and the Exchangeable Senior Notes, as compared to our prior year borrowings under the Convertible Senior Notes and 2014 Term Loan Facility.

Foreign Exchange Loss. During the year ended December 31, 2015, we reported a foreign exchange loss of $1.2 million.

Loss on Derivative Revaluation. During the year ended December 31, 2014, we recorded a $215.0 million non-cash charge related to the increase in the fair value of the embedded derivative associated with our Convertible Senior Notes. The loss on the derivative revaluation was primarily due to an increase in the market value of HPI's common stock during the period from January 1, 2014 until June 27, 2014, the date HPI's stockholders approved the issuance of in excess of 13,164,951 shares of HPI's common stock upon conversion of the Convertible Senior Notes. The derivative liability was re-measured to a final fair value and the entire fair value of the derivative liability of $324.4 million was reclassified to additional paid-in capital. As such, there was no derivative revaluation subsequent to June 2014.

Loss on Induced Conversion of Debt and Debt Extinguishment. The loss on induced conversion of debt and debt extinguishment during the year ended December 31, 2015 of $77.6 million was composed of $20.7 million related to the induced conversions of Convertible Senior Notes, including $10.0 million for cash inducement payments, a $10.1 million charge for the extinguishment of debt and $0.6 million of expenses, and $56.9 million related to the extinguishment of the 2014 Term Loan Facility, consisting of a $45.4 million early redemption premium and a $11.5 million charge for the extinguishment of debt. The loss on induced conversion and debt extinguishment during the year ended December 31, 2014 of $29.4 million was a result of the Convertible Senior Notes induced conversions in the fourth quarter of 2014, which consisted of $16.7 million of loss on induced conversion for cash inducement payments, a $11.7 million charge for the extinguishment of debt and $1.0 million of expenses related to the induced debt conversions. The number of shares issued equaled the number of shares based on the underlying conversion option. The aggregate cash payments to the holders for additional exchange consideration were recorded as part of the extinguishment loss.

Loss on Sale of Long-Term Investments. The loss on sale of long-term investments during the year ended December 31, 2015 was $29.0 million. During the third quarter of 2015, we purchased 2,250,000 shares of common stock of Depomed, representing 3.75% of Depomed's then outstanding common stock. The shares were acquired at a cost of $71.8 million. During the fourth quarter of 2015, following our decision to withdraw our offer to acquire Depomed, we sold all of our shares in Depomed, receiving sales proceeds of $42.8 million and recognized a realized loss of $29.0 million in the consolidated statement of comprehensive income.

Bargain Purchase Gain. During the year ended December 31, 2014, we recorded a bargain purchase gain of $22.2 million in connection with the Vidara Merger, representing the excess of the estimated fair values of net assets acquired over the acquisition consideration paid.

Other Expense, net. Other expense, net, during the year ended December 31, 2015 totaled $10.3 million, which primarily included the fees related to the Hyperion acquisition financing commitment. Other expense during the year ended December 31, 2014 totaled $11.3 million, representing $5.0 million of commitment fees incurred on the bridge financing in place prior to executing the 2014 Term Loan Facility in June 2014, $3.2 million of commitment fees incurred on the 2014 Term Loan Facility prior to its funding on September 19, 2014 and $2.9 million secondary offering expense fees incurred in the November 2014 underwritten public offering.

Benefit for Income Taxes. During the year ended December 31, 2015, we recorded an income tax benefit of $172.2 million compared to $6.1 million during the year ended December 31, 2014. The recognition of income tax benefit during the year ended December 31, 2015 was primarily attributable to the release of $103.1 million in valuation allowances in the U.S. tax consolidation group due to the recognition of significant deferred tax liabilities as a result of the Hyperion acquisition as well as the ability to recognize a tax benefit on losses incurred in the United States.

Non-GAAP Financial Measures

EBITDA, or earnings before interest, taxes, depreciation and amortization, and adjusted EBITDA are used and provided by us as non-GAAP financial measures. We provide certain other financial measures such as non-GAAP adjusted net sales, non-GAAP net income and non-GAAP earnings per share which include adjustments to GAAP figures. The exclusion of the $65.0 million litigation settlement from GAAP net sales is the only adjustment reflected in non-GAAP adjusted net sales for the year ended December 31, 2016. Adjusted EBITDA and non-GAAP net income are intended to provide additional information on our performance, operations and profitability. Adjustments to our GAAP figures as well as EBITDA exclude acquisition-related expenses, charges related to the discontinuation of ACTIMMUNE development for FA, an upfront fee for a license of a patent, the Express Scripts litigation settlement amount, loss on debt extinguishment and loss on sale of long-term investments, as well as non-cash items such as share-based compensation, inventory step-up expense, depreciation and amortization, remeasurement of royalties for medicines acquired through business combinations, royalty accretion, non-cash interest expense, the reversal of a pre-acquisition reserve upon the signing of a contract, intangible and other non-current asset impairment charges and other non-cash adjustments. Certain other special items or substantive events may also be included in the non-GAAP adjustments periodically when their magnitude is significant within the periods incurred. We maintain an established non-GAAP cost policy that guides the determination of what costs will be excluded in non-GAAP measures. We believe that these non-GAAP financial measures, when considered together with the GAAP figures, can enhance an overall understanding of our financial and operating performance. The non-GAAP financial measures are included with the intent of providing investors with a more complete understanding of our historical financial results and trends and to facilitate comparisons between periods and with respect to projected information. In addition, these non-GAAP financial measures are among the indicators our management uses for planning and forecasting purposes and measuring our performance. For example, adjusted EBITDA is used by us as one measure of management performance under certain incentive compensation arrangements. These non-GAAP financial measures should be considered in addition to, and not as a substitute for, or superior to, financial measures calculated in accordance with GAAP. The non-GAAP financial measures used by us may be calculated differently from, and therefore may not be comparable to, non-GAAP financial measures used by other companies.

Beginning in the second quarter of 2016, we modified the method of calculating non-GAAP income tax expense to align with guidance issued by the Securities and Exchange Commission on May 17, 2016. The new methodology calculates the income tax component of non-GAAP net income for each period by adjusting the GAAP tax expense (benefit) for the estimated tax impact of each non-GAAP adjustment based on the statutory income tax rate of the applicable jurisdictions for each non-GAAP adjustment. This new methodology does not reflect any use of net operating loss carryforwards that we potentially may have been able to use if our actual earnings for these periods had been the non-GAAP net income. Previously, we had calculated the income tax component of non-GAAP net income by using the estimated cash taxes that we expected to pay for the period. The non-GAAP net income and diluted net income per share amounts shown in the GAAP to non-GAAP reconciliation tables below are based on the new methodology.

Reconciliations of reported GAAP net sales to non-GAAP adjusted net sales, reported GAAP net (loss) income to EBITDA, adjusted EBITDA and non-GAAP net income, and the related per share amounts, are as follows (in thousands, except share and per share amounts):

	For the Years Ended December 31,		
	2016	2015	2014
GAAP Net Sales	**$ 981,120**	**$ 757,044**	**$ 296,955**
Litigation settlement	65,000	-	-
Non-GAAP Adjusted Net Sales	**$ 1,046,120**	**$ 757,044**	**$ 296,955**

	For the Years Ended December 31,		
	2016	2015	2014
GAAP Net (Loss) Income	**$ (166,834)**	**$ 39,532**	**$ (263,603)**
Non-GAAP adjustments:			
Remeasurement of royalties for medicines acquired through business combinations (1)	386	21,151	10,660
Acquisition-related costs	52,874	72,221	48,835
Upfront fee for license of global patent	2,000	—	—
Loss on sale of long-term investments	—	29,032	—
Loss on derivative revaluation	—	—	214,995
Loss on induced conversion of debt and debt extinguishment	—	77,624	29,390
Bargain purchase gain	—	—	(22,171)
Secondary offering costs	—	—	2,857
Amortization, accretion and step-up:			
Intangible amortization expense	216,875	132,923	32,306
Amortization of debt discount and deferred financing costs	18,546	18,810	9,273
Accretion of royalty liabilities	40,616	20,088	9,020
Inventory step-up expense	71,137	11,495	11,065
Share-based compensation	114,144	85,786	13,198
Depreciation expense	4,962	5,420	1,702
Litigation settlement	65,000	—	—
Reversal of pre-acquisition reserve upon signing of contract	(6,900)	—	—
Impairment of in-process research and development	66,000	—	—
Charges relating to discontinuation of Friedreich's ataxia program (2)	23,513	—	—
Royalties for medicines acquired through business combinations (1)	(37,593)	(29,834)	(18,264)
Total of pre-tax non-GAAP adjustments	631,560	444,716	342,866
Income tax effect of pre-tax non-GAAP adjustments (3)	(110,290)	(122,214)	(76)
Other non-GAAP income tax adjustments (4)	—	(105,133)	—
Total of non-GAAP adjustments	521,270	217,369	342,790
Non-GAAP Net Income	**354,436**	**256,901**	**79,187**
Non-GAAP Earnings Per Share:			
Weighted average ordinary shares – Basic	**160,699,543**	**148,788,020**	**83,751,129**
Non-GAAP Earnings Per Share – Basic			
GAAP (loss) earnings per share - Basic	**$ (1.04)**	**$ 0.27**	**$ (3.15)**
Non-GAAP adjustments	3.25	1.46	4.10
Non-GAAP earnings per share – Basic	**$ 2.21**	**$ 1.73**	**$ 0.95**
Weighted average ordinary shares – Diluted			
Weighted average ordinary shares – Basic	160,699,543	148,788,020	83,751,129
Ordinary share equivalents	3,626,570	7,135,231	20,737,726
Weighted average ordinary shares – Diluted	**164,326,113**	**155,923,251**	**104,488,855**
Non-GAAP Earnings Per Share – Diluted			
GAAP (loss) earnings per share – Diluted	**$ (1.04)**	**$ 0.25**	**(3.15)**
Non-GAAP adjustments	3.25	1.40	4.10
Diluted earnings per share effect of ordinary share equivalents	(0.05)	—	(0.19)
Non-GAAP earnings per share – Diluted	**$ 2.16**	**$ 1.65**	**$ 0.76**

	For the Years Ended December 31,		
	2016	2015	2014
GAAP Net (Loss) Income	**$ (166,834)**	**$ 39,532**	**$ (263,603)**
Depreciation	4,962	5,420	1,702
Amortization, accretion and step-up:			
Intangible amortization expense	216,875	132,923	32,306
Amortization of deferred revenue	(836)	(962)	(644)
Accretion of royalty liabilities	40,616	20,088	9,020
Inventory step-up expense	71,137	11,495	11,065
Interest expense, net (including amortization of debt discount and deferred financing costs)	86,610	69,900	23,826
Benefit for income taxes	(61,251)	(172,244)	(6,084)
EBITDA	**191,279**	**106,152**	**(192,412)**
Non-GAAP adjustments:			
Remeasurement of royalties for medicines acquired through business combinations (1)	386	21,151	10,660
Acquisition-related costs	52,874	72,221	48,835
Upfront fee for license of global patent	2,000	—	—
Impairment of in-process research and development	66,000	—	—
Charges relating to discontinuation of Friedreich's ataxia program (2)	23,513	—	—
Share-based compensation	114,144	85,786	13,198
Royalties for medicines acquired through business combinations (1)	(37,593)	(29,834)	(18,264)
Litigation settlement	65,000	—	—
Reversal of pre-acquisition reserve upon signing of contract	(6,900)	—	—
Loss on sale of long-term investments	—	29,032	—
Loss on derivative revaluation	—	—	214,995
Loss on induced conversion of debt and debt extinguishment	—	77,624	29,390
Bargain purchase gain	—	—	(22,171)
Secondary offering costs	—	—	2,857
Total of non-GAAP adjustments	279,424	255,980	279,500
Adjusted EBITDA	**$ 470,703**	**$ 362,132**	**$ 87,088**

(1) Royalties for medicines acquired through business combinations relate to ACTIMMUNE, BUPHENYL, KRYSTEXXA, MIGERGOT, PROCYSBI, RAVICTI and VIMOVO.

(2) Charges relating to the discontinuation of the STEADFAST program include a $14.3 million loss on inventory purchase commitments, a $5.3 million impairment of a non-current asset and $4.0 million of clinical trial wind-down costs.

(3) Adjustment to the GAAP tax (benefit) expense for the estimated tax impact of each non-GAAP adjustment based on the statutory tax rate of the applicable jurisdictions for each non-GAAP adjustment.

(4) Other non-GAAP income tax adjustments in the year ended December 31, 2015 of $105.1 million related to the release of certain valuation allowances in connection with the Hyperion acquisition.

Liquidity, Financial Position and Capital Resources

We have incurred losses since our inception in June 2005 and, as of December 31, 2016, we had an accumulated deficit of $848.0 million. We expect that our sales and marketing expenses will continue to increase as a result of our commercialization of our medicines, but we believe these cost increases will be more than offset by higher net sales and gross profits. We incurred an operating loss in 2016 primarily as a result of significant charges following the FA announcement in the fourth quarter of 2016, the litigation settlement with Express Scripts in September 2016 and costs incurred in connection with our acquisitions of Crealta and Raptor during the year. We expect our current operations to achieve operating profitability in 2017, absent unusual or non-recurring items.

We have financed our operations to date through equity financings, debt financings and the issuance of convertible notes, along with cash flows from operations during past three years. As of December 31, 2016, we had $509.1 million in cash and cash equivalents and total debt with a book value of $1,807.5 million and face value of $1,944.0 million. We believe our existing cash and cash equivalents and our expected cash flows from our operations will be sufficient to fund our business needs for the foreseeable future. Part of our strategy is to expand and leverage our commercial capabilities by identifying, developing, acquiring and commercializing differentiated and accessible medicines that address unmet medical needs. To the extent we enter into transactions to acquire medicines or businesses in the future, we will most likely need to finance a significant portion of those acquisitions through additional debt, equity or convertible debt financings.

In March 2015, April 2015 and June 2015, we entered into separate, privately negotiated conversion agreements with certain holders of the Convertible Senior Notes which were on substantially the same terms as prior conversion agreements entered into by us. Under these conversion agreements, the applicable holders agreed to convert an aggregate principal amount of $61.0 million of Convertible Senior Notes held by them and we agreed to settle such conversions by issuing an aggregate of 11,368,921 ordinary shares. In addition, pursuant to such conversion agreements, we made an aggregate cash payment of $10.0 million to the applicable holders for additional exchange consideration and $0.9 million for accrued and unpaid interest. Following these conversions, there were no Convertible Senior Notes remaining outstanding. The number of shares issued equaled the number of shares based on the underlying conversion option. The aggregate cash payments to the holders for additional exchange consideration were recorded as part of the extinguishment loss.

On March 13, 2015, Horizon Pharma Investment Limited, a wholly owned subsidiary of Horizon Pharma plc, or Horizon Investment, completed a private placement of $400.0 million aggregate principal amount of Exchangeable Senior Notes to several investment banks acting as initial purchasers who subsequently resold the Exchangeable Senior Notes to qualified institutional buyers as defined in Rule 144A under the Securities Act of 1933, as amended, or the Securities Act. The net proceeds from the offering of the Exchangeable Senior Notes were approximately $387.2 million, after deducting the initial purchasers' discount and offering expenses payable by Horizon Investment.

We have fully and unconditionally guaranteed the Exchangeable Senior Notes on a senior unsecured basis, referred to as the Guarantee. The Exchangeable Senior Notes and the Guarantee are Horizon Investment's and our senior unsecured obligations. The Exchangeable Senior Notes accrue interest at an annual rate of 2.50% payable semiannually in arrears on March 15 and September 15 of each year, beginning on September 15, 2015. The Exchangeable Senior Notes will mature on March 15, 2022, unless earlier exchanged, repurchased or redeemed. The initial exchange rate is 34.8979 of our ordinary shares per $1,000 principal amount of the Exchangeable Senior Notes (equivalent to an initial exchange price of approximately $28.66 per ordinary share).

On April 21, 2015, we closed an underwritten public offering of 17,652,500 of our ordinary shares at a price to the public of $28.25 per share, referred to as the 2015 Offering. The net proceeds to us from the 2015 Offering were approximately $475.7 million, after deducting underwriting discounts and other offering expenses payable by us.

On April 29, 2015, Horizon Pharma Financing Inc., our then wholly owned subsidiary, or Horizon Financing, completed a private placement of $475.0 million aggregate principal amount of 2023 Senior Notes to certain investment banks acting as initial purchasers who subsequently resold the 2023 Senior Notes to qualified institutional buyers as defined in Rule 144A under the Securities Act and in offshore transactions to non-U.S. Persons in reliance on Regulation S under the Securities Act. The net proceeds from the 2023 Senior Notes were approximately $462.3 million.

In connection with the closing of the Hyperion acquisition on May 7, 2015, Horizon Financing merged with and into HPI and, as a result, the 2023 Senior Notes became HPI's general unsecured senior obligations and we and all of our direct and indirect subsidiaries that are guarantors under the 2015 Senior Secured Credit Facility (as described below) fully and unconditionally guaranteed on a senior unsecured basis HPI's obligations under the 2023 Senior Notes.

The 2023 Senior Notes accrue interest at an annual rate of 6.625% payable semiannually in arrears on May 1 and November 1 of each year, beginning on November 1, 2015. The 2023 Senior Notes will mature on May 1, 2023, unless earlier exchanged, repurchased or redeemed.

Except as described below, the 2023 Senior Notes may not be redeemed before May 1, 2018. Thereafter, some or all of the 2023 Senior Notes may be redeemed at any time at specified redemption prices, plus accrued and unpaid interest to the redemption date. At any time prior to May 1, 2018, some or all of the 2023 Senior Notes may be redeemed at a price equal to 100% of the aggregate principal amount thereof, plus a make-whole premium and accrued and unpaid interest to, but not including the redemption date. Also prior to May 1, 2018, up to 35% of the aggregate principal amount of the 2023 Senior Notes may be redeemed at a redemption price of 106.625% of the aggregate principal amount thereof, plus accrued and unpaid interest, with the net proceeds of certain equity offerings; provided that: (1) at least 65% of the aggregate principal amount of notes originally issued under the indenture (excluding notes held by the parent and its subsidiaries) remains outstanding immediately after the occurrence of such redemption; and (2) the redemption occurs with 180 days of the date of closing such equity offering. In addition, the 2023 Senior Notes may be redeemed in whole but not in part at a redemption price equal to 100% of the principal amount plus accrued and unpaid interest and additional amounts, if any, to, but excluding, the redemption date, if on the next date on which any amount would be payable in respect of the 2023 Senior Notes, HPI or any guarantor is or would be required to pay additional amounts as a result of certain tax related events.

If we undergo a change of control, HPI will be required to make an offer to purchase all of the 2023 Senior Notes at a price in cash equal to 101% of the aggregate principal amount thereof plus accrued and unpaid interest to, but not including, the repurchase date. If we or certain of our subsidiaries engage in certain asset sales, HPI will be required under certain circumstances to make an offer to purchase the 2023 Senior Notes at 100% of the principal amount thereof, plus accrued and unpaid interest to the repurchase date.

On May 7, 2015, we, HPI, and certain of our subsidiaries entered into a credit agreement with Citibank N.A., as administrative agent and collateral agent, and the lenders from time to time party thereto, or, as amended, the credit agreement, providing for (i) the six-year $400.0 million 2015 Term Loan Facility; (ii) an uncommitted accordion facility subject to the satisfaction of certain financial and other conditions; and (iii) one or more uncommitted refinancing loan facilities with respect to loans thereunder. This is referred to as the 2015 Senior Secured Credit Facility. The initial borrower under the 2015 Term Loan Facility is HPI. The credit agreement allows for us and certain of our other subsidiaries to become borrowers under the accordion or refinancing facilities. Loans under the 2015 Term Loan Facility bear interest, at each borrower's option, at a rate equal to either the London Inter-Bank Offer Rate, or LIBOR, plus an applicable margin of 4.0% per year (subject to a 1.0% LIBOR floor), or the adjusted base rate plus 3.0%. The adjusted base rate is defined as the greater of (a) LIBOR (using one-month interest period) plus 1.0%, (b) prime rate, (c) fed funds plus ½ of 1% and (d) 2.0%. We borrowed the full $400.0 million available under the 2015 Term Loan Facility on May 7, 2015 as a LIBOR-based borrowing. The net proceeds from the 2015 Term Loan Facility were approximately $391.5 million.

The obligations under the credit agreement and any swap obligations and cash management obligations owing to a lender (or an affiliate of a lender) thereunder are and will be guaranteed by our and each of our existing and subsequently acquired or organized direct and indirect subsidiaries (other than certain immaterial subsidiaries, subsidiaries whose guarantee would result in material adverse tax consequences and subsidiaries whose guarantee is prohibited by applicable law). The obligations under the credit agreement and any such swap and cash management obligations are secured, subject to customary permitted liens and other agreed upon exceptions, by a perfected security interest in (i) all tangible and intangible assets of the borrowers and the guarantors, except for certain customary excluded assets, and (ii) all of the capital stock owned by the borrowers and guarantors thereunder (limited, in the case of the stock of certain non-U.S. subsidiaries of the borrowers, to 65% of the capital stock of such subsidiaries).

We are permitted to make voluntary prepayments at any time without payment of a premium. We are required to make mandatory prepayments of loans under the 2015 Term Loan Facility (without payment of a premium) with (a) net cash proceeds from certain non-ordinary course asset sales (subject to reinvestment rights and other exceptions), (b) casualty proceeds and condemnation awards (subject to reinvestment rights and other exceptions), (c) net cash proceeds from issuances of debt (other than certain permitted debt), and (d) beginning with the fiscal year ending December 31, 2016, 50% of our excess cash flow (subject to decrease to 25% or 0% if our first lien leverage ratio is less than 2.25:1 and 1.75:1, respectively). The loans under the 2015 Term Loan Facility will amortize in equal quarterly installments in an aggregate annual amount equal to 1% of the original principal amount thereof, with any remaining balance payable on the final maturity date of the loans under the 2015 Term Loan Facility.

We used the net proceeds from the 2015 Offering, the offering of the 2023 Senior Notes, borrowings under the 2015 Term Loan Facility and existing cash to fund our acquisition of Hyperion, repay the $300.0 million outstanding amounts under the 2014 Term Loan Facility plus the related $45.4 million make-whole fee, and pay prepayment premiums, fees and expenses in connection with the foregoing.

On October 25, 2016, HPI and Horizon Pharma USA, Inc., our wholly owned subsidiary, or HPUSA, and, together with HPI, the 2024 Issuers, completed a private placement of $300.0 million aggregate principal amount of 2024 Senior Notes to certain investment banks acting as initial purchasers who subsequently resold the 2024 Senior Notes to qualified institutional buyers as defined in Rule 144A under the Securities Act.

The 2024 Senior Notes are the 2024 Issuers' general unsecured senior obligations and we and all of our direct and indirect subsidiaries that are guarantors under the 2015 Senior Secured Credit Facility and the 2016 Incremental Loan Facility fully and unconditionally guaranteed on a senior unsecured basis the 2024 Issuers' obligations under the 2024 Senior Notes.

The 2024 Senior Notes accrue interest at an annual rate of 8.75% payable semiannually in arrears on May 1 and November 1 of each year, beginning on May 1, 2017. The 2024 Senior Notes will mature on November 1, 2024, unless earlier exchanged, repurchased or redeemed.

Except as described below, the 2024 Senior Notes may not be redeemed before November 1, 2019. Thereafter, some or all of the 2024 Senior Notes may be redeemed at any time at specified redemption prices, plus accrued and unpaid interest to the redemption date. At any time prior to November 1, 2019, some or all of the 2024 Senior Notes may be redeemed at a price equal to 100% of the aggregate principal amount thereof, plus a make-whole premium and accrued and unpaid interest to the redemption date. Also prior to November 1, 2019, up to 35% of the aggregate principal amount of the 2024 Senior Notes may be redeemed at a redemption price of 108.75% of the aggregate principal amount thereof, plus accrued and unpaid interest, with the net proceeds of certain equity offerings. In addition, the 2024 Senior Notes may be redeemed in whole but not in part at a redemption price equal to 100% of the principal amount plus accrued and unpaid interest and additional amounts, if any, to, but excluding, the redemption date, if on the next date on which any amount would be payable in respect of the 2024 Senior Notes, the 2024 Issuers or any guarantor is or would be required to pay additional amounts as a result of certain tax-related events.

If we undergo a change of control, the 2024 Issuers will be required to make an offer to purchase all of the 2024 Senior Notes at a price in cash equal to 101% of the aggregate principal amount thereof plus accrued and unpaid interest to, but not including, the repurchase date. If we or certain of our subsidiaries engage in certain asset sales, the 2024 Issuers will be required under certain circumstances to make an offer to purchase the 2024 Senior Notes at 100% of the principal amount thereof, plus accrued and unpaid interest to the repurchase date.

On October 25, 2016, HPI and HPUSA, together, in such capacity, the Incremental Borrowers, entered into an amendment to the credit agreement, or the 2016 Amendment, with Citibank, N.A., as administrative and collateral agent, and Bank of America, N.A., as the incremental B-1 lender thereunder, pursuant to which the Incremental Borrowers borrowed $375.0 million aggregate principal amount of loans under the 2016 Incremental Loan Facility. The 2016 Incremental Loan Facility was incurred as a separate class of term loans under the credit agreement with the same terms of loans under the 2015 Term Loan Facility, except as described below.

Loans under the 2016 Incremental Loan Facility bear interest, at each Incremental Borrowers' option, at a rate equal to either LIBOR plus an applicable margin of 4.50% per year (subject to a LIBOR floor of 1.0%), or the adjusted base rate plus 3.50%. The terms of the loans under the 2015 Term Loan Facility, or the 2015 Loans, provided for an amendment such that the effective yield of the 2015 Loans would not be less than the effective yield of the loans under the 2016 Incremental Loan Facility, or the 2016 Incremental Loans, minus 0.50%. Consequently, the issuance of the 2016 Incremental Loans resulted in an increase of the interest rate applicable to the 2015 Loans, as of October 25, 2016, to LIBOR plus 4.00%, subject to a LIBOR floor of 1.0% (an initial interest rate of 5.00%). Borrowers under the credit agreement are permitted to make voluntary prepayments of the loans under the credit agreement at any time without payment of a premium, except that with respect to the 2016 Incremental Loans, a 1% premium will apply to a repayment of the 2016 Incremental Loans in connection with a re-pricing of, or any amendment to the credit agreement in a re-pricing of, such loans effected on or prior to the date that is twelve months following October 25, 2016.

We used the net proceeds of the offering of the 2024 Senior Notes, borrowings under the 2016 Incremental Loan Facility and existing cash to fund our acquisition of Raptor, plus the related fees and expenses in connection with the foregoing.

We have a significant amount of debt outstanding on a consolidated basis. This substantial level of debt could have important consequences to our business, including, but not limited to: making it more difficult for us to satisfy our obligations; requiring a substantial portion of our cash flows from operations to be dedicated to the payment of principal and interest on our indebtedness, therefore reducing our ability to use our cash flows to fund acquisitions, capital expenditures, and future business opportunities; limiting our ability to obtain additional financing, including borrowing additional funds; increasing our vulnerability to, and reducing our flexibility to respond to, general adverse economic and industry conditions; limiting our flexibility in planning for, or reacting to, changes in our business and the industry in which we operate; and placing us at a disadvantage as compared to our competitors, to the extent that they are not as highly leveraged. We may not be able to generate sufficient cash to service all of our indebtedness and may be forced to take other actions to satisfy our obligations under our indebtedness.

In addition, the indentures governing the 2024 Senior Notes and 2023 Senior Notes and the credit agreement related to the 2015 Senior Secured Credit Facility and 2016 Incremental Loan Facility impose various covenants that limit our ability and/or our restricted subsidiaries' ability to, among other things, pay dividends or distributions, repurchase equity, prepay junior debt and make certain investments, incur additional debt and issue certain preferred stock, incur liens on assets, engage in certain asset sales or merger transactions, enter into transactions with affiliates, designate subsidiaries as unrestricted subsidiaries; and allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to us.

During the year ended December 31, 2016, we issued an aggregate of:

- 666,984 ordinary shares in net settlement of vested restricted stock units;
- 581,840 ordinary shares in connection with the exercise of stock options and received $3.9 million in proceeds;
- 513,659 ordinary shares pursuant to employee stock purchase plans and received $6.5 million in proceeds; and
- 13,584 ordinary shares in net settlement of vested performance stock units.

During the year ended December 31, 2016, we issued an aggregate of 1,750 ordinary shares upon the cash exercise of warrants and we received proceeds of $8,000 representing the aggregate exercise price for such warrants. In addition, warrants to purchase an aggregate of 207,110 of our ordinary shares were exercised in cashless exercises, resulting in the issuance of 161,259 ordinary shares. As of December 31, 2016, there were outstanding warrants to purchase 1,372,660 of our ordinary shares.

During the year ended December 31, 2016, we made payments of $5.5 million for employee withholding taxes relating to share-based awards.

In May 2016, our board of directors authorized a share repurchase program pursuant to which we may repurchase up to 5,000,000 of our ordinary shares. The timing and amount of repurchases, including whether we decide to repurchase any shares pursuant to the authorization, will depend on a variety of factors, including the price of our ordinary shares, alternative investment opportunities, our cash resources, restrictions under our credit agreement, and market conditions. As of December 31, 2016, we had not purchased any of our ordinary shares under this repurchase program.

Sources and Uses of Cash

The following table provides a summary of our cash position and cash flows for the years ended December 31, 2016, 2015 and 2014 (in thousands):

	For the Years Ended December 31,		
	2016	2015	2014
Cash and cash equivalents	$ 509,055	$ 859,616	$ 218,807
Cash provided by (used in):			
Operating activities	369,456	194,166	27,549
Investing activities	(1,375,881)	(995,048)	(227,720)
Financing activities	657,074	1,442,481	338,285

Net Cash Provided by Operating Activities

During the years ended December 31, 2016, 2015 and 2014, net cash provided by operating activities was $369.5 million, $194.2 million and $27.5 million, respectively.

The increase in net cash provided by operating activities during 2016 was primarily attributable to higher cash collections from accounts receivable balances as a result of an increase in sales of medicines, partially offset by cash outlays for patient access programs, contractual allowances and government rebates and chargebacks and $32.5 million outlay for fifty percent of the litigation settlement amount with Express Scripts. Net cash provided by operating activities was also negatively impacted during the year ended December 31, 2016 due to cash payments of $48.9 million for acquisition-related expenses and $60.8 million for interest payments made on our 2015 Term Loan Facility, 2016 Incremental Loan Facility, 2023 Senior Notes and Exchangeable Senior Notes.

Net cash provided by operating activities during 2015 was primarily attributable to cash collections from net sales. Cash provided by operating activities was negatively impacted during the year ended December 31, 2015 due to cash payments of $68.2 million for acquisition-related expenses, including the payment in April 2015 of approximately $11.2 million of employee and director excise taxes due to the Vidara Merger. Cash payments during the year ended December 31, 2015 also included a $45.4 million early redemption premium related to the 2014 Term Loan Facility, $42.0 million of interest payments made on our 2014 Term Loan Facility, 2015 Term Loan Facility, 2023 Senior Notes and Exchangeable Senior Notes, and $10.0 million of cash payments related to induced debt conversions.

Net cash provided by operating activities during 2014 was primarily attributable to cash collections from net sales, partially offset by cash outlays for related expenses. Cash provided by operating activities during 2014 was negatively impacted by $48.9 million in transaction costs related to the Vidara Merger, $2.9 million relating to the secondary offering of ordinary shares by certain stockholders in November 2014, and $16.7 million of cash payments related to induced debt conversions.

Net Cash Used in Investing Activities

During the years ended December 31, 2016, 2015 and 2014, net cash used in investing activities was $1,375.9 million, $995.0 million and $227.7 million, respectively.

Net cash used in investing activities during 2016 was primarily related to $835.9 million of payments for the acquisition of Raptor, net of cash acquired, $514.8 million of payments for the acquisition of Crealta, net of cash acquired, a $5.6 million (€5.0 million) initial payment for certain non-U.S. intellectual property rights to interferon gamma-1b and $15.7 million of payments for purchases of property and equipment.

Net cash used in investing activities during 2015 was primarily associated with $1,022.4 million of payments for the acquisition of Hyperion, net of cash acquired, and payments of $71.8 million made in relation to the purchase of 2,250,000 shares of common stock of Depomed. This was offset by proceeds of $42.8 million from the sale of such Depomed shares and proceeds from the liquidation of available-for-sale investments of $64.6 million.

Net cash used in investing activities during 2014 was primarily associated with the net cash paid for the Vidara Merger of $179.2 million and the acquisition of PENNSAID 2% of $45.0 million.

Net Cash Provided by Financing Activities

During the years ended December 31, 2016, 2015 and 2014, net cash provided by financing activities was $657.1 million, $1,442.5 million and $338.3 million, respectively.

Net cash provided by financing activities during 2016 was primarily related to $364.3 million of net proceeds received from borrowings under our 2016 Incremental Loan Facility and $291.9 million of net proceeds received from borrowings under our 2024 Senior Notes.

Net cash provided by financing activities during 2015 was primarily attributable to $387.2 million of net proceeds received from borrowings under the Exchangeable Senior Notes, $391.5 million net proceeds from the 2015 Term Loan Facility, $462.3 million net proceeds from the 2023 Senior Notes and $475.7 million of net proceeds from the issuance of 17,652,500 ordinary shares in the 2015 Offering, partially offset by the repayment of the 2014 Term Loan Facility and a partial repayment of the 2015 Term Loan Facility, which resulted in a financing outflow of $299.0 million.

Net cash provided by financing activities during 2014 was primarily attributable to $287.0 million of net proceeds received under our prior $300.0 million five-year senior secured credit facility in connection with the Vidara Merger in September 2014. In addition, during 2014, we received proceeds of $38.5 million in connection with the exercise of warrants to purchase 8,990,120 ordinary shares, and received $9.4 million of cash proceeds from the settlement of the capped call termination in September 2014.

Financial Condition as of December 31, 2016 compared to December 31, 2015

Accounts receivable, net. Accounts receivable, net, increased $95.3 million, from $210.4 million as of December 31, 2015 to $305.7 million as of December 31, 2016. The increase is due to growth in gross sales of our medicines, from 2015 to 2016. There has not been a material change to the ageing of our accounts receivable balances.

Inventories, net. Inventories, net, increased $156.4 million, from $18.4 million as of December 31, 2015 to $174.8 million as of December 31, 2016. This increase is primarily due to $95.3 million of stepped-up KRYSTEXXA and MIGERGOT inventory at December 31, 2016 recorded as a result of the Crealta acquisition in January 2016 and $44.0 million of stepped-up PROCYSBI and QUINSAIR inventory at December 31, 2016 recorded as a result of the Raptor acquisition in October 2016.

Prepaid expenses and other current assets. Prepaid expenses and other current assets increased $33.7 million, from $15.9 million as of December 31, 2015 to $49.6 million as of December 31, 2016. The increase is primarily due to $9.2 million of quarterly estimated income tax installments prepaid as of December 31, 2016, a $7.8 million deferred charge for taxes on intra-group profit, an increase of $5.5 million in medicine samples inventory, an increase of $3.4 million in value added tax receivable and an additional $2.3 million of rabbi trust assets held at December 31, 2016.

Developed technology, net. Developed technology, net, increased $1,158.1 million, from $1,609.1 million as of December 31, 2015 to $2,767.2 million as of December 31, 2016. The increase is due to $428.2 million of KRYSTEXXA and MIGERGOT developed technology acquired in the Crealta acquisition in January 2016 and $946.0 million of PROCYSBI developed technology acquired in the Raptor acquisition, offset by $216.1 million of amortization of developed technology during the year ended December 31, 2016.

In-process research and development. In-process research and development decreased $66.0 million, from $66.0 million as of December 31, 2015 to a zero balance as of December 31, 2016. Following the decision to discontinue the STEADFAST program, we determined that the IPR&D has no alternative use or economic value, and we recorded an impairment charge during the three months ended December 31, 2016 to fully write off the value of the asset on our consolidated balance sheet.

Goodwill. Goodwill increased $191.8 million, from $253.8 million as of December 31, 2015 to $445.6 million as of December 31, 2016. The increase is due to $189.1 million of goodwill recognized upon the acquisition of Raptor in October 2016 and $9.9 million of goodwill recognized upon the acquisition of Crealta in January 2016, offset by an adjustment related to deferred tax liabilities of Hyperion which resulted in a decrease to goodwill of $7.2 million during the year ended December 31, 2016.

Accounts payable. Accounts payable increased $35.9 million, from $16.6 million as of December 31, 2015 to $52.5 million as of December 31, 2016. This increase is primarily due to $16.8 million of trade discounts and rebates included within accounts payable as of December 31, 2016 and increased expenses and payments following our acquisitions of Crealta and Raptor during the year.

Accrued expenses. Accrued expenses increased $82.8 million, from $100.0 million as of December 31, 2015 to $182.8 million as of December 31, 2016. This is primarily due to a $32.5 million unpaid litigation settlement amount as of December 31, 2016, following the litigation settlement with Express Scripts in September 2016, an increase of $16.5 million in consulting and professional services fee accruals, an increase in payroll-related accrued expenses of $14.5 million, $9.5 million related to a loss on inventory purchase commitments and an increase of $8.3 million in accrued interest as a result of our increased borrowings to fund the acquisition of Raptor in October 2016.

Accrued trade discounts and rebates. Accrued trade discounts and rebates increased $113.8 million, from $183.8 million as of December 31, 2015 to $297.6 million as of December 31, 2016. This is due to a $74.3 million increase in accrued co-pay and other patient assistance, a $26.4 million increase in accrued wholesaler fees and commercial rebates, and a $13.1 million increase in accrued government rebates and chargebacks. These increases are in line with the increase in gross sales during the period.

Long-term debt, net, net of current. Long-term debt, net, net of current, increased $651.8 million, from $849.9 million as of December 31, 2015 to $1,501.7 million as of December 31, 2016. This increase is due to our increased borrowings to fund the acquisition of Raptor in October 2016 including the $371.3 million non-current portion of our 2016 Incremental Loan Facility and the $300.0 million 2024 Senior Notes, offset by a $15.5 million net increase in debt discount and deferred financing fees and $4.0 million reclassified to long-term debt, current portion, during the year relating to the 2015 Term Loan Facility.

Accrued royalties, net of current. Accrued royalties, net of current, increased $148.8 million, from $123.5 million as of December 31, 2015 to $272.3 million as of December 31, 2016. This increase is primarily due to KRYSTEXXA and MIGERGOT contingent royalties of $65.8 million at December 31, 2016 as a result of the Crealta acquisition in January 2016 and PROCYSBI contingent royalties of $94.9 million at December 31, 2016 as a result of the Raptor acquisition in October 2016.

Deferred tax liabilities, net. Deferred tax liabilities, net, increased $183.5 million, from $113.4 million as of December 31, 2015 to $296.6 million as of December 31, 2016. The increase is primarily due to the recording of $237.2 million of deferred tax liabilities in connection with the acquisition of Raptor on October 25, 2016 and $20.1 million of deferred tax liabilities in connection with the acquisition of Crealta on January 13, 2016. This was offset by the reduction of $9.2 million in acquired deferred tax liabilities as a result of a change in our U.S. state effective tax rate after our acquisition of Raptor on October 25, 2016 and a reduction of $8.1 million in the deferred tax liabilities of the U.S. group of companies following an the overall reduction in the U.S. state effective tax rate from December 31, 2015 to December 31, 2016. In addition, other activity during the year ended December 31, 2016 resulting from business operations further reduced the deferred tax liabilities, net by $56.5 million.

Other long-term liabilities. Other long-term liabilities increased $36.7 million, from $9.4 million as of December 31, 2015 to $46.1 million as of December 31, 2016. The increase is primarily due to a $25.5 million assumed contingent liability arising following our acquisition of Raptor in October 2016, a $4.8 million liability related to the non-current portion of the loss on purchase commitments for inventory which is in excess of our current forecasts for future demand and a $2.3 million increase in long-term deferred compensation plan liabilities.

Contractual Obligations

As of December 31, 2016, minimum future cash payments due under contractual obligations, including, among others, our debt agreements, minimum purchase agreements and non-cancelable operating lease agreements, were as follows (in thousands):

	2017	2018	2019	2020	2021	2022 & Thereafter	Total
Debt agreements – principal (1)	$ 7,750	$ 7,750	$ 7,750	$ 7,750	$ 738,000	$1,175,000	$1,944,000
Debt agreements - interest (1)	108,951	108,114	107,901	107,163	86,844	130,953	649,926
Purchase commitments (2)	46,940	13,000	9,717	9,570	6,180	46,981	132,388
Operating lease obligations (3)	7,716	7,611	6,753	5,968	5,316	15,856	49,220
Total contractual cash obligations	$ 171,357	$ 136,475	$ 132,121	$ 130,451	$ 836,340	$1,368,790	$2,775,534

(1) Represents the minimum contractual obligation due under the following debt agreements:

- $775.0 million under the 2015 Senior Secured Credit Facility and the 2016 Incremental Loan Facility, which includes quarterly interest payments and quarterly payments of 0.25% of the principal, and repayment of the remaining principal in May 2021.

- $475.0 million 2023 Senior Notes, which includes bi-annual interest payments and repayment of the principal in May 2023.
- $400.0 million Exchangeable Senior Notes, which includes bi-annual interest payments and repayment of the principal in March 2022.
- $300.0 million 2024 Senior Notes, which includes bi-annual interest payments and repayment of the principal in November 2024.

(2) These amounts reflect the following purchase commitments with our third-party manufacturers:

- Minimum annual order quantities required to be placed with Boehringer Ingelheim for final packaged ACTIMMUNE through July 2020 and additional units we also committed to purchase which were intended to cover anticipated demand if the results of the STEADFAST study of ACTIMMUNE for the treatment of FA had been successful. Following the FA announcement, we recorded a loss of $14.3 million in our consolidated statement of comprehensive loss for excess inventories.
- A commitment to spend $14.9 million with Boehringer Ingelheim related to the harmonization of the manufacturing process for ACTIMMUNE drug substance.
- Minimum purchase commitment for RAYOS/LODOTRA tablets from Jagotec AG through December 2023 (the end of the minimum term), which is the firm commitment term under the contract.
- Purchase commitment for final packaged DUEXIS tablets from Sanofi-Aventis U.S. through March 2017.
- Minimum purchase commitment for VIMOVO tablets from Patheon Pharmaceuticals Inc. through March 2017.
- Purchase commitment for final packaged PENNSAID 2% from Nuvo through March 2017.
- Purchase commitment for RAVICTI and BUPHENYL through 2017.
- Minimum purchase commitment for KRYSTEXXA through 2030.
- Purchase commitment for PROCYSBI and QUINSAIR through 2017.

(3) These amounts reflect payments due under our operating leases, which are principally for our facilities. For further details regarding these properties, see Item 2 of Part I, *Properties,* of this Annual Report on Form 10-K.

As of December 31, 2016, our contingent liability for uncertain tax positions amounted to $17.7 million (excluding interest and penalties). Due to the nature and timing of the ultimate outcome of these uncertain tax positions, we cannot make a reasonably reliable estimate of the amount and period of related future payments, if any. Therefore, our contingent liability has been excluded from the above contractual obligations table. We do not expect a significant tax payment related to these obligations within the next year.

In addition to the obligations set out in the above table, we have assumed material obligations to make royalty and milestone payments to certain third parties on net sales of certain of our medicines as outlined below.

Under the license agreement with Aralez Pharmaceuticals Inc., or Aralez, we are required to pay Aralez a flat 10% royalty on net sales of VIMOVO and such other medicines sold by us, our affiliates or sublicensees during the royalty term, subject to minimum annual royalty obligations of $5.0 million in 2014 and $7.5 million each year thereafter, which minimum royalty obligations will continue for each year during which one of Aralez's patents covers such medicines in the United States and there are no competing medicines in the United States. The royalty rate may be reduced to a mid-single digit royalty rate as a result of loss of market share to competing medicines. Our obligation to pay royalties to Aralez will expire upon the later of (a) expiration of the last-to-expire of certain patents covering such medicines in the United States, and (b) ten years after the first commercial sale of such medicines in the United States. In addition, we are obligated to reimburse Aralez for costs, including attorneys' fees, incurred by Aralez in connection with VIMOVO patent litigation moving forward, subject to agreed caps.

Under a letter agreement among AstraZeneca, Aralez and us, we and AstraZeneca agreed to pay Aralez milestone payments upon the achievement by us and AstraZeneca, collectively, of certain annual aggregate global net sales thresholds ranging from $550.0 million to $1.25 billion with respect to VIMOVO. The aggregate milestone payment amount that may be owed by AstraZeneca and us, collectively, under the letter agreement is $260.0 million, with the amount payable by each of us and AstraZeneca with respect to each milestone to be based upon the proportional sales achieved by each of us and AstraZeneca, respectively, in the applicable year.

Under the terms of a license agreement, as amended, with Genentech Inc., or Genentech, who was the original developer of ACTIMMUNE, we are or were obligated to pay royalties to Genentech on our net sales of ACTIMMUNE as follows:

- For the period from November 26, 2014 through May 5, 2018, the royalty payments are in the 20% to 30% range for the first $3.7 million in net sales achieved in any calendar year, and in the 1% to 9% range for all additional net sales in any year; and
- From May 6, 2018 and for so long as we continue to commercially sell ACTIMMUNE, we will be obligated to pay an annual royalty in the low single digits as a percentage of annual net sales.

Under the terms of an assignment and option agreement with Connetics Corporation (which was the predecessor parent company to InterMune Pharmaceuticals Inc. and is now part of GlaxoSmithKline), or Connetics, we are obligated to pay royalties to Connetics on our net sales of ACTIMMUNE as follows:

- Low-single digits as a percentage of net sales of ACTIMMUNE in the United States.

Under the terms of an asset purchase agreement with Ucyclyd Pharma, Inc., or Ucyclyd, we are obligated to pay to Ucyclyd tiered mid to high single-digit royalties on our global net sales of RAVICTI.

Under the terms of an amended and restated collaboration agreement with Ucyclyd, we are obligated to pay to Ucyclyd tiered mid to high single-digit royalties on our net sales in the United States of BUPHENYL to UCD patients outside of the FDA approved labeled age range for RAVICTI.

Under the terms of a license agreement with Saul W. Brusilow, M.D. and Brusilow Enterprises, Inc., or Brusilow, we are obligated to pay low single-digit royalties to Brusilow on net sales of RAVICTI that are covered by a valid claim of a licensed patent.

Under the terms of a license agreement with Duke University, or Duke, and Mountain View Pharmaceuticals, or MVP, we are obligated to pay Duke a mid-single digit royalty on our global net sales of KRYSTEXXA and a low-double digit royalty on any global sublicense revenue. We are also obligated to pay MVP a mid-single digit royalty on our net sales of KRYSTEXXA outside of the United States and a low-double digit to royalty on any sublicense revenue outside of the United States.

Under the terms of a license agreement with The Regents of the University of California, San Diego, or UCSD, we are obligated to pay to UCSD tiered low to mid single-digit royalties on our net sales of PROCYSBI.

On November 8, 2016, we entered into a collaboration and option agreement with a privately held life-science entity. Under the terms of the agreement, the privately held life-science entity will conduct certain research and pre-clinical and clinical development activities. Upon execution of the agreement, we paid $0.1 million for the option to acquire certain of the privately held life-science entity's assets for $25.0 million, which is exercisable on specified key dates. Under the collaboration and option agreement, we will be required to pay up to $9.8 million upon the attainment of various milestones, primarily to fund clinical development costs for the medicine.

Off-Balance Sheet Arrangements

Since our inception, we have not engaged in any off-balance sheet arrangements, including the use of structured finance, special purpose entities or variable interest entities, other than the indemnification agreements discussed in Note 15 in the notes to our consolidated financial statements included in this report.

Critical Accounting Policies and Significant Judgments and Estimates

The methods, estimates and judgments that we use in applying our critical accounting policies have a significant impact on the results that we report in our financial statements. Some of our accounting policies require us to make difficult and subjective judgments, often as a result of the need to make estimates regarding matters that are inherently uncertain.

We have identified the accounting policies and estimates listed below as those that we believe require management's most subjective and complex judgments in estimating the effect of inherent uncertainties. This section should also be read in conjunction with Note 2 in the notes to our consolidated financial statements included in this report, which includes a discussion of these and other significant accounting policies.

Revenue Recognition

Revenue is recognized when all of the following criteria are met: persuasive evidence of an arrangement exists; delivery has occurred or services have been rendered; the price is fixed or determinable; and collectability is reasonably assured. Some of our agreements contain multiple elements and in accordance with these agreements, we may be eligible for upfront license fees, marketing or commercial milestones and payment for medicine deliveries.

Revenue From Medicine Deliveries

Revenue from medicine deliveries comprises a significant amount of our gross sales. We recognize revenue from the sale of our medicines when delivery has occurred, title has transferred, the selling price is fixed or determinable, the right of return no longer exists (which is the earlier of medicine being dispensed through patient prescriptions or the expiration of the right of return) or medicine returns can be reasonably estimated, collectability is reasonably assured and we have no further performance obligations. Due to our ability to reasonably estimate and determine allowances for co-pay and other patient assistance, medicine returns, rebates and discounts based on our own internal data for DUEXIS and RAYOS or data relating to prior sales of our acquired medicines which was received in connection with the acquisition of those medicines, we recognize revenue at the point of sale to wholesale pharmaceutical distributors and retail chains for all currently distributed medicines.

Revenue From Upfront License Fees

We recognize revenues from the receipt of non-refundable, upfront license fees. In situations where the licensee is able to obtain stand-alone value from the license and no further performance obligations exist on our part, revenues are recognized on the earlier of when payments are received or collection is assured. Where continuing involvement by us is required in the form of technology transfer, medicine manufacturing or technical support, revenues are deferred and recognized over the term of the agreement.

Revenue From Milestone Receipts

Milestone payments are recognized as revenue based on achievement of the associated milestones, as defined in the relevant agreements. Revenue from a milestone achievement is recognized when earned, as evidenced by acknowledgment from our partner, provided that (1) the milestone event is substantive and its achievability was not reasonably assured at the inception of the agreement, (2) the milestone represents the culmination of an earnings process and (3) the milestone payment is non-refundable. If any of these criteria are not met, revenue from the milestone achievement is recognized over the remaining minimum period of our performance obligations under the agreement.

Medicine Sales Discounts and Allowances

We record allowances for medicine returns, rebates and discounts at the time of sale to wholesale pharmaceutical distributors and retail chains. We are also required to make significant judgments and estimates in determining some of these allowances. If actual results differ from our estimates, we will be required to make adjustments to these allowances in the future.

Commercial Rebates

We participate in certain commercial rebate programs. Under these rebate programs, we pay a rebate to the commercial entity or third-party administrator of the program. We accrue estimated rebates based on contract prices, estimated percentages of medicine sold to qualified patients and estimated levels of inventory in the distribution channel and record the rebate as a reduction of revenue. Accrued commercial rebates are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Distribution Service Fees

We include distribution service fees paid to our wholesalers for distribution and inventory management services as a reduction to revenue. We accrue estimated distribution fees based on contractually determined amounts, typically as a percentage of revenue, and record the fees as a reduction of revenue. Accrued distribution service fees are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Patient Access Programs

We offer discount card and other programs such as our HorizonCares program to patients under which the patient receives a discount on his or her prescription. In certain circumstances when a patient's prescription is rejected by a managed care vendor, we will pay for the full cost of the prescription. We reimburse pharmacies for this discount through third-party vendors. We reduce gross sales by the amount of actual co-pay and other patient assistance in the period based on the invoices received. We also record an accrual to reduce gross sales for estimated co-pay and other patient assistance on units sold to distributors that have not yet been prescribed/dispensed to a patient. The estimate is based on contract prices, estimated percentages of medicine that will be prescribed to qualified patients, average assistance paid based on reporting from the third-party vendors and estimated levels of inventory in the distribution channel. Accrued co-pay and other patient assistance fees are included in "accrued trade discounts and rebates" on the consolidated balance sheet. Patient assistance programs include both co-pay assistance and fully bought down prescriptions.

Sales Returns

Consistent with industry practice, we maintain a return policy that allows customers to return medicine within a specified period prior to and subsequent to the medicine expiration date. Generally, medicine may be returned for a period beginning six months prior to its expiration date and up to one year after its expiration date. The right of return expires on the earlier of one year after the medicine expiration date or the time that the medicine is dispensed to the patient. The majority of our medicine returns are the result of medicine dating, which falls within the range set by our policy, and are settled through the issuance of a credit to the customer. Our estimate of the provision for returns is based upon our historical experience with actual returns, which is applied to the level of sales for the period that corresponds to the period during which our customer may return medicine. This period is known to us based on the shelf lives of our medicines at the time of shipment. We record sales returns as an allowance against accounts receivable and a reduction of revenue.

Prompt Pay Discounts

As an incentive for prompt payment, we offer a 2% cash discount to customers. We expect that all customers will comply with the contractual terms to earn the discount. We record the discount as an allowance against accounts receivable and a reduction of revenue.

Government Rebates

We participate in certain federal government rebate programs, such as Medicare and Medicaid. We accrue estimated rebates based on estimated percentages of medicine sold to qualified patients, estimated rebate percentages and estimated levels of inventory in the distribution channel that will be sold to qualified patients and record the rebates as a reduction of revenue. Accrued government rebates are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Government Chargebacks

We provide discounts to federal government qualified entities with whom we have contracted. These federal entities purchase medicines from the wholesale pharmaceutical distributors at a discounted price, and the wholesale pharmaceutical distributors then charge back to us the difference between the current retail price and the contracted price that the federal entities paid for the medicine. We accrue estimated chargebacks based on contract prices and sell-through sales data obtained from third-party information and record the chargeback as a reduction of revenue. Accrued government chargebacks are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Cost of Goods Sold

We recognize cost of goods sold in connection with our sales of each of our distributed medicines. Cost of goods sold includes all costs directly related to the acquisition of our medicines from our third-party manufacturers, including freight charges and other direct expenses such as insurance and supply chain costs. Cost of goods sold also includes amortization of intellectual property as described in the intangible assets and goodwill accounting policy below, inventory step-up expense, royalty payments to third parties, royalty accretion expense, changes in estimates associated with the contingent royalty liability as described in the accrued contingent royalty accounting policy below and loss on inventory purchase commitments.

Intangible Assets

Definite-lived intangible assets are amortized over their estimated useful lives. We review our intangible assets when events or circumstances may indicate that the carrying value of these assets exceeds their fair value. We measure fair value based on the estimated future discounted cash flows associated with our assets in addition to other assumptions and projections that we deem to be reasonable and supportable. The total estimated useful lives, from the date of acquisition, for all identified intangible assets that are subject to amortization are as follows:

Intangible Asset	Estimated Useful Life
ACTIMMUNE developed technology	13 years
BUPHENYL developed technology	7 years
Customer relationships	10 years
KRYSTEXXA developed technology	12 years
LODOTRA and RAYOS developed technology	12 years
MIGERGOT developed technology	10 years
PENNSAID 2% developed technology	6 years
PROCYSBI developed technology (ex-U.S. rights)	9 years
PROCYSBI developed technology (U.S. rights)	13 years
RAVICTI developed technology	11 years
VIMOVO developed technology	5 years

We determined that no impairment of the above intangible assets existed as of December 31, 2016.

Indefinite-lived intangible assets consist of capitalized IPR&D. IPR&D assets represent capitalized incomplete research projects that we acquired through business combinations. Such assets are initially measured at their acquisition date fair values and are tested for impairment, until completion or abandonment of research and development efforts associated with the projects. An IPR&D asset is considered abandoned when research and development efforts associated with the asset have ceased, and there are no plans to sell or license the asset or derive value from the asset. At that point, the asset is considered to be disposed of and is written off. Upon successful completion of each project, we will make a determination about the then remaining useful life of the intangible asset and begin amortization. We test our indefinite-lived intangibles, including IPR&D assets, for impairment annually during the fourth quarter and more frequently if events or changes in circumstances indicate that it is more likely than not that the asset is impaired.

IPR&D as of December 31, 2015 related to the research and development project to evaluate ACTIMMUNE in the treatment of FA, which we acquired in the Vidara Merger. At the time of the Vidara Merger, IPR&D was considered separable from the business as the project could be sold to a third party, and we assigned a fair value of $66.0 million to the intangible asset using an income approach in our purchase accounting. On December 8, 2016, we announced that the Phase 3 trial, STEADFAST, evaluating ACTIMMUNE for the treatment of FA did not meet its primary endpoint of a statistically significant change from baseline in the modified FARS-mNeuro at twenty-six weeks versus treatment with placebo. In addition, the secondary endpoints did not meet statistical significance. No new safety findings were identified on initial review of data other than those already noted in the ACTIMMUNE prescribing information for approved indications. We, in conjunction with the independent Data Safety Monitoring Board, the principal investigator and FARA, Collaborative Clinical Research Network in FA, determined that, based on the trial results, the STEADFAST program would be discontinued, including the twenty-six week extension study and the long-term safety study. The IPR&D has no alternative use or economic value as a result of the cancellation of the project, and we recorded an impairment charge of $66.0 million during the three months ended December 31, 2016 to fully write off the value of the asset on our consolidated balance sheet.

Goodwill

Goodwill represents the excess of the purchase price of acquired businesses over the estimated fair value of the identifiable net assets acquired. Goodwill is not amortized but is tested for impairment at least annually at the reporting unit level or more frequently if events or changes in circumstances indicate that the asset might be impaired. Impairment loss, if any, is recognized based on a comparison of the fair value of the asset to its carrying value, without consideration of any recoverability. We test goodwill for impairment annually during the fourth quarter and whenever indicators of impairment exist by first assessing qualitative factors to determine whether it is more likely than not that the fair value is less than its carrying amount. If we conclude it is more likely than not that the fair value of a reporting unit is less than its carrying amount, a quantitative impairment test is performed. If we conclude that goodwill is impaired, we will record an impairment charge in our consolidated statement of comprehensive (loss) income. Based upon our most recent annual impairment test performed in the fourth quarter of 2016, we concluded goodwill was not impaired.

Business Combinations

We account for business combinations in accordance with the pronouncement guidance in ASC 805, *Business Combinations*, in which acquired assets and liabilities are measured at their respective estimated fair values as of the acquisition date. We may be required, as in the case of intangible assets or contingent royalties, to determine the fair value associated with these amounts by estimating the fair value using an income approach under the discounted cash flow method, which may include revenue projections and other assumptions made by us to determine the fair value. During the year ended December 31, 2014, we recorded a bargain purchase gain of $22.2 million in connection with the Vidara Merger, representing the excess of the estimated fair value of net assets acquired over the acquisition consideration paid. During the year ended December 31, 2015, we recorded goodwill of $253.8 million in connection with the acquisition of Hyperion, and we recorded an adjustment of $7.2 million to this amount during the year ended December 31, 2016. During the year ended December 31, 2016 we recorded goodwill of $9.9 million and $189.1 million in connection with our acquisitions of Crealta and Raptor, respectively.

Provision for Income Taxes

We account for income taxes based upon an asset and liability approach. Deferred tax assets and liabilities represent the future tax consequences of the differences between the financial statement carrying amounts of assets and liabilities versus the tax basis of assets and liabilities. Under this method, deferred tax assets are recognized for deductible temporary differences, and operating loss and tax credit carryforwards. Deferred tax liabilities are recognized for taxable temporary differences. Deferred tax assets are reduced by a valuation allowance when, in the opinion of management, it is more likely than not that some portion or all of the deferred tax assets will not be realized. The impact of tax rate changes on deferred tax assets and liabilities is recognized in the year that the change is enacted. We also account for the uncertainty in income taxes by utilizing a comprehensive model for the recognition, measurement, presentation and disclosure in financial statements of any uncertain tax positions that have been taken or are expected to be taken on an income tax return. Deferred tax assets and deferred tax liabilities are netted by jurisdiction on our consolidated balance sheets.

Share-Based Compensation

We account for employee share-based compensation by measuring and recognizing compensation expense for all share-based payments based on estimated grant date fair values. We use the straight-line method to allocate compensation cost to reporting periods over each awardee's requisite service period, which is generally the vesting period.

Accrued Contingent Royalties

Our accrued contingent royalties consist of the contingent royalty obligations assumed by us related to our acquisitions of rights to ACTIMMUNE, BUPHENYL, KRYSTEXXA, MIGERGOT, PROCYSBI, RAVICTI and VIMOVO. At the time of each acquisition, we assigned a fair value to the liability for royalties. The royalty liability was based on anticipated revenue streams utilizing the income approach under the discounted cash flow method. The estimated liability for royalties is increased or decreased over time to reflect the change in its present value, and accretion expense is recorded as part of cost of goods sold. We evaluate the adequacy of the estimated contingent royalty liability at least annually in the fourth quarter, or whenever events or changes in circumstances indicate that an evaluation of the estimate is necessary. As part of our evaluation, we adjust the carrying value of the liability to the present value of the revised estimated cash flows using the original discount rate.

Any adjustment to the liability is recorded as an increase or reduction in cost of goods sold. The royalty liability is included in current and long-term accrued royalties on the consolidated balance sheets.

During the year ended December 31, 2016, based on higher sales of KRYSTEXXA and RAVICTI versus our previous expectations and estimates for future sales of these medicines, we recorded a total charge of $24.6 million to cost of goods sold ($15.4 million related to KRYSTEXXA and $9.2 million related to RAVICTI). We also recorded a reduction of $24.2 million to cost of goods sold related to ACTIMMUNE and VIMOVO as a result of updated estimates of future sales of these medicines ($8.7 million related to ACTIMMUNE, including $2.5 million in connection with FA, and $15.5 million related to VIMOVO).

Fair Value of Financial Instruments

The carrying amounts of our financial instruments, including cash and cash equivalents, restricted cash, accounts receivable, accounts payable and accrued expenses, approximate their fair values due to their short maturities.

At December 31, 2013 and at the final measurement on June 27, 2014, the estimated fair value of our derivative liability related to the convertible portion of our Convertible Senior Notes was derived utilizing the binomial lattice approach for the valuation of convertible instruments. Assumptions used in the calculation included, among others, determining the appropriate credit spread using benchmarking analysis and solving for the implied credit spread, calculating the fair value of the stock component using a discounted risk free rate and borrowing cost and calculating the fair value of the note component using a discounted credit adjusted discount rate. Based on the assumptions used to determine the fair value of the derivative liability associated with the Convertible Senior Notes, we concluded that these inputs were Level 3 inputs.

New Accounting Pronouncements Impacting Critical Accounting Policies

Refer to Note 2 in the notes to our consolidated financial statements included in this report, which includes a discussion of the new accounting pronouncements impacting critical accounting policies.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

We are exposed to various market risks, which include potential losses arising from adverse changes in market rates and prices, such as interest rates and foreign exchange fluctuations. We do not enter into derivatives or other financial instruments for trading or speculative purposes.

Interest Rate Risk. We are subject to interest rate fluctuation exposure through our borrowings under the 2015 Term Loan Facility and our investment in money market accounts which bear a variable interest rate. The terms of the 2015 Term Loan Facility provided for an amendment such that the effective yield of the 2015 Term Loan Facility would not be less than the effective yield of the 2016 Incremental Loans minus 0.50%. Consequently, the issuance of the 2016 Incremental Loans resulted in an increase of the interest rate applicable to the 2015 Term Loan Facility, as of October 25, 2016, to LIBOR plus 4.00%, subject to a LIBOR floor of 1.0% (an initial interest rate of 5.00%). Thus, loans under the 2015 Term Loan Facility bear interest, at our option, at a rate equal to either the LIBOR rate, plus an applicable margin of 4.00% per annum (subject to a 1.00% LIBOR floor), or the adjusted base rate plus 3.00%. The adjusted base rate is defined as the greater of (a) LIBOR (using one-month interest period) plus 1%, (b) prime rate, (c) fed funds plus ½ of 1% and (d) 2%. Since drawing the full $400.0 million available in May 2015, our borrowings had been based on LIBOR. Since current LIBOR rates are below the 1.0% LIBOR floor, the interest rate on our borrowings is currently 5.00% per annum for the 2015 Term Loan Facility and 5.5% per annum for the 2016 Incremental Loans. An increase in the LIBOR of 100 basis points above the 1.0% LIBOR floor would increase our interest expense by $7.9 million per year.

The primary goals of our investment policy are the preservation of capital, fulfillment of liquidity needs and fiduciary control of cash. To achieve our secondary goal of maximizing income without assuming significant market risk, we maintain our excess cash and cash equivalents in money market funds and bank deposits. Because of the short-term maturities of our cash equivalents, we do not believe that a decrease in interest rates would have any material negative impact on the fair value of our cash equivalents.

Foreign Currency Risk. Our purchase cost of ACTIMMUNE under our contract with Boehringer Ingelheim as well as sales contracts relating to LODOTRA, QUINSAIR and sales of PROCYSBI outside the United States are principally denominated in Euros and are subject to foreign currency risk. We also incur certain operating expenses in currencies other than the U.S. dollar in relation to our Irish operations and foreign subsidiaries, including Horizon Pharma Switzerland GmbH. Following the acquisition of Raptor, we are subject to increased foreign currency risk for our operations in Europe due to an increased level of sales and operating expenses denominated in Euros. To date, we have not entered into any hedging contracts since exchange rate fluctuations have had minimal impact on our results of operations and cash flows.

Inflation Risk. We do not believe that inflation has had a material impact on our business or results of operations during the periods for which the consolidated financial statements are presented in this report.

Credit Risk. Historically, our accounts receivable balances have been highly concentrated with a select number of customers, consisting primarily of large wholesale pharmaceutical distributors who, in turn, sell the medicines to pharmacies, hospitals and other customers. As of December 31, 2016, 2015 and 2014, our top three customers accounted for approximately 78%, 72% and 68%, respectively, of our total outstanding accounts receivable balances.

Item 8. Financial Statements and Supplementary Data

The financial information required by Item 8 is contained in Part IV, Item 15 of this Annual Report on Form 10-K.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our Chief Executive Officer and Chief Financial Officer, after evaluating the effectiveness of our "disclosure controls and procedures" (as defined in Rule 13a-15(e) promulgated under the Securities Exchange Act of 1934, as amended, or the Exchange Act), have concluded that, as of December 31, 2016, our disclosure controls and procedures were effective to provide reasonable assurance that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the Securities and Exchange Commission's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by an issuer in the reports that it files or submits under the Exchange Act is accumulated and communicated to the issuer's management, including its principal executive officer or officers and principal financial officer or officers, or persons performing similar functions, as appropriate to allow timely decisions regarding required disclosure.

Management Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Our internal control system was designed to provide reasonable assurance to management and our board of directors regarding the preparation and fair presentation of published financial statements. All internal control systems, no matter how well designed, have inherent limitations. Therefore, even those systems determined to be effective can provide only reasonable assurance with respect to financial statement preparation and presentation.

Management assessed the effectiveness of our internal control over financial reporting as of December 31, 2016. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in *Internal Control – Integrated Framework (2013).* Management's assessment included an evaluation of the design of our internal control over financial reporting and testing of the operational effectiveness of our internal control over financial reporting. Based on management's assessment, management believes that, as of December 31, 2016, our internal control over financial reporting was effective based on those criteria.

Management's assessment of internal control over financial reporting as of December 31, 2016 excluded Raptor's internal controls over financial reporting because we acquired Raptor in a purchase business combination in October 2016. Raptor represented less than 1% of our total assets and 3% of our total net sales at and for the year ended December 31, 2016.

The effectiveness of our internal control over financial reporting as of December 31, 2016 has been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm, as stated in their report which appears herein.

Changes in Internal Control Over Financial Reporting

As discussed above, on October 25, 2016, we completed our acquisition of Raptor and Raptor became our wholly owned subsidiary. As a result of the Raptor acquisition, the internal control over financial reporting utilized by us prior to the acquisition became the internal control over financial reporting of Raptor, and we are currently in the process of evaluating and integrating Raptor's historical internal controls over financial reporting with ours.

During the three months ended December 31, 2016, other than continuing changes to our internal control processes resulting from the Raptor acquisition as discussed above, there have been no material changes to our internal control over financial reporting, as defined in Rules 13a-15(f) and 15d-15(f), that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The information required by this item is incorporated herein by reference from our definitive Proxy Statement to be filed in connection with our 2017 Annual General Meeting of Shareholders, or our 2017 Proxy Statement, which will be filed with the Securities and Exchange Commission within 120 days after December 31, 2016.

We have adopted a written Code of Business Conduct and Ethics, or Ethics Code, that applies to all officers, directors and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. The Ethics Code is available on our website at www.horizonpharma.com. If we make any substantive amendments to the Ethics Code or grant any waiver from a provision of the Ethics Code to any executive officer or director, we will promptly disclose the nature of the amendment or waiver on our website or in a current report on Form 8-K.

Item 11. Executive Compensation

The information required by this item is incorporated herein by reference from our 2017 Proxy Statement.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this item is incorporated herein by reference from our 2017 Proxy Statement.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this item is incorporated herein by reference from our 2017 Proxy Statement.

Item 14. Principal Accounting Fees and Services

The information required by this item is incorporated herein by reference from our 2017 Proxy Statement.

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a) Documents filed as part of this report.

1. Financial Statements

The financial statements listed on the Index to Financial Statements F-1 to F-70 are filed as part of this Annual Report on Form 10-K.

2. Financial Statement Schedules

Schedule II – Valuation and Qualifying Accounts and Reserves for each of the three fiscal years ended December 31, 2016, 2015 and 2014. Other financial statement schedules have been omitted because the required information is included in the consolidated financial statements or notes thereto or because they are not applicable or not required.

3. Exhibits

The exhibits listed on the Index to Exhibits are filed as part of this Annual Report on Form 10-K.

Item 16. Form 10-K Summary

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities and Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

HORIZON PHARMA PLC

Dated: February 27, 2017

By: /s/ TIMOTHY P. WALBERT
Timothy P. Walbert

President, Chief Executive Officer and
Chairman of the Board

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Timothy P. Walbert and Paul W. Hoelscher, and each of them, his true and lawful attorneys-in-fact and agents, with full power of substitution and resubstitution, for him and in his name, place and stead, in any and all capacities, to sign any and all amendments (including post-effective amendments) to this report, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as he might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or either of them, or their or his substitutes or substitute, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

SIGNATURE	TITLE	DATE
/s/ TIMOTHY P. WALBERT Timothy P. Walbert	President, Chief Executive Officer and Chairman of the Board *(Principal Executive Officer)*	February 27, 2017
/s/ PAUL W. HOELSCHER Paul W. Hoelscher	Executive Vice President and Chief Financial Officer *(Principal Financial Officer)*	February 27, 2017
/s/ MILES W. MCHUGH Miles W. McHugh	Senior Vice President and Chief Accounting Officer *(Principal Accounting Officer)*	February 27, 2017
/s/ MICHAEL GREY Michael Grey	Director	February 27, 2017
/s/ LIAM DANIEL Liam Daniel	Director	February 27, 2017
/s/ JEFF HIMAWAN Jeff Himawan, Ph.D.	Director	February 27, 2017
/s/ VIRINDER NOHRIA Virinder Nohria, M.D., Ph.D.	Director	February 27, 2017
/s/ RONALD PAULI Ronald Pauli	Director	February 27, 2017
/s/ GINO SANTINI Gino Santini	Director	February 27, 2017
/s/ H. THOMAS WATKINS H. Thomas Watkins	Director	February 27, 2017

HORIZON PHARMA PLC

Index to Consolidated Financial Statements

Report of Independent Registered Public Accounting Firm

To the Board of Directors and Shareholders of Horizon Pharma plc

In our opinion, the accompanying consolidated balance sheets and the related consolidated statements of comprehensive (loss) income, shareholders' equity (deficit), and cash flows present fairly, in all material respects, the financial position of Horizon Pharma plc and its subsidiaries at December 31, 2016 and 2015, and the results of their operations and their cash flows for each of the three years in the period ended December 31, 2016 in conformity with accounting principles generally accepted in the United States of America. In addition, in our opinion, the financial statement schedule listed in the index appearing under Item 15(a)(2) presents fairly, in all material respects, the information set forth therein when read in conjunction with the related consolidated financial statements. Also in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2016, based on criteria established in Internal Control - Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). The Company's management is responsible for these financial statements and financial statement schedule, for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting, included in Management's Report on Internal Control over Financial Reporting appearing under Item 9A. Our responsibility is to express opinions on these financial statements, on the financial statement schedule, and on the Company's internal control over financial reporting based on our integrated audits. We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the financial statements are free of material misstatement and whether effective internal control over financial reporting was maintained in all material respects. Our audits of the financial statements included examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audits also included performing such other procedures as we considered necessary in the circumstances. We believe that our audits provide a reasonable basis for our opinions.

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

As described in Management's Report on Internal Control over Financial Reporting, management has excluded Raptor Pharmaceutical Corp. ("Raptor") from its assessment of internal control over financial reporting as of December 31, 2016 because it was acquired by the Company in a purchase business combination during 2016. We have also excluded Raptor from our audit of internal control over financial reporting. Raptor is a wholly-owned subsidiary whose total assets and total revenues represent less than 1% and 3%, respectively, of the related consolidated financial statement amounts as of and for the year ended December 31, 2016.

/s/ PricewaterhouseCoopers LLP

Chicago, Illinois
February 27, 2017

HORIZON PHARMA PLC

CONSOLIDATED BALANCE SHEETS
(In thousands, except share data)

	As of December 31, 2016	As of December 31, 2015
ASSETS		
CURRENT ASSETS:		
Cash and cash equivalents	$ 509,055	$ 859,616
Restricted cash	7,095	1,860
Accounts receivable, net	305,725	210,437
Inventories, net	174,788	18,376
Prepaid expenses and other current assets	49,619	15,858
Total current assets	1,046,282	1,106,147
Property and equipment, net	23,484	14,020
Developed technology, net	2,767,184	1,609,049
In-process research and development	—	66,000
Other intangible assets, net	6,251	7,061
Goodwill	445,579	253,811
Deferred tax assets, net	911	2,278
Other assets	2,368	222
TOTAL ASSETS	$ 4,292,059	$ 3,058,588
LIABILITIES AND SHAREHOLDERS' EQUITY		
CURRENT LIABILITIES:		
Long-term debt—current portion	$ 7,750	$ 4,000
Accounts payable	52,479	16,590
Accrued expenses	182,765	100,046
Accrued trade discounts and rebates	297,556	183,769
Accrued royalties—current portion	61,981	51,700
Deferred revenues—current portion	3,321	1,447
Total current liabilities	605,852	357,552
LONG-TERM LIABILITIES:		
Exchangeable notes, net	298,002	282,889
Long-term debt, net, net of current	1,501,741	849,867
Accrued royalties, net of current	272,293	123,519
Deferred revenues, net of current	7,763	8,785
Deferred tax liabilities, net	296,568	113,400
Other long-term liabilities	46,061	9,431
Total long-term liabilities	2,422,428	1,387,891
COMMITMENTS AND CONTINGENCIES		
SHAREHOLDERS' EQUITY:		
Ordinary shares, $0.0001 nominal value; 300,000,000 shares authorized; 162,004,956 and 160,069,067 shares issued at December 31, 2016 and December 31, 2015, respectively, and 161,620,590 and 159,684,701 shares outstanding at December 31, 2016 and December 31, 2015, respectively	16	16
Treasury stock, 384,366 ordinary shares at December 31, 2016 and December 31, 2015	(4,585)	(4,585)
Additional paid-in capital	2,119,455	2,001,552
Accumulated other comprehensive loss	(3,086)	(2,651)
Accumulated deficit	(848,021)	(681,187)
Total shareholders' equity	1,263,779	1,313,145
TOTAL LIABILITIES AND SHAREHOLDERS' EQUITY	$ 4,292,059	$ 3,058,588

The accompanying notes are an integral part of these consolidated financial statements.

HORIZON PHARMA PLC

CONSOLIDATED STATEMENTS OF COMPREHENSIVE (LOSS) INCOME
(In thousands, except share and per share data)

	For the Years Ended December 31,		
	2016	**2015**	**2014**
Net sales	$ 981,120	$ 757,044	$ 296,955
Cost of goods sold	393,272	219,502	78,753
Gross profit	587,848	537,542	218,202
OPERATING EXPENSES:			
Research and development	60,707	41,865	17,460
Sales and marketing	320,366	220,444	120,276
General and administrative	287,942	219,861	88,957
Impairment of in-process research and development	66,000	—	—
Total operating expenses	735,015	482,170	226,693
Operating (loss) income	(147,167)	55,372	(8,491)
OTHER (EXPENSE) INCOME, NET:			
Interest expense, net	(86,610)	(69,900)	(23,826)
Foreign exchange loss	(1,005)	(1,237)	(3,905)
Loss on induced conversion of debt and debt extinguishment	—	(77,624)	(29,390)
Loss on sale of long-term investments	—	(29,032)	—
Bargain purchase gain	—	—	22,171
Loss on derivative fair value	—	—	(214,995)
Other income (expense), net	6,697	(10,291)	(11,251)
Total other (expense) income, net	(80,918)	(188,084)	(261,196)
Loss before benefit for income taxes	(228,085)	(132,712)	(269,687)
BENEFIT FOR INCOME TAXES	(61,251)	(172,244)	(6,084)
NET (LOSS) INCOME	$ (166,834)	$ 39,532	$ (263,603)
NET (LOSS) INCOME PER ORDINARY SHARE—Basic	$ (1.04)	$ 0.27	$ (3.15)
WEIGHTED AVERAGE ORDINARY SHARES OUTSTANDING—Basic	160,699,543	148,788,020	83,751,129
NET (LOSS) INCOME PER ORDINARY SHARE—Diluted	(1.04)	0.25	(3.15)
WEIGHTED AVERAGE ORDINARY SHARES OUTSTANDING—Diluted	160,699,543	155,923,251	83,751,129
OTHER COMPREHENSIVE (LOSS) INCOME, NET OF TAX			
Foreign currency translation adjustments	(302)	1,712	(1,960)
Pension remeasurements	(133)	—	—
Other comprehensive (loss) income	(435)	1,712	(1,960)
COMPREHENSIVE (LOSS) INCOME	$ (167,269)	$ 41,244	$ (265,563)

The accompanying notes are an integral part of these consolidated financial statements.

HORIZON PHARMA PLC

CONSOLIDATED STATEMENTS OF SHAREHOLDERS' EQUITY (DEFICIT)
(In thousands, except share data)

	Ordinary Shares		Treasury Stock		Additional Paid-in	Accumulated Other Comprehensive	Accumulated	Total Stockholders'
	Shares	Amount	Shares	Amount	Capital	Loss	Deficit	Equity (Deficit)
Balances at December 31, 2013	66,097,417	$ 7	—	$ —	$ 410,430	$ (2,403)	$ (457,116)	$ (49,082)
Issuance of ordinary shares in connection with Vidara merger	31,350,000	3	—	—	387,796	—	—	387,799
Issuance of ordinary shares in conjunction with inducement of convertible notes (net of the reacquisition of the equity component of $129,776)	16,594,793	2	—	—	78,437	—	—	78,439
Reclassification of derivative liability	—	—	—	—	324,405	—	—	324,405
Issuance of ordinary shares in conjunction with vesting of restricted stock units and stock option exercises	864,780	—	—	—	2,506	—	—	2,506
Ordinary shares withheld for payment of employees' withholding tax liability	—	—	—	—	(894)	—	—	(894)
Issuance of ordinary shares in conjunction with ESPP purchases	536,543	—	—	—	1,674	—	—	1,674
Share-based compensation	—	—	—	—	13,197	—	—	13,197
Issuance of ordinary shares in conjunction with warrant exercises	8,990,120	1	—	—	38,460	—	—	38,461
Proceeds from capped call transactions	—	—	384,366	(4,585)	13,970	—	—	9,385
Treasury stock purchase	—	—	7,800	(123)	—	—	—	(123)
Treasury stock retirement	(7,800)	—	(7,800)	123	(123)	—	—	—
Currency translation adjustment	—	—	—	—	—	(1,960)	—	(1,960)
Net loss	—	—	—	—	—	—	(263,603)	(263,603)
Balances at December 31, 2014	124,425,853	$ 13	384,366	$ (4,585)	$ 1,269,858	$ (4,363)	$ (720,719)	$ 540,204
Issuance of ordinary shares	17,652,500	2	—	—	475,683	—	—	475,685
Issuance of ordinary shares in conjunction with vesting of restricted stock units and stock option exercises	1,157,807	—	—	—	5,217	—	—	5,217
Ordinary shares withheld for payment of employees' withholding tax liability	—	—	—	—	(3,024)	—	—	(3,024)
Issuance of ordinary shares in conjunction with inducement of convertible notes (net of the reacquisition of the equity component of $243,984)	11,368,921	1	—	—	57,543	—	—	57,544
Issuance of ordinary shares in conjunction with ESPP purchases	591,277	—	—	—	4,452	—	—	4,452
Share-based compensation	—	—	—	—	83,553	—	—	83,553
Issuance of ordinary shares in conjunction with warrant exercises	4,872,709	—	—	—	18,124	—	—	18,124
Issuance of Exchangeable Senior Notes	—	—	—	—	119,080	—	—	119,080
Deferred tax on Exchangeable Senior Notes	—	—	—	—	(29,770)	—	—	(29,770)
Deferred tax on capped call transactions	—	—	—	—	836	—	—	836
Currency translation adjustment	—	—	—	—	—	1,712	—	1,712
Net income	—	—	—	—	—	—	39,532	39,532
Balances at December 31, 2015	160,069,067	$ 16	384,366	$ (4,585)	$ 2,001,552	$ (2,651)	$ (681,187)	$ 1,313,145
Issuance of ordinary shares in conjunction with vesting of restricted stock units and stock option exercises	1,245,637	—	—	—	3,875	—	—	3,875
Ordinary shares withheld for payment of employees' withholding tax liability	—	—	—	—	(5,539)	—	—	(5,539)
Issuance of ordinary shares in conjunction with ESPP purchases	513,659	—	—	—	6,540	—	—	6,540
Issuance of ordinary shares in conjunction with PSU vesting	13,584	—	—	—	—	—	—	—
Share-based compensation	—	—	—	—	113,019	—	—	113,019
Issuance of ordinary shares in conjunction with warrant exercises	163,009	—	—	—	8	—	—	8
Currency translation adjustment	—	—	—	—	—	(302)	—	(302)
Pension remeasurements	—	—	—	—	—	(133)	—	(133)
Net loss	—	—	—	—	—	—	(166,834)	(166,834)
Balances at December 31, 2016	162,004,956	$ 16	384,366	$ (4,585)	$ 2,119,455	$ (3,086)	$ (848,021)	$ 1,263,779

The accompanying notes are an integral part of these consolidated financial statements.

HORIZON PHARMA PLC

CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	For the Years Ended December 31,		
	2016	**2015**	**2014**
CASH FLOWS FROM OPERATING ACTIVITIES:			
Net (loss) income	$ (166,834)	$ 39,532	$ (263,603)
Adjustments to reconcile net (loss) income to net cash provided by operating activities:			
Depreciation and amortization expense	221,837	138,343	34,009
Equity-settled share-based compensation	113,019	83,553	13,198
Royalty accretion	40,616	20,088	9,020
Royalty liability remeasurement	386	21,151	10,660
Impairment of in-process research and development	66,000	—	—
Impairment of non-current asset	5,260	—	—
Loss on induced conversions of debt and debt extinguishment	—	21,581	11,709
Amortization of debt discount and deferred financing costs	18,546	18,810	9,273
Loss on sale of long-term investments	—	29,032	—
Loss on derivative revaluation	—	—	214,995
Bargain purchase gain	—	—	(22,171)
Deferred income taxes	(65,561)	(180,549)	(7,516)
Foreign exchange loss and other adjustments	420	1,495	3,916
Changes in operating assets and liabilities:			
Accounts receivable	(67,496)	(124,766)	(46,183)
Inventories	67,633	12,216	7,173
Prepaid expenses and other current assets	(28,239)	1,014	(9,208)
Accounts payable	32,065	(8,362)	9,383
Accrued trade discounts and rebates	112,381	94,046	54,090
Accrued expenses and accrued royalties	13,854	20,169	(1,270)
Deferred revenues	1,114	1,693	(562)
Payment of original issue discount upon repayment of 2014 Term Loan Facility	—	(3,000)	—
Other non-current assets and liabilities	4,455	8,120	636
Net cash provided by operating activities	369,456	194,166	27,549
CASH FLOWS FROM INVESTING ACTIVITIES:			
Payments for acquisitions, net of cash acquired	(1,356,271)	(1,022,361)	(224,220)
Proceeds from liquidation of available-for-sale investments	—	64,623	—
Purchases of long-term investments	—	(71,813)	—
Proceeds from sale of long-term investments	—	42,781	—
Purchases of property and equipment	(15,731)	(7,156)	(3,500)
Change in restricted cash	(3,879)	(1,122)	—
Net cash used in investing activities	(1,375,881)	(995,048)	(227,720)
CASH FLOWS FROM FINANCING ACTIVITIES:			
Net proceeds from the Incremental Loan Facility	364,297	—	—
Net proceeds from issuance of 2024 Senior Notes	291,893	—	—
Net proceeds from issuance of Exchangeable Senior Notes	—	387,181	—
Net proceeds from issuance of 2023 Senior Notes	—	462,340	—
Net proceeds from the 2015 Term Loan Facility	—	391,506	—
Repayment of the 2015 Term Loan Facility	(4,000)	(2,000)	—
Net proceeds from issuance of ordinary shares	—	475,685	—
Proceeds from the settlement of capped call transactions	—	—	9,385
Proceeds from the issuance of ordinary shares in connection with warrant exercises	8	18,124	38,461
Proceeds from the issuance of ordinary shares through ESPP programs	6,540	4,452	1,674
Proceeds from the issuance of ordinary shares in connection with stock option exercises	3,875	5,217	2,693
Payment of employee withholding taxes relating to share-based awards	(5,539)	(3,024)	(894)
Net proceeds from the 2014 Term Loan Facility	—	—	286,966
Repayment of the 2014 Term Loan Facility	—	(297,000)	—
Net cash provided by financing activities	657,074	1,442,481	338,285
Effect of foreign exchange rate changes on cash	(1,210)	(790)	213
NET (DECREASE) INCREASE IN CASH AND CASH EQUIVALENTS	(350,561)	640,809	138,327
CASH AND CASH EQUIVALENTS, beginning of the year	859,616	218,807	80,480
CASH AND CASH EQUIVALENTS, end of the year	$ 509,055	$ 859,616	$ 218,807

HORIZON PHARMA PLC

CONSOLIDATED STATEMENTS OF CASH FLOWS (CONTINUED)
(In thousands)

	For the Years Ended December 31,		
	2016	**2015**	**2014**
Supplemental cash flow information:			
Cash paid for interest	$ 60,817	$ 42,021	$ 14,109
Cash paid for income taxes	22,339	1,880	37
Fees paid for debt commitments	—	9,000	8,222
Cash paid for induced conversions	—	10,005	16,690
Cash paid for debt extinguishment	—	45,367	—
Supplemental non-cash flow information:			
Conversion of Convertible Senior Notes to ordinary shares	—	60,985	89,015
Purchases of property and equipment included in accounts payable and accrued expenses	700	4,940	1,463

The accompanying notes are an integral part of these consolidated financial statements.

NOTE 1 – BASIS OF PRESENTATION

On September 19, 2014, the businesses of Horizon Pharma, Inc. ("HPI") and Vidara Therapeutics International Public Limited Company ("Vidara") were combined in a merger transaction (the "Vidara Merger"), accounted for as a reverse acquisition under the acquisition method of accounting for business combinations, with HPI treated as the acquiring company in the Vidara Merger for accounting purposes. As part of the Vidara Merger, a wholly owned subsidiary of Vidara merged with and into HPI, with HPI surviving the Vidara Merger as a wholly owned subsidiary of Vidara. Prior to the Vidara Merger, Vidara changed its name to Horizon Pharma plc (or the "Company"). Upon the consummation of the Vidara Merger, the historical financial statements of HPI became the Company's historical financial statements. Accordingly, the historical financial statements of HPI are included in the comparative prior periods. The consolidated financial statements presented herein include the accounts of the Company and its wholly owned subsidiaries. All inter-company transactions and balances have been eliminated.

Unless otherwise indicated or the context otherwise requires, references to the "Company", "we", "us" and "our" refer to Horizon Pharma plc and its consolidated subsidiaries, including its predecessor, HPI. All references to "Vidara" are references to Horizon Pharma plc (formerly known as Vidara Therapeutics International Public Limited Company) and its consolidated subsidiaries prior to the effective time of the Vidara Merger on September 19, 2014. The disclosures in this report relating to the pre-Vidara Merger business of Horizon Pharma plc, unless noted as being the business of Vidara prior to the Vidara Merger, pertain to the business of HPI prior to the Vidara Merger.

On October 17, 2014, the Company acquired the U.S. rights to PENNSAID 2% from Nuvo Research Inc. ("Nuvo") for $45.0 million in cash.

On May 7, 2015, the Company completed its acquisition of Hyperion Therapeutics Inc. ("Hyperion") in which the Company acquired all of the issued and outstanding shares of Hyperion's common stock for $46.00 per share in cash or approximately $1.1 billion on a fully-diluted basis. Following the completion of the acquisition, Hyperion became a wholly owned subsidiary of the Company and was renamed as Horizon Therapeutics, Inc. (which subsequently converted to a limited liability company, Horizon Therapeutics, LLC).

On January 13, 2016, the Company completed its acquisition of Crealta Holdings LLC ("Crealta") for approximately $539.7 million, including cash acquired of $24.9 million. Following completion of the acquisition, Crealta became a wholly owned subsidiary of the Company and was renamed as Horizon Pharma Rheumatology LLC.

On October 25, 2016, the Company completed its acquisition of Raptor Pharmaceutical Corp. ("Raptor") in which the Company acquired all of the issued and outstanding shares of Raptor's common stock for $9.00 per share in cash. The total consideration was $860.8 million, including cash acquired of $24.9 million and $56.0 million to repay Raptor's outstanding debt. Following completion of the acquisition, Raptor became a wholly owned subsidiary of the Company and converted to a limited liability company, changing its name to Horizon Pharmaceutical LLC. The Company financed the transaction through $300.0 million aggregate principal amount of 8.75% Senior Notes due 2024 (the "2024 Senior Notes"), $375.0 million aggregate principal amount of loans pursuant to an amendment to the Company's existing credit agreement and cash on hand.

The consolidated financial statements presented herein include the results of operations of the acquired Vidara, Hyperion, Crealta and Raptor businesses from the applicable dates of acquisition. See Note 4 for further details of business acquisitions.

Overview

The Company is a biopharmaceutical company focused on improving patients' lives by identifying, developing, acquiring and commercializing differentiated and accessible medicines that address unmet medical needs. The Company markets eleven medicines through its orphan, rheumatology and primary care business units. The Company's marketed medicines are ACTIMMUNE® (interferon gamma-1b), BUPHENYL® (sodium phenylbutyrate) Tablets and Powder, DUEXIS® (ibuprofen/famotidine), KRYSTEXXA® (pegloticase), MIGERGOT® (ergotamine tartrate & caffeine suppositories), PENNSAID® (diclofenac sodium topical solution) 2% w/w ("PENNSAID 2%"), PROCYSBI® (cysteamine bitartrate) delayed-release capsules, QUINSAIR™ (aerosolized form of levofloxacin), RAVICTI® (glycerol phenylbutyrate) Oral Liquid, RAYOS® (prednisone) delayed-release tablets and VIMOVO® (naproxen/esomeprazole magnesium).

On May 18, 2016, the Company entered into a definitive agreement with Boehringer Ingelheim International GmbH ("Boehringer Ingelheim International") to acquire certain rights to interferon gamma-1b, which Boehringer Ingelheim International currently commercializes under the trade names IMUKIN®, IMUKINE®, IMMUKIN® and IMMUKINE® in an estimated thirty countries, primarily in Europe and the Middle East. Under the terms of the agreement, the Company paid Boehringer Ingelheim International €5.0 million ($5.6 million when converted using a Euro-to-Dollar exchange rate at date of payment of 1.1132) upon signing and will pay €20.0 million upon closing, for certain rights for interferon gamma-1b in all territories outside of the United States, Canada and Japan, as the Company currently holds marketing rights to interferon gamma-1b in these territories. The Company currently markets interferon gamma-1b as ACTIMMUNE® in the United States. The transaction is expected to close in 2017 and the Company is continuing to work with Boehringer Ingelheim International to enable the transfer of applicable marketing authorizations.

On December 8, 2016, the Company announced that the Phase 3 trial, Safety, Tolerability and Efficacy of ACTIMMUNE Dose Escalation in Friedreich's Ataxia study ("STEADFAST") evaluating ACTIMMUNE for the treatment of Friedreich's ataxia ("FA") did not meet its primary endpoint of a statistically significant change from baseline in the modified Friedreich's Ataxia Rating Scale ("FARS-mNeuro"), at twenty-six weeks versus treatment with placebo. In addition, the secondary endpoints did not meet statistical significance. No new safety findings were identified on initial review of data other than those already noted in the ACTIMMUNE prescribing information for approved indications. The Company, in conjunction with the independent Data Safety Monitoring Board, the principal investigator and the Friedreich's Ataxia Research Alliance ("FARA") Collaborative Clinical Research Network in FA, determined that, based on the trial results, the STEADFAST program would be discontinued, including the twenty-six week extension study and the long-term safety study. Following this announcement, the Company recorded in "general and administrative expenses" an impairment charge to fully write off the carrying value of the €5.0 million initial payment ($5.3 million when converted using a Euro-to-Dollar exchange rate at date of impairment of 1.052) for the acquisition of certain rights to interferon gamma-1b, as described above, in the Company's consolidated statement of comprehensive loss for the three months ended December 31, 2016. Upon closing, the Company expects to record the additional €20.0 million payment, as described above, as an expense in its consolidated statement of comprehensive (loss) income.

The Company

The Company is a public limited company formed under the laws of Ireland. The Company operates through a number of international and U.S. subsidiaries with principal business purposes to either perform research and development or manufacturing operations, serve as distributors of the Company's medicines, hold intellectual property assets or provide services and financial support to the Company.

Part of the Company's commercial strategy for RAYOS and its primary care medicines is to offer physicians the opportunity to have their patients fill prescriptions through pharmacies participating in the Company's HorizonCares patient access program. For commercial patients who are prescribed the Company's primary care medicines or RAYOS, the HorizonCares program offers co-pay assistance when a third-party commercial payer covers a prescription but requires an eligible patient to pay a co-pay or deductible, and offers full subsidization when a third-party commercial payer rejects coverage for an eligible patient. During 2016, the Company entered into business arrangements with pharmacy benefit managers ("PBMs") and other payers to secure formulary status and reimbursement of the Company's medicines, such as the Company's arrangements with Express Scripts, Inc. ("Express Scripts"), CVS Caremark and Prime Therapeutics LLC. While the Company believes that this strategy will result in broader inclusion of certain of the Company's primary care medicines on healthcare plan formularies, and therefore increase payer reimbursement and lower the Company's cost of providing patient access programs, these arrangements generally require the Company to pay administrative and rebate payments to the PBMs and/or other payers.

The Company has a comprehensive compliance program in place to address adherence with various laws and regulations relating to the selling, marketing and manufacturing of the Company's medicines, as well as certain third-party relationships, including pharmacies. Specifically with respect to pharmacies, the compliance program utilizes a variety of methods and tools to monitor and audit pharmacies, including those that participate in the Company's patient access programs, to confirm their activities, adjudication and practices are consistent with the Company's compliance policies and guidance.

The Company markets its medicines in the United States through a combined field sales force, which numbered approximately 480 representatives as of December 31, 2016. The Company's strategy is to continue to build a well-balanced, diversified, high-growth biopharmaceutical company, and is executing this strategy through the successful commercialization of its existing medicines, a strong commitment to patient access and support and business development efforts focused on transformative acquisitions to accelerate its rare disease leadership as well as on-market and development-stage medicines to fill out its pipeline. The Company is building a sustainable biopharmaceutical company by helping ensure that patients have access to their medicines and support services, and by investing in the further development of medicines for patients with rare or underserved diseases. The Company's growing business is diversified across three business units: orphan, rheumatology and primary care, and is driven by a successful commercial model that focuses on differentiated, long-life medicines, innovative patient access programs and a disciplined business development strategy.

NOTE 2 – SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Basis of Presentation

The accompanying consolidated financial statements have been prepared in accordance with the accounting principles generally accepted in the United States of America ("GAAP") and in accordance with the instructions for Form 10-K and Article 3 of Regulation S-X.

Principles of Consolidation

The consolidated financial statements include the Company's accounts and those of its wholly owned subsidiaries. All intercompany accounts and transactions have been eliminated. Additionally, certain reclassifications have been made to prior-period financial statements to conform to the 2016 presentation.

Segment Information

The Company operates as one segment. Management does not segment its business for internal reporting.

Use of Estimates

The preparation of the accompanying consolidated financial statements in conformity with GAAP requires management to make certain estimates and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent liabilities at the date of the financial statements and reported amounts of revenues and expenses during the reporting period. Actual results could differ from those estimates.

Foreign Currency Translation and Transactions

The reporting currency of the Company and its subsidiaries is the U.S. dollar.

The U.S. dollar is the functional currency for the Company's U.S. based businesses and the majority of its subsidiaries. Other foreign subsidiaries have the following functional currencies: Euro, Canadian Dollar, Israeli New Shekel and the British Pound. Foreign currency-denominated assets and liabilities of these subsidiaries are translated into U.S. dollars based on exchange rates prevailing at the end of the period, revenues and expenses are translated at average exchange rates prevailing during the corresponding period, and shareholders' equity (deficit) accounts are translated at historical exchange rates as of the date of any equity transaction. The effects of foreign exchange gains and losses arising from the translation of assets and liabilities of those entities where the functional currency is not the U.S. dollar are included as a component of accumulated other comprehensive (loss) income.

Gains and losses resulting from foreign currency transactions are reflected within the Company's results of operations. During the years ended December 31, 2016, 2015 and 2014, the Company recorded a foreign exchange loss of $1.0 million, $1.2 million and $3.9 million, respectively. The Company does not currently utilize and has not in the past utilized any foreign currency hedging strategies to mitigate the effect of its foreign currency exposure.

Revenue Recognition

Revenue is recognized when all of the following criteria are met: persuasive evidence of an arrangement exists; delivery has occurred or services have been rendered; the price is fixed or determinable; and collectability is reasonably assured. Some of the Company's agreements contain multiple elements and in accordance with these agreements, the Company may be eligible for upfront license fees, marketing or commercial milestones and payment for medicine deliveries.

Revenue From Medicine Deliveries

Revenue from medicine deliveries comprises a significant amount of the Company's gross sales. The Company recognizes revenue from the sale of its medicines when delivery has occurred, title has transferred, the selling price is fixed or determinable, collectability is reasonably assured and the Company has no further performance obligations. In addition, revenue is only recognized when the right of return no longer exists (which is the earlier of the medicine being dispensed through patient prescriptions or the expiration of the right of return) or when medicine returns can be reasonably estimated. Due to the Company's ability to reasonably estimate and determine allowances for co-pay and other patient assistance, medicine returns, rebates and discounts based on its own internal data for DUEXIS and RAYOS or data relating to prior sales of its acquired medicines which was received in connection with the acquisition of those medicines, the Company recognizes revenue at the point of sale to wholesale pharmaceutical distributors and retail chains for all currently distributed medicines.

Revenue From Upfront License Fees

The Company recognizes revenues from the receipt of non-refundable, upfront license fees. In situations where the licensee is able to obtain stand-alone value from the license and no further performance obligations exist on the Company's part, revenues are recognized on the earlier of when payments are received or collection is reasonably assured. Where continuing involvement by the Company is required in the form of technology transfer, medicine manufacturing or technical support, revenues are deferred and recognized over the term of the agreement.

Revenue From Milestone Receipts

Milestone payments are recognized as revenue based on achievement of the associated milestones, as defined in the relevant agreements. Revenue from a milestone achievement is recognized when earned, as evidenced by acknowledgment from the Company's partner, provided that (1) the milestone event is substantive and its achievability was not reasonably assured at the inception of the agreement, (2) the milestone represents the culmination of an earnings process and (3) the milestone payment is non-refundable. If any of these criteria are not met, revenue from the milestone achievement is recognized over the remaining minimum period of the Company's performance obligations under the agreement.

As of December 31, 2016 and 2015, deferred revenues related to milestone and upfront payments received were $11.1 million and $10.2 million, respectively.

Medicine Sales Discounts and Allowances

The Company records allowances for medicine returns, rebates and discounts at the time of sale to wholesale pharmaceutical distributors and retail chains. The Company is required to make significant judgments and estimates in determining some of these allowances. If actual results differ from its estimates, the Company will be required to make adjustments to these allowances in the future.

Commercial Rebates

The Company participates in certain commercial rebate programs. Under these rebate programs, the Company pays a rebate to the commercial entity or third-party administrator of the program. The Company accrues estimated rebates based on contract prices, estimated percentages of medicine sold to qualified patients and estimated levels of inventory in the distribution channel and records the rebate as a reduction of revenue. Accrued commercial rebates are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Distribution Service Fees

The Company includes distribution service fees paid to its wholesalers for distribution and inventory management services as a reduction to revenue. The Company accrues estimated distribution fees based on contractually determined amounts, typically as a percentage of revenue, and records the fees as a reduction of revenue. Accrued distribution service fees are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Patient Access Programs

The Company offers discount card and other programs such as its HorizonCares program to patients under which the patient receives a discount on his or her prescription. In certain circumstances when a patient's prescription is rejected by a managed care vendor, the Company will pay for the full cost of the prescription. The Company reimburses pharmacies for this discount through third-party vendors. The Company reduces gross sales by the amount of actual co-pay and other patient assistance in the period based on the invoices received. The Company also records an accrual to reduce gross sales for estimated co-pay and other patient assistance on units sold to distributors that have not yet been prescribed/dispensed to a patient. The estimate is based on contract prices, estimated percentages of medicine that will be prescribed to qualified patients, average assistance paid based on reporting from the third-party vendors and estimated levels of inventory in the distribution channel. Accrued co-pay and other patient assistance fees are included in "accrued trade discounts and rebates" on the consolidated balance sheet. Patient assistance programs include both co-pay assistance and fully bought down prescriptions.

Sales Returns

Consistent with industry practice, the Company maintains a return policy that allows customers to return medicine within a specified period prior to and subsequent to the medicine expiration date. Generally, medicine may be returned for a period beginning six months prior to its expiration date and up to one year after its expiration date. The right of return expires on the earlier of one year after the medicine expiration date or the time that the medicine is dispensed to the patient. The majority of medicine returns result from medicine dating, which falls within the range set by the Company's policy, and are settled through the issuance of a credit to the customer. The estimate of the provision for returns is based upon the Company's historical experience with actual returns, which is applied to the level of sales for the period that corresponds to the period during which the customer may return medicines. This period is known to the Company based on the shelf life of medicines at the time of shipment. The Company records sales returns as an allowance against accounts receivable and a reduction of revenue.

Prompt Pay Discounts

As an incentive for prompt payment, the Company offers a 2% cash discount to customers. The Company expects that all customers will comply with the contractual terms to earn the discount. The Company records the discount as an allowance against accounts receivable and a reduction of revenue.

Government Rebates

The Company participates in certain federal government rebate programs, such as Medicare and Medicaid. The Company accrues estimated rebates based on percentages of medicine sold to qualified patients, estimated rebate percentages and estimated levels of inventory in the distribution channel that will be sold to qualified patients and records the rebates as a reduction of revenue. Accrued government rebates are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Government Chargebacks

The Company provides discounts to federal government qualified entities with whom the Company has contracted. These federal entities purchase medicines from the wholesale pharmaceutical distributors at a discounted price, and the wholesale pharmaceutical distributors then charge back to the Company the difference between the current retail price and the contracted price that the federal entities paid for the medicines. The Company accrues estimated chargebacks based on contract prices and sell-through sales data obtained from third-party information and records the chargeback as a reduction of revenue. Accrued government chargebacks are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Bad Debt Expense

The Company's medicines are sold to wholesale pharmaceutical distributors and retail chains. The Company monitors its accounts receivable balances to determine the impact, if any, of such factors as changes in customer concentration, credit risk and the realizability of its accounts receivable, and records a bad debt reserve when applicable. The Company has established an immaterial reserve for bad debt expense and recorded an immaterial amount of bad debt expense for the years ended December 31, 2016 and 2015.

Inventories

Inventories are stated at the lower of cost or market value, using the first-in, first-out convention. Inventories consist of raw materials, work-in-process and finished goods. The Company has entered into manufacturing and supply agreements for the manufacture or purchase of raw materials and production supplies. The Company's inventories include the direct purchase cost of materials and supplies and manufacturing overhead costs. The Company reviews its inventory balance and purchase obligations to assess if it has obsolete or excess inventory, and records a charge to "cost of goods sold" when applicable.

Inventories acquired in business combinations are recorded at their estimated fair values. "Step-up" represents the write-up of inventory from the lower of cost or market value (the historical book value as previously recorded on the acquired company's balance sheet) to fair market value at the acquisition date. Inventory step-up expense is recorded in the consolidated statement of comprehensive (loss) income based on actual sales, or usage, using the first-in, first-out convention.

Inventories exclude medicine sample inventory, which is included in other current assets and is expensed as a component of sales and marketing expense when shipped to sales representatives. As of December 31, 2016 and 2015, the Company had medicine sample inventory of $10.2 million and $4.7 million, respectively.

Cost of Goods Sold

The Company recognizes cost of goods sold in connection with its sales of each of its distributed medicines. Cost of goods sold includes all costs directly related to the acquisition of the Company's medicines from its third-party manufacturers, including freight charges and other direct expenses such as insurance and supply chain costs. Cost of goods sold also includes amortization of intellectual property as described in the intangible assets and goodwill accounting policy below, inventory step-up expense, royalty payments to third parties, royalty accretion expense, changes in estimates associated with the contingent royalty liability as described in the accrued contingent royalty accounting policy below and loss on inventory purchase commitments.

Preclinical Studies and Clinical Trial Accruals

The Company's preclinical studies and clinical trials have historically been conducted by third-party contract research organizations and other vendors. Preclinical study and clinical trial expenses are based on the services received from these contract research organizations and vendors. Payments depend on factors such as the milestones accomplished, successful enrollment of certain numbers of patients and site initiation. In accruing service fees, the Company estimates the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from the estimate, the Company adjusts the accrual accordingly. To date, the Company has had no significant adjustments to accrued clinical expenses. As of December 31, 2016 and December 31, 2015, the Company had preclinical study and clinical trial accruals of $11.0 million and $4.7 million, respectively.

Net (Loss) Income Per Share

Basic net (loss) income per share is computed by dividing net (loss) income by the weighted-average number of ordinary shares outstanding during the period. Diluted earnings per share ("EPS") reflects the potential dilution beyond shares for basic EPS that could occur if securities or other contracts to issue ordinary shares were exercised, converted into ordinary shares, or resulted in the issuance of ordinary shares that would have shared in the Company's earnings.

Cash and Cash Equivalents

We consider all highly liquid investments, readily convertible to cash, that mature within three months or less from date of purchase to be cash equivalents. Cash and cash equivalents primarily consist of cash balances and money market funds. Cash and cash equivalents were $509.1 million and $859.6 million as of December 31, 2016 and 2015, respectively. The Company generally invests excess cash in money market funds and other financial instruments with short-term durations, based upon operating requirements.

Restricted Cash

Restricted cash consists primarily of balances in interest-bearing money market accounts required by a vendor for the Company's sponsored employee business credit card program and collateral for a letter of credit. As of December 31, 2016 and 2015, the Company had restricted cash of $7.1 million and $1.9 million, respectively.

Fair Value of Financial Instruments

The carrying amounts of the Company's financial instruments, including cash and cash equivalents, restricted cash, accounts receivable, accounts payable and accrued expenses, approximate their fair values due to their short maturities.

At December 31, 2013 and at the final measurement date of June 27, 2014, the estimated fair value of the Company's derivative liability related to the convertible portion of the 5.00% Convertible Senior Notes due 2018 (the "Convertible Senior Notes") was derived utilizing the binomial lattice approach for the valuation of convertible instruments. Assumptions used in the calculation included, among others, determining the appropriate credit spread using benchmarking analysis and solving for the implied credit spread, calculating the fair value of the stock component using a discounted risk free rate and borrowing cost and calculating the fair value of the note component using a discounted credit adjusted discount rate. Based on the assumptions used to determine the fair value of the derivative liability associated with the Convertible Senior Notes, the Company concluded that these inputs were Level 3 inputs.

Business Combinations

The Company accounts for business combinations in accordance with the guidance in ASC 805, *Business Combinations,* in which acquired assets and liabilities are measured at their respective estimated fair values as of the acquisition date. The Company may be required, as in the case of intangible assets, contingent royalties or derivatives, to determine the fair value associated with these amounts by estimating the fair value using an income approach under the discounted cash flow method, which may include revenue projections and other assumptions made by the Company to determine the fair value. As further described in the "Recent Accounting Pronouncements" section below, the Company plans to adopt Accounting Standards Update ("ASU") No. 2017-01, *Business Combinations (Topic 805): Clarifying the Definition of a Business* in the first quarter of 2017. The adoption is not expected to have a material impact on the consolidated financial statements.

Property and Equipment, Net

Property and equipment are stated at cost less accumulated depreciation. Depreciation is recognized using the straight-line method over the estimated useful lives of the related assets for financial reporting purposes and an accelerated method for income tax reporting purposes. Upon retirement or sale of an asset, the cost and related accumulated depreciation and amortization are removed from the balance sheet and the resulting gain or loss is reflected in operations. Repair and maintenance costs are charged to expenses as incurred and improvements are capitalized.

Leasehold improvements are amortized on a straight-line basis over the term of the applicable lease, or the useful life of the assets, whichever is shorter.

Depreciation and amortization periods for the Company's property and equipment are as follows:

Machinery and equipment	5 to 7 years
Furniture and fixtures	3 to 5 years
Computer equipment	3 years
Software	3 years
Trade show equipment	3 years

The Company capitalizes software development costs associated with internal use software, including external direct costs of materials and services and payroll costs for employees devoting time to a software project. Costs incurred during the preliminary project stage, as well as costs for maintenance and training, are expensed as incurred.

Software includes internal-use software acquired and modified to meet the Company's internal requirements. Amortization commences when the software is ready for its intended use.

Intangible Assets

Definite-lived intangible assets are amortized over their estimated useful lives. The Company reviews its intangible assets when events or circumstances may indicate that the carrying value of these assets exceeds their fair value. The Company measures fair value based on the estimated future discounted cash flows associated with these assets in addition to other assumptions and projections that the Company deems to be reasonable and supportable. The total estimated useful lives, from the date of acquisition, for all identified intangible assets that are subject to amortization are as follows:

Intangible Asset	Estimated Useful Life
ACTIMMUNE developed technology	13 years
BUPHENYL developed technology	7 years
Customer relationships	10 years
KRYSTEXXA developed technology	12 years
LODOTRA and RAYOS developed technology	12 years
MIGERGOT developed technology	10 years
PENNSAID 2% developed technology	6 years
PROCYSBI developed technology (ex-U.S. rights)	9 years
PROCYSBI developed technology (U.S. rights)	13 years
RAVICTI developed technology	11 years
VIMOVO developed technology	5 years

The Company determined that no impairment of the above definite-lived intangible assets existed as of December 31, 2016.

Indefinite-lived intangible assets consist of capitalized in-process research and development ("IPR&D"). IPR&D assets represent capitalized incomplete research projects that the Company acquired through business combinations. Such assets are initially measured at their acquisition date fair values and are tested for impairment, until completion or abandonment of research and development efforts associated with the projects. An IPR&D asset is considered abandoned when research and development efforts associated with the asset have ceased, and there are no plans to sell or license the asset or derive value from the asset. At that point, the asset is considered to be disposed of and is written off. Upon successful completion of each project, the Company will make a determination about the then remaining useful life of the intangible asset and begin amortization. The Company tests its indefinite-lived intangible assets, including IPR&D assets, for impairment annually during the fourth quarter and more frequently if events or changes in circumstances indicate that it is more likely than not that the asset is impaired.

IPR&D as of December 31, 2015 related to the research and development project to evaluate ACTIMMUNE in the treatment of FA, which the Company acquired in the Vidara Merger. At the time of the Vidara Merger, IPR&D was considered separable from the business as the project could be sold to a third party, and the Company assigned a fair value of $66.0 million to the intangible asset using an income approach in its purchase accounting. On December 8, 2016, the Company announced that the Phase 3 trial, STEADFAST, evaluating ACTIMMUNE for the treatment of FA did not meet its primary endpoint of a statistically significant change from baseline in the modified FARS-mNeuro at twenty-six weeks versus treatment with placebo. In addition, the secondary endpoints did not meet statistical significance. No new safety findings were identified on initial review of data other than those already noted in the ACTIMMUNE prescribing information for approved indications. The Company, in conjunction with the independent Data Safety Monitoring Board, the principal investigator and FARA, Collaborative Clinical Research Network in FA, determined that, based on the trial results, the STEADFAST program would be discontinued, including the twenty-six week extension study and the long-term safety study. The IPR&D has no alternative use or economic value as a result of the cancellation of the project, and the Company recorded an impairment charge of $66.0 million during the three months ended December 31, 2016 to fully write off the value of the asset on its consolidated balance sheet.

Goodwill

Goodwill represents the excess of the purchase price of acquired businesses over the estimated fair value of the identifiable net assets acquired. Goodwill is not amortized but is tested for impairment at least annually at the reporting unit level or more frequently if events or changes in circumstances indicate that the asset might be impaired. Impairment loss, if any, is recognized based on a comparison of the fair value of the asset to its carrying value, without consideration of any recoverability. The Company tests goodwill for impairment annually during the fourth quarter and whenever indicators of impairment exist by first assessing qualitative factors to determine whether it is more likely than not that the fair value is less than its carrying amount. If the Company concludes it is more likely than not that the fair value of a reporting unit is less than its carrying amount, a quantitative impairment test is performed. If the Company concludes that goodwill is impaired, it will record an impairment charge in its consolidated statement of comprehensive (loss) income. Based upon the Company's most recent annual impairment test performed in the fourth quarter of 2016, the Company concluded goodwill was not impaired.

Research and Development Expenses

Research and development expenses include, but are not limited to, payroll and other personnel expenses, consultant expenses, expenses incurred under agreements with contract research organizations to conduct clinical trials and expenses incurred to manufacture clinical trial materials.

Sales and Marketing Expenses

Sales and marketing expenses consist principally of payroll of sales representatives and marketing and support staff, travel and other personnel-related expenses, marketing materials and distributed sample inventories. In addition, sales and marketing expenses include the Company's medical affairs expenses, which consist of expenses related to scientific publications, health outcomes, biostatistics, medical education and information, and medical communications.

Deferred Financing Costs

Costs incurred in connection with debt financings have been capitalized to "Long-term debt, net, net of current" and "Exchangeable notes, net" in the Company's consolidated balance sheets as deferred financing costs, and are charged to interest expense using the effective interest method over the terms of the related debt agreements. These costs include document preparation costs, commissions, fees and expenses of investment bankers and underwriters, and accounting and legal fees.

Concentration of Credit Risk and Other Risks and Uncertainties

Financial instruments that may potentially subject the Company to significant concentrations of credit risk consist of cash and cash equivalents. The Company's cash and cash equivalents are invested in deposits with various banks in the United States, Ireland, Bermuda, Switzerland, Luxembourg and Germany that management believes are creditworthy. At times, deposits in these banks may exceed the amount of insurance provided on such deposits. To date, the Company has not experienced any losses on its deposits of cash and cash equivalents.

The purchase cost of ACTIMMUNE under a contract with Boehringer Ingelheim RCV GmbH & Co. KG ("Boehringer Ingelheim") as well as sales contracts relating to LODOTRA and QUINSAIR, and sales of PROCYSBI outside the United States are principally denominated in Euros and are subject to foreign currency risk. The Company also incurs certain operating expenses in currencies other than the U.S. dollar in relation to its Ireland operations and other foreign subsidiaries, including Horizon Pharma Switzerland GmbH. Following the acquisition of Raptor, the Company is subject to increased foreign currency risk for its operations in Europe due to an increased level of sales and operating expenses denominated in Euros. The Company does not currently utilize and has not in the past utilized any foreign currency hedging strategies to mitigate the effect of its foreign currency.

Historically, the Company's accounts receivable balances have been highly concentrated with a select number of customers, consisting primarily of large wholesale pharmaceutical distributors who, in turn, sell the medicines to pharmacies, hospitals and other customers. As of December 31, 2016, 2015 and 2014, the Company's top three customers accounted for approximately 78%, 72% and 68%, respectively, of the Company's total outstanding accounts receivable balances.

The Company depends on single-source suppliers and manufacturers for certain of its medicines, medicine candidates and their active pharmaceutical ingredients.

Comprehensive (Loss) Income

Comprehensive (loss) income is composed of net (loss) income and other comprehensive (loss) income ("OCI"). OCI includes certain changes in shareholders' equity that are excluded from net (loss) income, which consist of foreign currency translation adjustments and pension remeasurements. The Company reports the effect of significant reclassifications out of accumulated OCI on the respective line items in net income if the amount being reclassified is required under GAAP to be reclassified in its entirety to net income. For other amounts that are not required under GAAP to be reclassified in their entirety to net income in the same reporting period, the Company cross-references other disclosures required under GAAP that provide additional detail about those amounts. As of December 31, 2016, 2015 and 2014 accumulated other comprehensive loss was $3.1 million, $2.7 million and $4.4 million, respectively.

Share-Based Compensation

The Company accounts for employee share-based compensation by measuring and recognizing compensation expense for all share-based payments based on estimated grant date fair values. The Company uses the straight-line method to allocate compensation cost to reporting periods over each awardee's requisite service period, which is generally the vesting period.

Accrued Contingent Royalties

The Company's accrued contingent royalties consist of the contingent royalty obligations assumed by the Company related to the Company's acquisitions of rights to ACTIMMUNE, BUPHENYL, KRYSTEXXA, MIGERGOT, PROCYSBI, RAVICTI and VIMOVO. At the time of each acquisition, the Company assigned an estimated fair value to its contingent liability for royalties. The estimated royalty liability is based on anticipated revenue streams utilizing the income approach under the discounted cash flow method. The estimated liability for royalties is increased or decreased over time to reflect the change in its present value and accretion expense is recorded as part of cost of goods sold. The Company evaluates the adequacy of the estimated contingent royalty liability at least annually in the fourth quarter, or whenever events or changes in circumstances indicate that an evaluation of the estimate is necessary. As part of its evaluation, the Company adjusts the carrying value of the liability to the present value of the revised estimated cash flows using the original discount rate. Any adjustment to the liability is recorded as an increase or reduction in cost of goods sold. The royalty liability is included in current and long-term accrued royalties on the consolidated balance sheets.

Contingencies

From time to time, the Company may become involved in claims and other legal matters arising in the ordinary course of business. The Company records accruals for loss contingencies to the extent that it concludes that it is probable that a liability has been incurred and the amount of the related loss can be reasonably estimated. Legal fees and other expenses related to litigation are expensed as incurred and included in selling, general and administrative expenses.

Recent Accounting Pronouncements

From time to time, the Company adopts, as of the specified effective date, new accounting pronouncements issued by the Financial Accounting Standards Board ("FASB") or other standard setting bodies. Unless otherwise discussed, the Company believes that the impact of recently issued standards that are not yet effective will not have a material impact on the Company's financial position or results of operations upon adoption.

In May 2014, the FASB issued ASU No. 2014-09, *Revenue from Contracts with Customers* ("ASC 606"). The new standard aims to achieve a consistent application of revenue recognition within the United States, resulting in a single revenue model to be applied by reporting companies under GAAP. Under the new model, recognition of revenue occurs when a customer obtains control of promised goods or services in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. In addition, the new standard requires that reporting companies disclose the nature, amount, timing, and uncertainty of revenue and cash flows arising from contracts with customers. The new standard is required to be applied retrospectively to each prior reporting period presented or retrospectively with the cumulative effect of initially applying it recognized at the date of initial application. In March 2016, April 2016 and December 2016, the FASB issued ASU No. 2016-08, *Revenue From Contracts with Customers (Topic 606): Principal Versus Agent Considerations*, ASU No. 2016-10, *Revenue From Contracts with Customers (Topic 606): Identifying Performance Obligations and Licensing, and ASU No. 2016-20, Technical Corrections and Improvements to Topic 606, Revenue From Contracts with Customers*, respectively, which further clarify the implementation guidance on principal versus agent considerations contained in ASU No. 2014-09. In May 2016, the FASB issued ASU 2016-12, narrow-scope improvements and practical expedients which provides clarification on assessing the collectability criterion, presentation of sales taxes, measurement date for non-cash consideration and completed contracts at transition. These standards will be effective for the Company beginning in the first quarter of 2018. Early adoption is permitted. The Company expects to elect the modified retrospective method and expects to identify similar performance obligations under ASC 606 as compared with deliverables and separate units of account previously identified. As a result, the Company expects the timing of the majority of its revenue to remain the same. Certain of the Company's contracts for sales outside the United States include contingent amounts of variable consideration that the Company was precluded from recognizing because of the requirement for amounts to be "fixed or determinable". However, the Company anticipates that ASC 606 will require it to estimate these amounts and as a result, the Company expects to recognize the majority of its revenue under such contracts earlier under ASC 606 than it would have recognized under current guidance. Otherwise, the adoption is not expected to have a material impact on the consolidated financial statements and related disclosures.

In August 2014, the FASB issued ASU No. 2014-15, *Presentation of Financial Statements — Going Concern (Subtopic 205-40): Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern.* ASU No. 2014-15 is intended to define management's responsibility to evaluate whether there is substantial doubt about an organization's ability to continue as a going concern and to provide related footnote disclosures. Substantial doubt about an entity's ability to continue as a going concern exists when relevant conditions and events, considered in the aggregate, indicate that it is probable that the entity will be unable to meet its obligations as they become due within one year after the date that the financial statements are issued (or available to be issued). ASU No. 2014-15 provides guidance to an organization's management, with principles and definitions that are intended to reduce diversity in the timing and content of disclosures that are commonly provided by organizations in the financial statement footnotes. ASU No. 2014-15 is effective for annual reporting periods ending after December 15, 2016 and to annual and interim periods thereafter. Early adoption is permitted. The Company adopted ASU No. 2014-15 on April 1, 2016, and the adoption did not have a material impact on the consolidated financial statements and related disclosures.

In April 2015, the FASB issued ASU No. 2015-03, *Interest-Imputation of Interest (Subtopic 835-30): Simplifying the Presentation of Debt Issuance Costs.* The amendments in this ASU require that debt issuance costs related to a recognized debt liability be presented in the balance sheet as a direct deduction from the carrying amount of that debt liability, consistent with debt discounts. In August 2015, the FASB issued ASU No. 2015-15, *Interest-Imputation of Interest (Subtopic 835-30): Presentation and Subsequent Measurement of Debt Issuance Costs Associated with Line-of-Credit Arrangements* which further clarifies the implementation guidance of ASU No. 2015-03. The amendments in these ASUs are effective for the financial statements issued for fiscal years beginning after December 15, 2015, and interim periods within those fiscal years. The Company adopted ASU No. 2015-03 on January 1, 2016. The following table summarizes the adjustments made to conform prior-period classifications as a result of the new guidance (in thousands):

	As of December 31, 2015		
	As filed	Reclassification	As adjusted
Other non-current assets	$ 8,581	$ (8,359)	$ 222
Exchangeable notes, net	(283,675)	786	(282,889)
Long-term debt, net, net of current	(857,440)	7,573	(849,867)

In April 2015, the FASB issued ASU No. 2015-05: *Intangibles—Goodwill and Other—Internal-Use Software (Subtopic 350-40): Customer's Accounting for Fees Paid in a Cloud Computing Arrangement* which provides guidance on a customer's accounting for fees paid in a cloud computing arrangement. Under the new standard, customers apply the same criteria as vendors to determine whether a cloud computing arrangement contains a software license or is solely a service contract. The amendments in this ASU, which may be applied prospectively or retrospectively, are effective for annual and interim periods beginning after December 15, 2015. The Company adopted ASU No. 2015-05 on January 1, 2016. The adoption did not have a material impact on the consolidated financial statements and related disclosures.

In July 2015, the FASB issued ASU No. 2015-11, *Inventory (Topic 330): Simplifying the Measurement of Inventory.* Under this new guidance, entities that measure inventory using any method other than last-in, first-out or the retail inventory method will be required to measure inventory at the lower of cost and net realizable value. The amendments in this ASU, which should be applied prospectively, are effective for annual and interim periods beginning after December 15, 2016. Early adoption is permitted. The Company adopted ASU No. 2015-11 on April 1, 2016, and the adoption did not have a material impact on the consolidated financial statements and related disclosures.

In September 2015, the FASB issued ASU No. 2015-16, *Business Combinations (Topic 805): Simplifying the Accounting for Measurement-Period Adjustments* ("ASC 805"). Under this guidance, an acquirer is required to recognize adjustments to provisional amounts that are identified during the measurement period in the reporting period in which the adjustment amounts are determined. The amendments in this ASU require that the acquirer record, in the same period's financial statements, the effect on earnings of changes in depreciation, amortization or other income effects, if any, as a result of the change to the provisional amounts, calculated as if the accounting had been completed at the acquisition date. The amendments in this ASU require an entity to present separately on the face of the income statement or disclose in the notes the portion of the amount recorded in current-period earnings by line item that would have been recorded in previous reporting periods if the adjustment to the provisional amounts had been recognized as of the acquisition date. The amendments in this ASU, which should be applied prospectively, are effective for annual and interim periods beginning after December 15, 2015. The Company adopted ASU No. 2015-16 on January 1, 2016, and the adoption did not have a material impact on the consolidated financial statements and related disclosures.

In February 2016, the FASB issued ASU No. 2016-02, *Leases (Topic 842).* Under ASU No. 2016-02, an entity will be required to recognize right-of-use assets and lease liabilities on its balance sheet and disclose key information about leasing arrangements. ASU No. 2016-02 offers specific accounting guidance for a lessee, a lessor and sale and leaseback transactions. Lessees and lessors are required to disclose qualitative and quantitative information about leasing arrangements to enable a user of the financial statements to assess the amount, timing and uncertainty of cash flows arising from leases. ASU No. 2016-02 is effective for annual reporting periods beginning after December 15, 2018, including interim periods within that reporting period, with early adoption permitted. At adoption, this update will be applied using a modified retrospective approach. The Company is currently in the process of evaluating the impact of adoption of ASU No. 2016-02 on its consolidated financial statements and related disclosures.

In March 2016, the FASB issued ASU No. 2016-09, *Compensation-Stock Compensation (Topic 718): Improvements to Employee Share-Based Payment Accounting*. The updated guidance will change how companies account for certain aspects of share-based payments to employees. Entities will be required to recognize the income tax effects of awards in the statement of income when the awards vest or are settled. The guidance on accounting for an employee's use of shares to satisfy the statutory income tax withholding obligation and for forfeitures is changing, and the update requires companies to present excess tax benefits as an operating activity on the statement of cash flows rather than as a financing activity. The amendments in this update will be effective for annual periods beginning after December 15, 2016 and interim periods within those annual periods. Early adoption is permitted. The Company is currently in the process of evaluating the impact of adoption of ASU No. 2016-09 on its consolidated financial statements and related disclosures.

In August 2016, the FASB issued ASU No. 2016-15, *Statement of Cash Flows (Topic230): Classification of Certain Cash Receipts and Cash Payments*. The amendments in this ASU provide guidance on the following eight specific cash flow classification issues: (1) debt prepayment or debt extinguishment costs; (2) settlement of zero-coupon debt instruments or other debt instruments with coupon interest rates that are insignificant in relation to the effective interest rate of the borrowing; (3) contingent consideration payments made after a business combination; (4) proceeds from the settlement of insurance claims; (5) proceeds from the settlement of corporate-owned life insurance policies, including bank-owned life insurance policies; (6) distributions received from equity method investees; (7) beneficial interests in securitization transactions; and (8) separately identifiable cash flows and application of the predominance principle. Current GAAP does not include specific guidance on these eight cash flow classification issues. The amendments of this ASU are effective for reporting periods beginning after December 15, 2017, with early adoption permitted. The adoption of ASU No. 2016-15 is not expected to have a material impact on the consolidated financial statements and related disclosures.

In October 2016, the FASB issued ASU No. 2016-16, *Income Taxes (Topic 740): Intra-Entity Transfers of Assets Other Than Inventory*. ASU No. 2016-16 was issued to improve the accounting for the income tax consequences of intra-entity transfers of assets other than inventory. Current GAAP prohibits the recognition of current and deferred income taxes for an intra-entity asset transfer until the asset has been sold to an outside party which has resulted in diversity in practice and increased complexity within financial reporting. ASU No. 2016-16 would require an entity to recognize the income tax consequences of an intra-entity transfer of an asset other than inventory when the transfer occurs and do not require new disclosure requirements. ASU No. 2016-16 is effective for annual reporting periods beginning after December 15, 2017, and interim periods within those annual periods. Early adoption is permitted and the adoption of ASU No. 2016-16 should be applied on a modified retrospective basis through a cumulative-effect adjustment directly to retained earnings as of the beginning of the period of adoption. The Company is currently in the process of evaluating the impact of adoption of ASU No. 2016-16 on its consolidated financial statements and related disclosures.

In November 2016, the FASB issued ASU No. 2016-18, *Statement of Cash Flows (Topic 230): Restricted Cash*, which addresses diversity in practice related to the classification and presentation of changes in restricted cash on the statement of cash flows. ASU No. 2016-18 will require that a statement of cash flows explain the change during the period in the total of cash, cash equivalents, and amounts generally described as restricted cash or restricted cash equivalents. Therefore, amounts generally described as restricted cash and restricted cash equivalents should be included with cash and cash equivalents when reconciling the beginning-of-period and end-of-period total amounts shown on the statement of cash flows. ASU No. 2016-18 is effective for fiscal years, and interim periods within those years, beginning after December 15, 2017. Early adoption is permitted. The adoption of ASU No. 2016-18 is not expected to have a material impact on the consolidated financial statements and related disclosures.

In January 2017, the FASB issued ASU No. 2017-01, *Business Combinations (Topic 805): Clarifying the Definition of a Business*. The amendments in ASU No. 2017-01 clarify the definition of a business with the objective of adding guidance to assist entities with evaluating whether transactions should be accounted for as acquisitions (or disposals) of assets or businesses. The definition of a business affects many areas of accounting including acquisitions, disposals, goodwill, and consolidation. The guidance is effective for annual periods beginning after December 15, 2017, including interim periods within those periods. Early adoption is permitted. The Company plans to adopt ASU No. 2017-01 in the first quarter of 2017. The adoption is not expected to have a material impact on the consolidated financial statements and related disclosures.

In January 2017, the FASB issued ASU No. 2017-04, *Intangibles - Goodwill and Other (Topic 350): Simplifying the Test for Goodwill Impairment*, to eliminate the second step of the goodwill impairment test. ASU No. 2017-04 requires an entity to measure a goodwill impairment loss as the amount by which the carrying value of a reporting unit exceeds its fair value. Additionally, an entity should include the income tax effects from any tax deductible goodwill on the carrying value of the reporting unit when measuring a goodwill impairment loss, if applicable. ASU No. 2017-04 is effective for fiscal years, and interim periods within those years, beginning after December 15, 2019. Early adoption is permitted for interim or annual goodwill impairment tests performed on testing dates after January 1, 2017. The Company does not expect the adoption of ASU No. 2017-04 to have a material impact to its consolidated financial position, results of operations or cash flow.

NOTE 3 – NET (LOSS) INCOME PER SHARE

The following table presents basic net (loss) income per share for the years ended December 31, 2016, 2015 and 2014 (in thousands, except share and per share data):

	For the Years Ended December 31,		
	2016	2015	2014
Basic earnings per share calculation:			
Net (loss) income	$ (166,834)	$ 39,532	$ (263,603)
Weighted average of ordinary shares outstanding	160,699,543	148,788,020	83,751,129
Basic net (loss) income per share	$ (1.04)	$ 0.27	$ (3.15)

The following table presents diluted net (loss) income per share for the years ended December 31, 2016, 2015 and 2014 (in thousands, except share and per share data):

	For the Years Ended December 31,		
	2016	2015	2014
Diluted earnings per share calculation:			
Net (loss) income	$ (166,834)	$ 39,532	$ (263,603)
Weighted average of ordinary shares outstanding	160,699,543	155,923,251	83,751,129
Diluted net (loss) income per share	$ (1.04)	$ 0.25	$ (3.15)

Basic net (loss) income per share is computed by dividing net (loss) income by the weighted-average number of ordinary shares outstanding during the period. Diluted EPS reflects the potential dilution beyond shares for basic EPS that could occur if securities or other contracts to issue ordinary shares were exercised, converted into ordinary shares, or resulted in the issuance of ordinary shares that would have shared in the Company's earnings.

The outstanding securities listed in the table below were excluded from the computation of diluted loss per ordinary share for the years ended December 31, 2016, 2015 and 2014 due to being anti-dilutive:

	For the Years Ended December 31,		
	2016	2015	2014
Stock options	7,515,297	2,853,821	7,027,683
Restricted stock units	492,030	817,168	1,618,502
Performance stock units	5,247,987	1,074	—
Employee stock purchase plans	56,805	1,046,275	—
Warrants	1,123,737	2,416,894	6,683,811
Convertible Senior Notes	—	—	11,369,398
	14,435,856	7,135,232	26,699,394

The potentially dilutive impact of the Horizon Pharma Investment Limited ("Horizon Investment"), a wholly owned subsidiary of the Company, March 2015 private placement of $400.0 million aggregate principal amount of 2.50% Exchangeable Senior Notes due 2022 (the "Exchangeable Senior Notes") is determined using a method similar to the treasury stock method. Under this method, no numerator or denominator adjustments arise from the principal and interest components of the Exchangeable Senior Notes because the Company has the intent and ability to settle the Exchangeable Senior Notes' principal and interest in cash. Instead, the Company is required to increase the diluted EPS denominator by the variable number of shares that would be issued upon conversion if it settled the conversion spread obligation with shares. For diluted EPS purposes, the conversion spread obligation is calculated based on whether the average market price of the Company's ordinary shares over the reporting period is in excess of the exchange price of the Exchangeable Senior Notes. There was no calculated spread added to the denominator for the years ended December 31, 2016 and 2015.

NOTE 4 – BUSINESS ACQUISITIONS AND OTHER ARRANGEMENTS

Business acquisitions

Raptor Acquisition

On October 25, 2016, the Company completed its acquisition of Raptor and acquired all of the issued and outstanding shares of Raptor's common stock for $9.00 per share. The acquisition added two medicines, PROCYSBI and QUINSAIR, to the Company's medicine portfolio. Through the acquisition, the Company expects to leverage as well as expand the existing infrastructure of its orphan disease business. Following completion of the acquisition, Raptor became a wholly owned subsidiary of the Company and converted to a limited liability company, changing its name to Horizon Pharmaceutical LLC. The Company financed the transaction through $300.0 million of aggregate principal amount of 2024 Senior Notes, $375.0 million aggregate principal amount of loans pursuant to an amendment to the Company's existing credit agreement, as described in Note 17, and cash on hand. The total consideration for the acquisition was approximately $860.8 million, including cash acquired of $24.9 million and $56.0 million to repay Raptor's outstanding debt, and was composed of the following (in thousands):

Cash	$	841,494
Net settlements on the exercise of stock options and restricted stock units		19,268
Total consideration	$	860,762

During the year ended December 31, 2016, the Company incurred $38.3 million in Raptor acquisition-related costs including advisory, legal, accounting, valuation, severance, retention bonuses and other professional and consulting fees, which were accounted for as "general and administrative" expenses in the consolidated statements of comprehensive loss.

Pursuant to ASC 805, the Company accounted for the Raptor acquisition as a business combination using the acquisition method of accounting. Identifiable assets and liabilities of Raptor, including identifiable intangible assets, were recorded based on their estimated fair values as of the date of the closing of the acquisition. The excess of the purchase price over the fair value of the net assets acquired was recorded as goodwill. Significant judgment was required in determining the estimated fair values of developed technology intangible assets, inventories and certain other assets and liabilities. Such preliminary valuation required estimates and assumptions including, but not limited to, estimating future cash flows and direct costs in addition to developing the appropriate discount rates and current market profit margins. The Company's management believes the fair values recognized for the assets acquired and the liabilities assumed are based on reasonable estimates and assumptions. Accordingly, the purchase price adjustments are preliminary and are subject to further adjustments as additional information becomes available and as additional analyses are performed, and such further adjustments may be material.

The following table summarizes the preliminary fair values assigned to the assets acquired and the liabilities assumed by the Company, along with the resulting goodwill (in thousands):

(Liabilities assumed) and assets acquired:	Allocation
Accounts payable	$ (4,572)
Accrued expenses	(23,773)
Accrued trade discounts and rebates	(6,377)
Deferred tax liabilities	(237,166)
Contingent royalty liability	(102,000)
Accrued royalties	(2,705)
Other non-current liability	(25,500)
Cash and cash equivalents	24,897
Restricted cash	1,350
Accounts receivable, net	17,767
Inventories	74,463
Prepaid expenses and other current assets	4,194
Property and equipment	3,373
Developed technology	946,000
Other non-current assets	1,765
Goodwill	189,046
Fair value of consideration paid	$ 860,762

Inventories acquired included raw materials, work in process and finished goods for PROCYSBI and QUINSAIR. Inventories were recorded at their preliminary estimated fair values. The fair value of finished goods has been determined based on the estimated selling price, net of selling costs and a margin on the selling costs. The fair value of work in process has been determined based on estimated selling price, net of selling costs and costs to complete the manufacturing, and a margin on the selling and manufacturing costs. The fair value of raw materials was estimated to equal the replacement cost. A step-up in the value of inventory of $67.0 million was recorded in connection with the acquisition. During the three months ended December 31, 2016, the Company recorded inventory step-up expense of $22.4 million related to PROCYSBI and QUINSAIR.

Other tangible assets and liabilities were valued at their respective carrying amounts as management believes that these amounts approximated their acquisition date fair values.

Other non-current liability of $25.5 million represents the fair value of an assumed contingent liability, arising from contingent payments associated with development, regulatory and commercial milestones following Raptor's acquisition of QUINSAIR.

Identifiable intangible assets and liabilities acquired include developed technology and contingent royalties. The preliminary estimated fair values of the developed technology and contingent royalties represent preliminary valuations performed with the assistance of an independent appraisal firm based on management's estimates, forecasted financial information and reasonable and supportable assumptions.

Developed technology intangible asset reflects the estimated fair value of Raptor's rights to its currently marketed medicine, PROCYSBI. The preliminary fair value of developed technology was determined using an income approach. The income approach explicitly recognizes that the fair value of an asset is premised upon the expected receipt of future economic benefits such as earnings and cash inflows based on current sales projections and estimated direct costs for Raptor's medicines. Indications of value were developed by discounting these benefits to their acquisition-date worth at a discount rate of 12.5%. The fair value of the PROCYSBI developed technology was capitalized as of the Raptor acquisition date and is subsequently being amortized over approximately thirteen years and nine years for the U.S. rights and ex-U.S. rights, respectively, which are the periods in which over 90% of the estimated cash flows are expected to be realized. The Company assigned no preliminary fair value to QUINSAIR developed technology as projections of future net sales do not exceed the related costs.

The Company has assigned a preliminary fair value of $102.0 million to a contingent liability for royalties potentially payable under previously existing agreements related to PROCYSBI. The royalties for PROCYSBI are payable under the terms of a license agreement with The Regents of the University of California, San Diego ("UCSD"). See Note 15 for details of the percentages of royalties payable under this agreement. The initial fair value of this liability was determined using a discounted cash flow analysis incorporating the estimated future cash flows of royalty payments resulting from future sales. The discount rate used was the same as for the fair value of the developed technology.

Deferred tax assets and liabilities arise from acquisition accounting adjustments where book values of certain assets and liabilities differ from their tax bases. Deferred tax assets and liabilities are recorded at the currently enacted rates which will be in effect at the time when the temporary differences are expected to reverse in the country where the underlying assets and liabilities are located. Raptor's developed technology as of the acquisition date was located primarily in the United States where a U.S. tax rate of 36.6% is being utilized and a significant deferred tax liability is recorded. Goodwill represents the excess of the preliminary acquisition consideration over the estimated fair value of net assets acquired and was recorded in the consolidated balance sheet as of the acquisition date. The Company does not expect any portion of this goodwill to be deductible for tax purposes.

Acquisition of Additional Rights to Interferon Gamma-1b

On May 18, 2016, the Company entered into a definitive agreement with Boehringer Ingelheim International to acquire certain rights to interferon gamma-1b, which Boehringer Ingelheim International currently commercializes under the trade names IMUKIN, IMUKINE, IMMUKIN and IMMUKINE (collectively, "IMUKIN") in an estimated thirty countries primarily in Europe and the Middle East. Under the terms of the agreement, the Company paid Boehringer Ingelheim International €5.0 million ($5.6 million when converted using a Euro-to-Dollar exchange rate at date of payment of 1.1132) upon signing and will pay €20.0 million upon closing, for certain rights for interferon gamma-1b in all territories outside of the United States, Canada and Japan, as the Company currently holds marketing rights to interferon gamma-1b in these territories. The transaction is expected to close in 2017 and the Company is continuing to work with Boehringer Ingelheim International to enable the transfer of applicable marketing authorizations. The Company currently markets interferon gamma-1b as ACTIMMUNE in the United States. The €5.0 million upfront amount paid in May 2016 had been included in "other assets" in the Company's consolidated balance sheet. Following the discontinuation of the STEADFAST program for ACTIMMUNE, as further described in Note 1, the Company recorded an impairment charge of €5.0 million ($5.3 million when converted using a Euro-to-Dollar exchange rate at date of impairment of 1.052) to fully write off the asset on its consolidated balance sheet during the three months ended December 31, 2016 as projections for future net sales of IMUKIN in these territories do not exceed the related costs. Upon closing, the Company expects to record the additional €20.0 million payment as an expense in its consolidated statement of comprehensive (loss) income.

Crealta Acquisition

On January 13, 2016, the Company completed its acquisition of all the membership interests of Crealta. The acquisition added two medicines, KRYSTEXXA and MIGERGOT, to the Company's medicine portfolio. The Crealta acquisition further diversified the Company's portfolio of medicines and aligned with its focus of acquiring value-enhancing, clinically differentiated, long-life medicines that treat orphan diseases. The total consideration for the acquisition was approximately $539.7 million, including cash acquired of $24.9 million, and was composed of the following before and after the measurement period adjustments (in thousands):

	Before	Adjustments	After
Cash	$ 536,181	$ 25	$ 536,206
Net settlements on the exercise of stock options and unrestricted units	3,526	—	3,526
Total consideration	$ 539,707	$ 25	$ 539,732

During the year ended December 31, 2016, the Company incurred $13.0 million in Crealta acquisition-related costs including advisory, legal, accounting, valuation, severance, retention bonuses and other professional and consulting fees, of which $12.4 million was accounted for as "general and administrative" expenses, $0.2 million was accounted for as "research and development" expenses and $0.4 million was accounted for as "costs of goods sold" in the consolidated statements of comprehensive loss.

Pursuant to ASC 805, the Company accounted for the Crealta acquisition as a business combination using the acquisition method of accounting. Identifiable assets and liabilities of Crealta, including identifiable intangible assets, were recorded based on their estimated fair values as of the date of the closing of the acquisition. The excess of the purchase price over the fair value of the net assets acquired was recorded as goodwill. Significant judgment was required in determining the estimated fair values of developed technology intangible assets, inventories and certain other assets and liabilities. Such preliminary valuation required estimates and assumptions including, but not limited to, estimating future cash flows and direct costs in addition to developing the appropriate discount rates and current market profit margins. The Company's management believes the fair values recognized for the assets acquired and the liabilities assumed are based on reasonable estimates and assumptions. Accordingly, the purchase price adjustments are preliminary and are subject to further adjustments as additional information becomes available and as additional analyses are performed, and such further adjustments may be material.

During the year ended December 31, 2016, the Company recorded measurement period adjustments related to developed technology, inventory and deferred tax liabilities, which resulted in a net increase in goodwill of $8.1 million. The measurement period adjustments were the result of an adjustment for inventory that was subsequently discovered to have been damaged and defective as of the acquisition date, a net working capital true-up adjustment and the alignment of Crealta's inventory and obsolescence reserve policy to the Company's policy.

The following table summarizes the preliminary fair values assigned to the assets acquired and the liabilities assumed by the Company, along with the resulting goodwill before and after the measurement period adjustments (in thousands):

(Liabilities assumed) and assets acquired:	Before	Adjustments	After
Accounts payable and accrued expenses	$ (4,543)	$ —	$ (4,543)
Accrued trade discounts and rebates	(1,424)	—	(1,424)
Deferred tax liabilities	(20,835)	694	(20,141)
Other non-current liabilities	(6,900)	—	(6,900)
Contingent royalty liabilities	(51,300)	—	(51,300)
Cash and cash equivalents	24,893	—	24,893
Accounts receivable	10,014	—	10,014
Inventories	169,054	(19,691)	149,363
Prepaid expenses and other current assets	1,382	—	1,382
Developed technology	417,300	10,900	428,200
Other non-current assets	275	—	275
Goodwill	1,791	8,122	9,913
Fair value of consideration paid	$ 539,707	$ 25	$ 539,732

Inventories acquired included raw materials, work in process and finished goods for KRYSTEXXA and MIGERGOT. Inventories were recorded at their preliminary estimated fair values. The fair value of finished goods has been determined based on the estimated selling price, net of selling costs and a margin on the selling costs. The fair value of work in process has been determined based on estimated selling price, net of selling costs and costs to complete the manufacturing, and a margin on the selling and manufacturing costs. The fair value of raw materials was estimated to equal the replacement cost. A step-up in the value of inventory of $163.6 million was originally recorded in connection with the acquisition and this was reduced to $144.3 million following the recording of $19.3 million in measurement period adjustments during the year ended December 31, 2016. During the year ended December 31, 2016, the Company recorded inventory step-up expense of $48.8 million.

Other tangible assets and liabilities were valued at their respective carrying amounts as management believes that these amounts approximated their acquisition date fair values.

Other non-current liabilities represented an assumed $6.9 million probable contingent liability which was released to "other income (expense)" in the consolidated statement of comprehensive loss during the year ended December 31, 2016. See Note 15 for further details.

Identifiable intangible assets and liabilities acquired include developed technology and contingent royalties. The preliminary estimated fair values of the developed technology and contingent royalties represent preliminary valuations performed with the assistance of an independent appraisal firm based on management's estimates, forecasted financial information and reasonable and supportable assumptions.

Developed technology intangible assets reflect the estimated fair value of Crealta's rights to its currently marketed medicines, KRYSTEXXA and MIGERGOT. The preliminary fair value of developed technology was determined using an income approach. The income approach explicitly recognizes that the fair value of an asset is premised upon the expected receipt of future economic benefits such as earnings and cash inflows based on current sales projections and estimated direct costs for Crealta's medicines. Indications of value were developed by discounting these benefits to their acquisition-date worth at a discount rate of 27% for KRYSTEXXA and 23% for MIGERGOT. The fair value of the KRYSTEXXA and MIGERGOT developed technologies were capitalized as of the Crealta acquisition date and are subsequently being amortized over approximately twelve and ten years, respectively, which are the periods in which over 90% of the estimated cash flows are expected to be realized.

The Company has assigned a preliminary fair value of $51.3 million to a contingent liability for royalties potentially payable under previously existing agreements related to KRYSTEXXA and MIGERGOT. The royalties for KRYSTEXXA are payable under the terms of a license agreement with Duke University ("Duke") and Mountain View Pharmaceuticals ("MVP"). See Note 15 for details of the percentages of royalties payable under such agreements. The initial fair value of this liability was determined using a discounted cash flow analysis incorporating the estimated future cash flows of royalty payments resulting from future sales. The discount rate used was the same as for the fair value of the developed technology.

The preliminary deferred tax liability recorded represents deferred tax liabilities assumed as part of the acquisition, net of deferred tax assets, related to net operating tax loss carryforwards of Crealta.

Goodwill represents the excess of the preliminary acquisition consideration over the estimated fair value of net assets acquired and was recorded in the consolidated balance sheet as of the acquisition date. The Company does not expect any portion of this goodwill to be deductible for tax purposes.

Hyperion Acquisition

On May 7, 2015, the Company completed the acquisition of Hyperion in which it acquired all of the issued and outstanding shares of Hyperion's common stock for $46.00 per share. The acquisition added two important medicines, RAVICTI and BUPHENYL, to the Company's medicine portfolio. Through the acquisition, the Company leveraged as well as expanded the existing infrastructure of its orphan disease business. The total consideration for the acquisition was approximately $1.1 billion and was composed of the following (in thousands, except share and per share data):

Fully diluted equity value (21,425,909 shares at $46.00 per share)	$	985,592
Net settlements on the exercise of stock options, restricted stock and performance stock units		89,806
Total consideration	$	1,075,398

During the year ended December 31, 2016, the Company recorded a net expense reduction of $0.7 million in Hyperion acquisition-related costs due to a reduction in severance and other payroll-related payments required. Net expense reductions of $0.6 million and $0.4 million were accounted for as "general and administrative" and "other cost of sales", respectively, and a net expense of $0.3 million was recorded as "research and development" expenses in the consolidated statement of comprehensive loss. No further significant acquisition-related costs are expected to be incurred in relation to the Hyperion acquisition.

During the year ended December 31, 2015, the Company incurred $53.7 million in Hyperion acquisition-related costs including advisory, legal, accounting, valuation, severance, retention bonuses, and other professional and consulting fees, of which $40.6 million, $10.0 million and $3.1 million were accounted for as "general and administrative", "other, net" and "research and development" expenses, respectively, in the consolidated statement of comprehensive income.

Pursuant to ASC 805, the Company accounted for the Hyperion acquisition as a business combination using the acquisition method of accounting. Identifiable assets and liabilities of Hyperion, including identifiable intangible assets, were recorded based on their estimated fair values as of the date of the closing of the acquisition. The excess of the purchase price over the fair value of the net assets acquired was recorded as goodwill. Significant judgment was required in determining the estimated fair values of developed technology intangible assets and certain other assets and liabilities. Such a valuation required estimates and assumptions including, but not limited to, estimating future cash flows and direct costs in addition to developing the appropriate discount rates and current market profit margins. The Company's management believes the fair values recognized for the assets acquired and the liabilities assumed are based on reasonable estimates and assumptions.

During the year ended December 31, 2016, the Company recorded an adjustment related to deferred tax liabilities which resulted in a decrease to goodwill of $7.2 million. In evaluating whether the Company's previously issued consolidated financial statements were materially misstated, the Company considered the guidance in FASB ASC Topic 250, Accounting Changes and Error Corrections, ASC Topic 250-10-S99-1, Assessing Materiality, and ASC Topic 250-10-S99-2, Considering the Effects of Prior Year Misstatements when Quantifying Misstatements in Current Year Financial Statements. The adjustment was the result of a correction of an error in the Hyperion pre-acquisition deferred tax calculation. The Company concluded that this misstatement was not material, individually or in the aggregate, to any of the reporting periods impacted. As such, the correction for this error was made during the year ended December 31, 2016.

The following table summarizes the final fair values assigned to the assets acquired and the liabilities assumed by the Company (in thousands):

(Liabilities assumed) and assets acquired:	As Reported	Adjustment	As Adjusted
Deferred tax liability, net	$ (262,732)	$ 7,191	$ (255,541)
Accounts payable	(2,439)	—	(2,439)
Accrued trade discounts and rebates	(9,792)	—	(9,792)
Accrued expenses	(7,566)	—	(7,566)
Contingent royalties	(86,800)	—	(86,800)
Cash and cash equivalents	53,037	—	53,037
Short-term investments	39,049	—	39,049
Long-term investments	25,574	—	25,574
Accounts receivable, net	11,858	—	11,858
Inventory	13,498	—	13,498
Prepaid expenses and other current assets	2,533	—	2,533
Property and equipment	1,044	—	1,044
Other non-current assets	123	—	123
Developed technology	1,044,200	—	1,044,200
Goodwill	253,811	(7,191)	246,620
Fair value of consideration paid	$ 1,075,398	$ —	$ 1,075,398

Inventories acquired included raw materials and finished goods. Inventories were recorded at their current fair values. The fair value of finished goods has been determined based on the estimated selling price, net of selling costs and a margin on the selling costs. The fair value of raw materials was estimated to equal the replacement cost. A step-up in the value of inventory of $8.7 million was recorded in connection with the acquisition and has subsequently been fully recognized in the consolidated statements of comprehensive (loss) income.

Other tangible assets and liabilities were valued at their respective carrying amounts as management believes that these amounts approximated their acquisition date fair values.

Identifiable intangible assets and liabilities acquired include developed technology and contingent royalties. The fair values of the developed technology and contingent royalties represent valuations performed with the assistance of an independent appraisal firm based on management's estimates, forecasted financial information and reasonable and supportable assumptions.

Developed technology intangible assets reflect the estimated value of Hyperion's rights to its currently marketed medicines, RAVICTI and BUPHENYL. The fair value of developed technology was determined using an income approach. The income approach explicitly recognizes that the fair value of an asset is premised upon the expected receipt of future economic benefits such as earnings and cash inflows based on current sales projections and estimated direct costs for Hyperion's medicines. Indications of value were developed by discounting these benefits to their acquisition-date worth at a discount rate of 8.5% that reflected the then-current return requirements of the market. The fair value of the RAVICTI and BUPHENYL developed technologies were capitalized as of the Hyperion acquisition date and are subsequently being amortized over 11 and 7 years, respectively, which are the periods in which over 90% of the estimated cash flows are expected to be realized.

The Company has assigned a fair value to a contingent liability for royalties potentially payable under previously existing agreements related to RAVICTI and BUPHENYL. The royalties are payable under the terms of an asset purchase agreement and an amended and restated collaboration agreement with Ucyclyd Pharma, Inc. ("Ucyclyd") and a license agreement with Saul W. Brusilow, M.D. and Brusilow Enterprises Inc. ("Brusilow"). See Note 15 for details of the percentages payable under such agreements. The initial fair value of this liability was $86.8 million and was determined using a discounted cash flow analysis incorporating the estimated future cash flows of royalty payments resulting from future sales. The discount rate used was the same as for the fair value of the developed technology. See Note 2 for details of the Company's accounting policies for accrued contingent royalties.

Deferred tax assets and liabilities arise from acquisition accounting adjustments where book values of certain assets and liabilities differ from their tax bases. Deferred tax assets and liabilities are recorded at the currently enacted rates which will be in effect at the time when the temporary differences are expected to reverse in the country where the underlying assets and liabilities are located. Hyperion's developed technology as of the acquisition date was located primarily in the United States where a U.S. tax rate of 39% is being utilized and a significant deferred tax liability is recorded. Upon consummation of the Hyperion acquisition, Hyperion became a member of the Company's U.S. tax consolidation group. As such, its tax assets and liabilities were considered in determining the appropriate amount (if any) of valuation allowances that should be recognized in assessing the realizability of the group's deferred tax assets. The Hyperion acquisition adjustments resulted in the recognition of significant net deferred tax liabilities. Per ASC Topic 740, *Accounting for Uncertainty in Income Taxes*, ("ASC 740") future reversals of existing taxable temporary differences provide objectively verifiable evidence that should be considered as a source of taxable income to realize a tax benefit for deductible temporary differences and carryforwards. Generally, the existence of sufficient taxable temporary differences will enable the use of the tax benefit of existing deferred tax assets. As of the first quarter of 2015, the Company had significant U.S. federal and state valuation allowances. These valuation allowances were released in the second quarter of 2015 to reflect the recognition of Hyperion's deferred tax liabilities that will provide taxable temporary differences that will be realized within the carryforward period of the Company's U.S. tax consolidation group's available net operating losses and other deferred tax assets. Accordingly, the Company recorded an income tax benefit of $105.1 million in the second quarter of 2015 relating to the release of existing U.S. federal and state valuation allowances.

Short-term and long-term investments included in the table above represent available-for-sale securities that were reported in short-term investments or long-term investments based on maturity dates and whether such assets are reasonably expected to be realized in cash or sold or consumed during the normal cycle of business. Available-for-sale investments were recorded at fair value and were liquidated shortly after the acquisition.

Goodwill represents the excess of the acquisition consideration over the estimated fair value of net assets acquired and was recorded in the consolidated balance sheet as of the acquisition date. The Company does not expect any portion of this goodwill to be deductible for tax purposes.

Other arrangements

On November 8, 2016, the Company entered into a collaboration and option agreement with a privately held life-science entity. Under the terms of the agreement, the privately held life-science entity will conduct certain research and pre-clinical and clinical development activities. Upon execution of the agreement, the Company paid $0.1 million for the option to acquire certain of the privately held life-science entity's assets for $25.0 million, which is exercisable on specified key dates. Under the collaboration and option agreement, the Company will be required to pay up to $9.8 million upon the attainment of various milestones, primarily to fund clinical development costs for the medicine. The Company paid $0.2 million in the fourth quarter of 2016 and a further $0.9 million in the first quarter of 2017. The Company has determined that the privately held life-science entity is a variable interest entity ("VIE") as it does not have enough equity to finance its activities without additional financial support. As the Company does not have the power to direct the activities of the VIE that most significantly affect its economic performance, it is not the primary beneficiary of, and does not consolidate the results of, the VIE. The Company will reassess the appropriate accounting treatment for this arrangement throughout the life of the agreement and modify these accounting conclusions accordingly. The initial upfront amount paid of $0.1 million has been included in "other assets" in the Company's consolidated balance sheet as of December 31, 2016, and the milestone amounts of $1.1 million paid to date were recorded as "research and development" expenses in the consolidated statement of comprehensive loss during the year ended December 31, 2016.

Pro Forma Information

The following table represents consolidated financial information for the Company on a pro forma basis. The 2016 pro forma adjustments assume that the Crealta and Raptor acquisitions occurred as of January 1, 2016, the 2015 pro forma adjustments assume that the Hyperion, Crealta and Raptor acquisitions occurred as of January 1, 2015 and the 2014 pro forma adjustments assume that the Hyperion acquisition and the Vidara Merger occurred as of January 1, 2014.

The results of Raptor from October 25, 2016 to December 31, 2016 and the results of Crealta from January 13, 2016 to December 31, 2016 are included in the 2016 as reported figures, the results of Hyperion from May 7, 2015 to December 31, 2016 are included in the 2015 and 2016 as reported figures and the results of Vidara from September 19, 2014 to December 31, 2016 are included in the 2014, 2015 and 2016 as reported figures.

The historical financial information has been adjusted to give effect to pro forma items that are directly attributable to the Hyperion, Crealta and Raptor acquisitions and the Vidara Merger, and are expected to have a continuing impact on the consolidated results. These items include, among others, adjustments to record the amortization of definite-lived intangible assets, interest expense, debt discount and deferred financing costs associated with the debt in connection with the acquisitions. Additionally, the following table sets forth unaudited financial information and has been compiled from historical financial statements and other information, but is not necessarily indicative of the results that actually would have been achieved had the transactions occurred on the dates indicated or that may be achieved in the future (in thousands, except per share data):

	For the Year Ended December 31,								
	2016			2015			2014		
	As reported	Pro forma adjustments (Unaudited)	Pro forma (Unaudited)	As reported	Pro forma adjustments (Unaudited)	Pro forma (Unaudited)	As reported	Pro forma adjustments (Unaudited)	Pro forma (Unaudited)
Net sales	$ 981,120	$ 109,298	$ 1,090,418	$ 757,044	$ 200,611	$ 957,655	$ 296,955	$ 164,149	$ 461,104
Net (loss) income	(166,834)	(201,765)	(368,599)	39,532	(127,801)	(88,269)	(263,603)	(70,803)	(334,406)
Basic net (loss) income per share	$ (1.04)	$ (1.26)	$ (2.30)	$ 0.27	$ (0.86)	$ (0.59)	$ (3.15)	$ (0.15)	$ (3.30)
Diluted net (loss) income per share	(1.04)	(1.26)	(2.30)	0.25	(0.86)	(0.59)	(3.15)	(0.15)	(3.30)

The Company's consolidated statements of comprehensive loss for the year ended December 31, 2016 include KRYSTEXXA and MIGERGOT net sales as a result of the acquisition of Crealta in January 2016 of $91.1 million and $4.7 million, respectively, and PROCYSBI and QUINSAIR net sales as a result of the acquisition of Raptor in October 2016 of $25.3 million and $1.0 million, respectively. The Company's consolidated statements of comprehensive income for the year ended December 31, 2015 include RAVICTI and BUPHENYL net sales as a result of the acquisition of Hyperion in May 2015 of $86.9 million and $13.5 million, respectively. The Company's consolidated statements of comprehensive loss for the year ended December 31, 2014 include ACTIMMUNE net sales as a result of the Vidara Merger of $25.3 million.

Vidara, Hyperion, Crealta and Raptor have been fully integrated into the Company's business and as a result of these integration efforts, the Company cannot distinguish between these operations and those of the Company's legacy business.

NOTE 5 – INVENTORIES

Inventories are stated at the lower of cost or market value. Inventories consist of raw materials, work-in-process and finished goods. The Company has entered into manufacturing and supply agreements for the manufacture or purchase of raw materials and production supplies. The Company's inventories include the direct purchase cost of materials and supplies and manufacturing overhead costs.

The components of inventories as of December 31, 2016 and 2015 consisted of the following (in thousands):

	As of December 31,	
	2016	2015
Raw materials	$ 10,233	$ 6,232
Work-in-process	85,022	631
Finished goods	79,533	11,513
Inventories, net	$ 174,788	$ 18,376

Because inventory step-up expense is acquisition-related, will not continue indefinitely and has a significant effect on the Company's gross profit, gross margin percentage and net income (loss) for all affected periods, the Company discloses balance sheet and income statement amounts related to inventory step-up within the notes to the consolidated financial statements.

Finished goods at December 31, 2016 included $27.7 million of stepped-up KRYSTEXXA and MIGERGOT inventory and $38.1 million of stepped-up PROCYSBI and QUINSAIR inventory. Work-in-process at December 31, 2016 included $67.6 million of stepped-up KRYSTEXXA and MIGERGOT inventory and $5.9 million of stepped-up PROCYSBI and QUINSAIR inventory. The Company recorded $48.8 million of KRYSTEXXA and MIGERGOT inventory step-up expense during the year ended December 31, 2016. The Company recorded $22.4 million of PROCYSBI and QUINSAIR inventory step-up expense during the year ended December 31, 2016.

The Company expects that the KRYSTEXXA and MIGERGOT inventory step-up will be fully expensed by the end of the first quarter of 2018. Following that period, the Company expects the costs of goods sold related to KRYSTEXXA and MIGERGOT to decrease significantly to levels consistent with the historical cost of goods sold of Crealta. The Company expects the PROCYSBI and QUINSAIR inventory step-up will be fully expensed by the end of the third quarter of 2017. Following that period, the Company expects the costs of goods sold related to PROCYSBI and QUINSAIR to decrease significantly to levels consistent with the historical cost of goods sold of Raptor.

During the year ended December 31, 2015, the Company recorded $8.4 million of RAVICTI and BUPHENYL inventory step-up expense and $3.2 million of ACTIMMUNE inventory step-up expense.

During the year ended December 31, 2016, the Company committed to purchase additional units of ACTIMMUNE from Boehringer Ingelheim. These additional units of ACTIMMUNE were intended to cover anticipated demand if the results of the STEADFAST study of ACTIMMUNE for the treatment of FA had been successful. Following the discontinuation of the STEADFAST program, the Company recorded a loss of $14.3 million for firm, non-cancellable and unconditional purchase commitments for quantities in excess of the Company's current forecasts for future demand. Inventories, net at December 31, 2016 does not include an amount related to these additional units of ACTIMMUNE. During the year ended December 31, 2016, the Company also committed to incur an additional $14.9 million for the harmonization of the drug substance manufacturing process with Boehringer Ingelheim. These additional costs have not been included in the Company's consolidated statement of comprehensive loss or the Company's consolidated balance sheet at December 31, 2016.

NOTE 6 – PREPAID EXPENSES AND OTHER CURRENT ASSETS

Prepaid expenses and other current assets as of December 31, 2016 and 2015 consisted of the following (in thousands):

	As of December 31,	
	2016	2015
Medicine samples inventory	$ 10,192	4,697
Prepaid income taxes	9,155	4
Deferred charge for taxes on intra-group profit	7,801	—
Rabbi trust assets	3,073	773
Prepaid co-pay expenses	2,070	1,881
Other prepaid expenses	17,328	8,503
Prepaid expenses and other current assets	$ 49,619	$ 15,858

NOTE 7 – PROPERTY AND EQUIPMENT

Property and equipment as of December 31, 2016 and 2015 consisted of the following (in thousands):

	As of December 31,	
	2016	2015
Software	$ 10,876	$ 1,360
Leasehold improvements	9,184	1,966
Machinery and equipment	4,566	2,946
Computer equipment	3,069	2,514
Other	2,664	276
	30,359	9,062
Less accumulated depreciation	(8,319)	(3,791)
Construction in process	17	3,492
Software implementation in process	1,427	5,257
Property and equipment, net	$ 23,484	$ 14,020

The Company capitalizes development costs associated with internal use software, including external direct costs of materials and services and payroll costs for employees devoting time to a software project. Costs incurred during the preliminary project stage, as well as costs for maintenance and training, are expensed as incurred.

Software implementation in process as of December 31, 2016 and December 31, 2015 is related to new enterprise resource planning software being implemented by the Company. The software is being implemented on a phased basis starting January 2016 and depreciation is not recorded on capitalized costs relating to a phase which has not yet entered service. Once a particular phase of the project enters service, associated capitalized costs are moved from "software implementation in process" to "software" in the table above, and depreciation commences.

Depreciation expense for the years ended December 31, 2016, 2015 and 2014 was $5.0 million, $5.4 million and $1.7 million, respectively.

NOTE 8 – GOODWILL AND INTANGIBLE ASSETS

Goodwill

The gross carrying amount of goodwill as of December 31, 2016 was as follows (in thousands):

Balance at December 31, 2014	$ —
Goodwill recognized on acquisition of Hyperion	253,811
Balance at December 31, 2015	253,811
Goodwill recognized on acquisition of Crealta	9,913
Goodwill recognized on acquisition of Raptor	189,046
Adjustment relating to the acquisition of Hyperion in the prior year	(7,191)
Balance at December 31, 2016	$ 445,579

In May 2015, the Company recognized goodwill with a value of $253.8 million in connection with the Hyperion acquisition, which represented the excess of the purchase price over the fair value of the net assets acquired. During the year ended December 31, 2016, the Company recorded an adjustment related to deferred tax liabilities which resulted in a decrease to goodwill of $7.2 million. The adjustment was the result of a correction of an error in the Hyperion pre-acquisition deferred tax calculation. The Company concluded that this misstatement was not material, individually or in the aggregate, to any of the reporting periods impacted. As such, the correction for this error was made during the year ended December 31, 2016.

In January 2016, the Company recognized goodwill with a preliminary value of $1.8 million in connection with the Crealta acquisition, which represented the excess of the purchase price over the fair value of the net assets acquired. During the year ended December 31, 2016, the Company recorded measurement period adjustments related to developed technology, inventory and deferred tax liabilities, which resulted in a net increase in goodwill of $8.1 million, to $9.9 million.

In October 2016, the Company recognized goodwill with a preliminary value of $189.1 million in connection with the Raptor acquisition, which represented the excess of the purchase price over the fair value of the net assets acquired.

As of December 31, 2016, there were no accumulated goodwill impairment losses.

See Note 4 for further details of goodwill acquired in business acquisitions.

Intangible Assets

As of December 31, 2016, the Company's intangible assets consist of developed technology related to ACTIMMUNE, BUPHENYL, KRYSTEXXA, MIGERGOT, PENNSAID 2%, PROCYSBI, RAVICTI, RAYOS and VIMOVO in the United States, and AMMONAPS, BUPHENYL, LODOTRA and PROCYSBI outside the United States, as well as customer relationships for ACTIMMUNE.

In May 2015, in connection with the acquisition of Hyperion, the Company capitalized $1,021.6 million of developed technology related to RAVICTI and $22.6 million of developed technology related to BUPHENYL.

In January 2016, in connection with the acquisition of Crealta, the Company capitalized $392.7 million of developed technology related to KRYSTEXXA and $24.6 million of developed technology related to MIGERGOT. During the year ended December 31, 2016, the Company recorded measurement period adjustments which increased the cost basis of KRYSTEXXA and MIGERGOT developed technology by $9.5 million to $402.2 million, and $1.4 million to $26.0 million, respectively.

In October 2016, in connection with the acquisition of Raptor, the Company capitalized $946.0 million of developed technology related to PROCYSBI.

See Note 4 for further details of intangible assets acquired in business acquisitions.

IPR&D of $66.0 million was related to one research and development project to evaluate ACTIMMUNE in the treatment of FA. The fair value of the IPR&D was recorded as an indefinite-lived intangible asset and was being tested for impairment annually until completion or abandonment of the research and development efforts associated with the project. On December 8, 2016, the Company announced that the Phase 3 trial, STEADFAST, evaluating ACTIMMUNE for the treatment of FA did not meet its primary endpoint of a statistically significant change from baseline in the FARS-mNeuro at twenty-six weeks versus treatment with placebo. In addition, the secondary endpoints did not meet statistical significance. No new safety findings were identified on initial review of data other than those already noted in the ACTIMMUNE prescribing information for approved indications. The Company, in conjunction with the independent Data Safety Monitoring Board, the principal investigator and FARA, Collaborative Clinical Research Network in FA, determined that, based on the trial results, the STEADFAST program would be discontinued, including the twenty-six week extension study and the long-term safety study. The IPR&D has no alternative use or economic value as a result of the cancellation of the project, and the Company recorded an impairment charge of $66.0 million to "impairment of in-process research and development" in its consolidated statements of comprehensive loss during the three months ended December 31, 2016 to fully write off the value of the asset on its consolidated balance sheet.

The Company tests its intangible assets for impairment when events or circumstances may indicate that the carrying value of these assets exceeds their fair value. The Company does not believe there have been any circumstances or events that would indicate that the carrying value of any of its intangible assets, except for IPR&D as described above, was impaired at December 31, 2016 or December 31, 2015.

As of December 31, 2016 and December 31, 2015, amortizable intangible assets consisted of the following (in thousands):

	As of December 31,					
	2016			2015		
	Cost Basis	Accumulated Amortization	Net Book Value	Cost Basis	Accumulated Amortization	Net Book Value
Developed technology	$ 3,166,695	$ (399,511)	$ 2,767,184	$ 1,792,495	$ (183,446)	$ 1,609,049
Customer relationships	8,100	(1,849)	6,251	8,100	(1,039)	7,061
Amortizable intangible assets	$ 3,174,795	$ (401,360)	$ 2,773,435	$ 1,800,595	$ (184,485)	$ 1,616,110

Amortization expense for the years ended December 31, 2016, 2015 and 2014 was $216.9 million, $132.9 million and $32.3 million, respectively. As of December 31, 2016, estimated future amortization expense was as follows (in thousands):

2017	$ 280,088
2018	280,088
2019	267,096
2020	266,879
2021	259,377
Thereafter	1,419,907
Total	$ 2,773,435

NOTE 9 – ACCRUED TRADE DISCOUNTS AND REBATES

Accrued trade discounts and rebates as of December 31, 2016 and December 31, 2015 consisted of the following (in thousands):

	As of December 31,	
	2016	2015
Accrued wholesaler fees and commercial rebates	$ 47,460	$ 21,112
Accrued co-pay and other patient assistance	188,504	114,201
Accrued government rebates and chargebacks	61,592	48,456
Accrued trade discounts and rebates	$ 297,556	$ 183,769
Invoiced wholesaler fees and commercial rebates, co-pay and other patient assistance, and government rebates and chargebacks in accounts payable	16,830	—
Total customer-related accruals and allowances	$ 314,386	$ 183,769

The following table summarizes changes in the Company's customer-related accruals and allowances from December 31, 2014 to December 31, 2016 (in thousands):

	Wholesaler Fees and Commercial Rebates	Co-Pay and Other Patient Assistance	Government Rebates and Chargebacks	Total
Balance at December 31, 2014	$ 30,852	$ 30,047	$ 20,437	$ 81,336
Current provisions relating to sales in the year ended December 31, 2015	67,762	1,020,327	162,157	1,250,246
Adjustments relating to prior year sales	(1,657)	(121)	(3,842)	(5,620)
Payments relating to sales in the year ended December 31, 2015	(47,848)	(906,126)	(123,299)	(1,077,273)
Payments relating to sales in prior years	(28,241)	(29,926)	(16,545)	(74,712)
Hyperion acquisition on May 7, 2015	244	—	9,548	9,792
Balance at December 31, 2015	$ 21,112	$ 114,201	$ 48,456	$ 183,769
Current provisions relating to sales in the year ended December 31, 2016	133,012	1,701,287	278,877	2,113,176
Adjustments relating to prior year sales	671	—	(6,875)	(6,204)
Payments relating to sales in the year ended December 31, 2016	(87,147)	(1,496,240)	(224,343)	(1,807,730)
Payments relating to sales in prior years	(20,644)	(114,201)	(41,581)	(176,426)
Crealta acquisition on January 13, 2016	492	—	932	1,424
Raptor acquisition on October 25, 2016	155	96	6,126	6,377
Balance at December 31, 2016	$ 47,651	$ 205,143	$ 61,592	$ 314,386

NOTE 10 – ACCRUED EXPENSES

Accrued expenses as of December 31, 2016 and 2015 consisted of the following (in thousands):

	As of December 31	
	2016	2015
Payroll-related expenses	$ 61,691	$ 47,205
Consulting and professional services	33,614	17,160
Litigation settlement	32,500	—
Accrued interest	18,938	10,637
Accrued other	36,022	25,044
Accrued expenses	$ 182,765	$ 100,046

Accrued payroll-related expenses at December 31, 2016 included $15.0 million of severance and related employee costs as a result of the Raptor acquisition. The Company anticipates that a significant amount of the Raptor acquisition-related cash payments will be complete by the fourth quarter of 2017. Accrued payroll-related expenses at December 31, 2015 included $8.5 million of severance and related employee costs as a result of the Hyperion acquisition.

Accrued expenses as of December 31, 2016 included $32.5 million in relation to a litigation settlement with Express Scripts. See Note 15 for further details of this settlement.

"Accrued other" as of December 31, 2016 included $9.5 million related to a loss on inventory purchase commitments. During the year ended December 31, 2016, the Company committed to purchase additional units of ACTIMMUNE from Boehringer Ingelheim. These additional units of ACTIMMUNE were intended to cover anticipated demand if the results of the STEADFAST study of ACTIMMUNE for the treatment of FA had been successful. Following the discontinuation of the STEADFAST program, the Company recorded a loss of $14.3 million in "cost of goods sold" in the consolidated statement of comprehensive loss for firm, non-cancellable and unconditional purchase commitments for quantities in excess of the Company's current forecasts for future demand. "Other long-term liabilities" as of December 31, 2016 includes an additional $4.8 million related to this loss on inventory purchase commitments. "Accrued other" as of December 31, 2016 also included $4.0 million related to costs to be incurred to discontinue the clinical trial.

NOTE 11 – ACCRUED ROYALTIES

Changes to the liability for royalties for medicines acquired through business combinations during the years ended December 31, 2016 and 2015 consisted of the following (in thousands):

Balance as of December 31, 2014	$	74,212
Assumed RAVICTI and BUPHENYL contingent royalty liabilities		86,800
Assumed RAVICTI and BUPHENYL accrued royalties		579
Remeasurement of royalty liabilities		21,151
Royalty payments		(27,611)
Accretion expense		20,088
Balance as of December 31, 2015		175,219
Accrued royalties - current portion as of December 31, 2015		51,700
Accrued royalties, net of current as of December 31, 2015		123,519
Assumed KRYSTEXXA and MIGERGOT contingent royalty liabilities		51,300
Assumed KRYSTEXXA and MIGERGOT accrued royalties		1,401
Assumed PROCYSBI contingent royalty liabilities		102,000
Assumed PROCYSBI and QUINSAIR accrued royalties		2,705
Remeasurement of royalty liabilities		386
Royalty payments		(39,448)
Accretion expense		40,616
Other royalty expense		95
Balance as of December 31, 2016		334,274
Accrued royalties - current portion as of December 31, 2016		61,981
Accrued royalties, net of current as of December 31, 2016	$	272,293

During the year ended December 31, 2016, based on higher sales of KRYSTEXXA and RAVICTI versus the Company's previous expectations and estimates for future sales of these medicines, the Company recorded a total charge of $24.6 million to cost of goods sold ($15.4 million related to KRYSTEXXA and $9.2 million related to RAVICTI). The Company also recorded a reduction of $24.2 million to cost of goods sold related to ACTIMMUNE and VIMOVO as a result of updated estimates of future sales of these medicines ($8.7 million related to ACTIMMUNE, including $2.5 million in connection with FA, and $15.5 million related to VIMOVO).

NOTE 12 – LONG-TERM INVESTMENTS

During the third quarter of 2015, the Company purchased 2,250,000 shares of common stock of Depomed, Inc. ("Depomed"), representing 3.75% of Depomed's then outstanding common stock. The shares were acquired at a cost of $71.8 million. During the fourth quarter of 2015, following the Company's decision to withdraw its offer to acquire Depomed, the Company sold all of its shares in Depomed, receiving sales proceeds of $42.8 million and the Company recognized a realized loss of $29.0 million in the consolidated statement of comprehensive income.

There were no gains or losses on long-term investments during the years ended December 31, 2016 or 2014.

NOTE 13 – SEGMENT AND OTHER INFORMATION

The Company has determined that it operates in one operating segment, which is the identification, development, acquisition and commercialization of differentiated and accessible medicines that address unmet medical needs. The Company's operating segment is reported in a manner consistent with the internal reporting provided to the chief operating decision maker ("CODM"). The Company's CODM has been identified as its chief executive officer.

The following table presents a summary of total net revenues by medicine (in thousands):

	Year Ended December 31,		
	2016	2015	2014
PENNSAID 2%	$ 304,433	$ 147,010	$ —
DUEXIS	173,728	190,357	83,243
RAVICTI	151,532	86,875	—
VIMOVO	121,315	166,672	162,954
ACTIMMUNE	104,624	107,444	25,251
KRYSTEXXA	91,102	—	—
RAYOS	47,356	40,329	19,020
PROCYSBI	25,268	—	—
BUPHENYL	16,879	13,458	—
MIGERGOT	4,651	—	—
LODOTRA	4,193	4,899	6,487
QUINSAIR	1,039	—	—
Litigation settlement	(65,000)	—	—
Total net revenues	$ 981,120	$ 757,044	$ 296,955

The following table presents a summary of total net revenues by geography (in thousands):

	Year Ended December 31,		
	2016	2015	2014
United States	$ 964,041	$ 744,036	$ 290,396
Rest of world	17,079	13,008	6,559
Total net revenues	$ 981,120	$ 757,044	$ 296,955

The following table presents the amount and percentage of gross sales from customers that represented more than 10% of the Company's gross sales included in its single operating segment (in thousands):

	Year ended December 31,					
	2016		2015		2014	
	Amount	% of Gross Sales	Amount	% of Gross Sales	Amount	% of Gross Sales
Customer A	$ 1,413,774	44%	$ 607,771	30%	$ 256,237	43%
Customer B	667,031	21%	166,661	8%	105,487	17%
Customer C	355,920	11%	207,009	10%	113,751	19%
Other Customers	797,463	24%	1,075,853	52%	125,356	21%
Gross Sales	$ 3,234,188	100%	$ 2,057,294	100%	$ 600,831	100%

The following table presents total tangible long-lived assets by location (in thousands):

	As of December 31,	
	2016	2015
United States	$ 19,542	$ 11,734
Ireland	3,550	1,985
Other	392	301
Total long-lived assets (1)	$ 23,484	$ 14,020

(1) Long-lived assets consist of property and equipment.

NOTE 14 – FAIR VALUE MEASUREMENTS

The following tables and paragraphs set forth the Company's financial instruments that are measured at fair value on a recurring basis within the fair value hierarchy. Assets and liabilities measured at fair value are classified in their entirety based on the lowest level of input that is significant to the fair value measurement. The Company's assessment of the significance of a particular input to the fair value measurement in its entirety requires management to make judgments and consider factors specific to the asset or liability. The following describes three levels of inputs that may be used to measure fair value:

Level 1—Observable inputs such as quoted prices in active markets for identical assets or liabilities.

Level 2—Observable inputs other than Level 1 prices such as quoted prices for similar assets or liabilities, quoted prices in markets that are not active, or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.

Level 3—Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

The Company utilizes the market approach to measure fair value for its money market funds. The market approach uses prices and other relevant information generated by market transactions involving identical or comparable assets or liabilities.

As of December 31, 2016, the Company's restricted cash included bank time deposits which were measured at fair value using Level 2 inputs and their carrying values were approximately equal to their fair values. Level 2 inputs, obtained from various third-party data providers, represent quoted prices for similar assets in active markets, or these inputs were derived from observable market data, or if not directly observable, were derived from or corroborated by other observable market data.

Other current assets recorded at fair value on a recurring basis are composed of investments held in a rabbi trust related to deferred compensation arrangements. Quoted prices for these investments, primarily in mutual funds, are available in active markets. Thus, the Company's investments related to deferred compensation arrangements are classified as Level 1 measurements in the fair value hierarchy.

There were no transfers between the different levels of the fair value hierarchy in 2016 or in 2015.

Assets and liabilities measured at fair value on a recurring basis

The following table sets forth the Company's financial assets and liabilities at fair value on a recurring basis as of December 31, 2016 and December 31, 2015 (in thousands):

	December 31, 2016			
	Level 1	Level 2	Level 3	Total
Assets:				
Bank time deposits	$ —	$ 3,000	$ —	$ 3,000
Money market funds	170,000	—	—	170,000
Other current assets	3,038	—	—	3,038
Total assets at fair value	$ 173,038	$ 3,000	$ —	$ 176,038

	December 31, 2015			
	Level 1	Level 2	Level 3	Total
Assets:				
Bank time deposits	$ —	$ 1,000	$ —	$ 1,000
Money market funds	280,053	—	—	280,053
Other current assets	773	—	—	773
Total assets at fair value	$ 280,826	$ 1,000	$ —	$ 281,826

In accordance with the pronouncement guidance in ASC Topic 815 "*Derivatives and Hedging",* the conversion option included within the Convertible Senior Notes was deemed to include an embedded derivative, which required the Company to bifurcate and separately account for the embedded derivative as a separate liability on its consolidated balance sheets. The estimated fair value was derived utilizing the binomial lattice approach for the valuation of convertible instruments. Assumptions used in the calculation included, among others, determining the appropriate credit spread using benchmarking analysis and solving for the implied credit spread, calculating the fair value of the stock component using a discounted risk free rate and borrowing cost and calculating the fair value of the note component using a discounted credit adjusted discount rate. Based on the assumptions used to determine the fair value of the derivative liability associated with the Convertible Senior Notes, the Company concluded that these inputs were Level 3 inputs.

The following table presents the assumptions used by the Company to determine the fair value of the conversion option embedded in the Convertible Senior Notes as of June 27, 2014, the date the HPI stockholders approved the issuance of in excess of 13,164,951 shares of HPI's common stock upon conversion of the Convertible Senior Notes:

	June 27, 2014
Stock price	$ 15.96
Risk free rate	1.43%
Borrowing cost	3.75%
Weights	—
Credit spread (in basis points)	900
Volatility	40.00%
Initial conversion price	$ 5.36
Remaining time to maturity (in years)	4.4

On June 27, 2014, the Company conducted a fair value assessment to reflect the market value adjustments for the embedded derivative due to the increase in HPI's common stock value and for changes in the fair value assumptions, and the Company recorded a $215.0 million loss in its results of operations for the three and six months ended June 30, 2014, respectively. The entire fair value of the derivative liability of $324.4 million was reclassified to additional paid-in capital on June 27, 2014.

NOTE 15 – COMMITMENTS AND CONTINGENCIES

Lease Obligations

The Company has the following office space lease agreements in place for real properties:

Location	Approximate Square Footage	Lease Expiry Date
Dublin, Ireland	18,900	November 3, 2029
Lake Forest, Illinois (1)	160,000	March 31, 2024
Novato, California	61,000	August 31, 2021
Deerfield, Illinois (2)	53,500	June 30, 2018
Brisbane, California	20,100	November 30, 2019
Mannheim, Germany	14,300	December 31, 2018
Chicago, Illinois	6,500	December 31, 2018
Utrecht, the Netherlands	5,400	October 31, 2019
Reinach, Switzerland	3,500	May 31, 2020

(1) In connection with the Lake Forest lease, the Company has provided a $2.0 million letter of credit to the landlord, through a commercial bank.

(2) The Company vacated the premises in Deerfield, Illinois, and began occupying the premises in Lake Forest, Illinois, in January 2016.

The Company recognizes rent expense on a monthly basis over the lease term based on a straight-line method. Rent expense was $5.1 million, $2.5 million and $0.6 million for the years ended December 31, 2016, 2015 and 2014, respectively.

As of December 31, 2016, minimum future cash payments due under lease obligations were as follows (in thousands):

	2017	2018	2019	2020	2021	2022 & Thereafter	Total
Operating lease obligations	$ 7,716	$ 7,611	$ 6,753	$ 5,968	$ 5,316	$ 15,856	$ 49,220

Annual Purchase Commitments

In August 2007, the Company entered into a manufacturing and supply agreement with Jagotec AG ("Jagotec"), which was amended in March 2011 and in January 2017. Under the agreement, Jagotec or its affiliates are required to manufacture and supply RAYOS/LODOTRA exclusively to the Company in bulk. The earliest the agreement can expire is December 31, 2023, and the minimum purchase commitment is in force until December 2023. At December 31, 2016, the minimum purchase commitment based on tablet pricing in effect under the agreement was $6.9 million through December 2023.

In May 2011, the Company entered into a manufacturing and supply agreement with Sanofi-Aventis U.S. LLC ("Sanofi-Aventis U.S."), and amended the agreement effective as of September 25, 2013. Pursuant to the agreement, as amended, Sanofi-Aventis U.S. is obligated to manufacture and supply DUEXIS to the Company in final, packaged form, and the Company is obligated to purchase DUEXIS exclusively from Sanofi-Aventis U.S. for the commercial requirements of DUEXIS in North America, South America and certain countries and territories in Europe, including the European Union member states and Scandinavia. At December 31, 2016, the Company had a binding purchase commitment to Sanofi-Aventis U.S. for DUEXIS of $3.0 million, which is to be delivered through March 2017.

In July 2013, Vidara and Boehringer Ingelheim entered into an exclusive supply agreement, which the Company assumed as a result of the Vidara Merger and amended effective as of June 1, 2015. Under the agreement, Boehringer Ingelheim is required to manufacture and supply interferon gamma-1b (ACTIMMUNE) to the Company. The Company is required to purchase minimum quantities of finished medicine per annum through July 2020. During the year ended December 31, 2016, the Company committed to purchase additional amounts of ACTIMMUNE from Boehringer Ingelheim. These additional amounts were intended to cover anticipated demand if the results of the STEADFAST study of ACTIMMUNE for the treatment of FA had been successful. As of December 31, 2016, the minimum binding purchase commitment to Boehringer Ingelheim was $23.9 million (converted using a Dollar-to-Euro exchange rate of 1.052) through July 2020. Following the discontinuation of the STEADFAST program, the Company recorded a loss of $14.3 million in "cost of goods sold" in the consolidated statement of comprehensive loss for a portion of this commitment which represented firm, non-cancellable and unconditional purchase commitments for quantities in excess of the Company's current forecasts for future demand. During the year ended December 31, 2016, the Company also committed to incur an additional $14.9 million for the harmonization of the drug substance manufacturing process with Boehringer Ingelheim. These additional costs will be incurred during the years 2017 through 2021 and have not been included in the Company's consolidated statement of comprehensive loss or consolidated balance sheet at December 31, 2016.

In November 2013, the Company entered into a long-term master manufacturing services and product agreement with Patheon Pharmaceuticals Inc. ("Patheon") pursuant to which Patheon is obligated to manufacture VIMOVO for the Company through December 31, 2019. The Company agreed to purchase a specified percentage of VIMOVO requirements for the United States from Patheon. The Company must pay an agreed price for final, packaged VIMOVO supplied by Patheon as set forth in the Patheon manufacturing agreement, subject to adjustments, including certain unilateral adjustments by Patheon, such as annual adjustments for inflation and adjustments to account for certain increases in the cost of components of VIMOVO other than active materials. The Company issues 12-month forecasts of the volume of VIMOVO that the Company expects to order. The first six months of the forecast are considered binding firm orders. At December 31, 2016, the Company had a binding purchase commitment with Patheon for VIMOVO of $1.1 million through March 2017.

In October 2014, in connection with the acquisition of the U.S. rights to PENNSAID 2% from Nuvo, the Company and Nuvo entered into an exclusive supply agreement. Under the supply agreement, which was amended in February 2016, Nuvo is obligated to manufacture and supply PENNSAID 2% to the Company. The term of the supply agreement is through December 31, 2029, but the agreement may be terminated earlier by either party for any uncured material breach by the other party of its obligations under the supply agreement or upon the bankruptcy or similar proceeding of the other party. At least 90 days prior to the first day of each calendar month during the term of the supply agreement, the Company submits a binding written purchase order to Nuvo for PENNSAID 2% in minimum batch quantities. At December 31, 2016, the Company had a binding purchase commitment with Nuvo for PENNSAID 2% of $3.6 million through March 2017.

In November 2010, Raptor and Patheon entered into a manufacturing services agreement, which the Company assumed as a result of its acquisition of Raptor. Under the agreement, which was amended in April 2012 and June 2013, Patheon is obligated to manufacture PROCYSBI for the Company through December 31, 2019. The Company must provide Patheon with rolling, non-binding forecasts of PROCYSBI, with a portion of the forecast being a firm written order. In November 2010, Raptor and Cambrex Profarmaco Milano ("Cambrex") entered into an API supply agreement, which the Company assumed as a result of its acquisition of Raptor. Under the agreement, which was amended in April 2013 and August 2016, Cambrex is obligated to manufacture PROCYSBI API for the Company through November 30, 2020. The Company must provide Cambrex with rolling, non-binding forecasts, with a portion of the forecast being the minimum floor of the firm order that must be placed. At December 31, 2016, the Company had a binding purchase commitment with Patheon for PROCYSBI of $1.2 million through April 2017 and with Cambrex for PROCYSBI API of $1.6 million through March 2017.

Excluding the above, additional purchase orders relating to the manufacture of BUPHENYL, PROCYSBI, QUINSAIR and RAVICTI of $6.1 million were outstanding at December 31, 2016. In addition to these purchase orders, the Company's manufacturing agreement with Lyne Laboratories Inc. in relation to RAVICTI provides for a minimum purchase amount of $0.5 million for 2017.

In March 2007, Savient Pharmaceuticals, Inc. (as predecessor in interest to Crealta), entered into a commercial supply agreement with Bio-Technology General (Israel) Ltd ("BTG Israel") for the production of the bulk KRYSTEXXA medicine ("bulk product"). The Company assumed this agreement as part of the Crealta acquisition and amended the agreement in September 2016 (the "September 2016 Amendment"). Under this agreement, the Company has agreed to purchase certain minimum annual order quantities and is obligated to purchase at least 80 percent of its annual world-wide bulk product requirements from BTG Israel. The term of the agreement runs until December 31, 2030, and will automatically renew for successive three year periods unless earlier terminated by either party upon three years prior written notice. The agreement may be terminated earlier by either party in the event of a force majeure, liquidation, dissolution, bankruptcy or insolvency of the other party, uncured material breach by the other party or after January 1, 2024, upon three years prior written notice. Under the agreement if the manufacture of the bulk product is moved out of Israel, the Company may be required to obtain the approval of the Israeli Office of the Chief Scientist ("OCS") because certain KRYSTEXXA intellectual property was initially developed with a grant funded by the OCS and the Company may be required to pay the OCS additional amounts as a repayment for the OCS grant funding. In December 2015, Crealta received a notice of termination from BTG Israel and, as of the Crealta acquisition date, it had been considered probable that the manufacture of the KRYSTEXXA bulk product would be moved outside of Israel and the Company would have been required to pay additional amounts to OCS, estimated at approximately $6.9 million. This estimated obligation was recorded as an assumed contingent liability as of the Crealta acquisition date (see Note 4 for further details) and was included in "Other long-term liabilities" in the consolidated balance sheet. Following the execution of the September 2016 Amendment, the Company determined it would not move the manufacture of the KRYSTEXXA bulk product outside of Israel, and released the $6.9 million assumed contingent liability to "other income (expense)" in the consolidated statement of comprehensive loss during the year ended December 31, 2016. The Company issues 18-month forecasts of the volume of KRYSTEXXA that the Company expects to order. The first six months of the forecast are considered binding firm orders. At December 31, 2016, the Company has a binding purchase commitment with BTG Israel for KRYSTEXXA of $5.0 million per annum through December 31, 2030.

Royalty Agreements

RAYOS/LODOTRA

In connection with an August 2004 development and license agreement with Vectura Group plc (as successor in interest to SkyePharma AG) ("Vectura"), and Jagotec, a wholly owned subsidiary of Vectura, regarding certain proprietary technology and know-how owned by Vectura, Jagotec is entitled to receive a single digit percentage royalty on net sales of RAYOS/LODOTRA and on any sub-licensing income, which includes any payments not calculated based on the net sales of RAYOS/LODOTRA, such as license fees, lump sum and milestone payments.

VIMOVO

The Company entered into a license agreement with Pozen Inc. who subsequently entered into a business combination with Tribute Pharmaceuticals Canada Inc. to become known as Aralez Pharmaceuticals Inc. ("Aralez"). Under this agreement, the Company is required to pay Aralez a flat 10% royalty on net sales of VIMOVO and other medicines sold by the Company, its affiliates or sublicensees during the royalty term that contain gastroprotective agents in a single fixed combination oral solid dosage form with nonsteroidal anti-inflammatory drugs, subject to minimum annual royalty obligations of $7.5 million. These minimum royalty obligations will continue for each year during which one of Aralez's patents covers such medicines in the United States and there are no competing medicines in the United States. The royalty rate may be reduced to a mid-single digit royalty rate as a result of loss of market share to competing medicines. The Company's obligation to pay royalties to Aralez will expire upon the later of (a) expiration of the last-to-expire of certain patents covering such medicines in the United States, and (b) ten years after the first commercial sale of such medicines in the United States.

In November 2013, the Company, AstraZeneca AB ("AstraZeneca") and Aralez entered into a letter agreement. Under the letter agreement, the Company and AstraZeneca agreed to pay Aralez milestone payments upon the achievement by the Company and AstraZeneca, collectively, of certain annual aggregate global net sales thresholds ranging from $550.0 million to $1.25 billion with respect to VIMOVO. The aggregate milestone payment amount that may be owed by AstraZeneca and the Company, collectively, under the letter agreement is $260.0 million, with the amount payable by each of the Company and AstraZeneca with respect to each milestone to be based upon the proportional sales achieved by each of the Company and AstraZeneca, respectively, in the applicable year.

ACTIMMUNE

Under a license agreement, as amended, with Genentech Inc. ("Genentech"), who was the original developer of ACTIMMUNE, the Company is or was obligated to pay royalties to Genentech on its net sales of ACTIMMUNE as follows:

- For the period from November 26, 2014 through May 5, 2018, a royalty in the 20% to 30% range for the first $3.7 million in net sales achieved in any calendar year and in the 1% to 9% range for all additional net sales in any year; and
- From May 6, 2018 and for so long as the Company continues to commercially sell ACTIMMUNE, an annual royalty in the low single digits as a percentage of annual net sales.

Under the terms of an assignment and option agreement with Connetics Corporation (which was the predecessor parent company to InterMune Pharmaceuticals Inc. and is now part of GlaxoSmithKline), ("Connetics"), the Company is obligated to pay royalties to Connetics on the Company's net sales of ACTIMMUNE as follows:

- Low-single digits as a percentage of net sales of ACTIMMUNE in the United States.

RAVICTI

Under the terms of an asset purchase agreement with Ucyclyd, the Company is obligated to pay to Ucyclyd tiered mid to high single-digit royalties on its global net sales of RAVICTI. Under the terms of a license agreement with Saul W. Brusilow, M.D. and Brusilow, the Company is obligated to pay low single-digit royalties to Brusilow on net sales of RAVICTI that are covered by a valid claim of a licensed patent.

BUPHENYL

Under the terms of an amended and restated collaboration agreement with Ucyclyd, the Company is obligated to pay to Ucyclyd tiered mid to high single-digit royalties on its net sales in the United States of BUPHENYL to urea cycle disorder patients outside of the U.S. Food and Drug Administration ("FDA")-approved labeled age range for RAVICTI.

KRYSTEXXA

Under the terms of a license agreement with Duke and MVP, the Company is obligated to pay Duke a mid-single digit royalty on its global net sales of KRYSTEXXA and a low-double digit royalty on any global sublicense revenue. The Company is also obligated to pay MVP a mid-single digit royalty on its net sales of KRYSTEXXA outside of the United States and a low-double digit royalty on any sublicense revenue outside of the United States.

PROCYSBI

Under the terms of a license agreement with UCSD, the Company is obligated to pay to UCSD tiered low to mid single-digit royalties on its net sales of PROCYSBI.

The royalty obligations for ACTIMMUNE, BUPHENYL, KRYSTEXXA, MIGERGOT, PROCYSBI, QUINSAIR, RAVICTI and VIMOVO are included in accrued royalties on the Company's consolidated balance sheets.

For all of the royalty agreements entered into by the Company, a total expense of $46.5 million, $45.5 million and $21.4 million was recorded in cost of goods sold for the years ended December 31, 2016, 2015 and 2014, respectively.

Other Agreements

On November 8, 2016, the Company entered into a collaboration and option agreement with a privately held life-science entity. Under the terms of the agreement, the privately held life-science entity will conduct certain research and pre-clinical and clinical development activities. Upon execution of the agreement, the Company paid $0.1 million for the option to acquire certain of the privately held life-science entity's assets for $25.0 million, which is exercisable on specified key dates. Under the collaboration and option agreement, the Company will be required to pay up to $9.8 million upon the attainment of various milestones, primarily to fund clinical development costs for the medicine.

Contingencies

The Company is subject to claims and assessments from time to time in the ordinary course of business. The Company's management does not believe that any such matters, individually or in the aggregate, will have a material adverse effect on the Company's business, financial condition, results of operations or cash flows. In addition, the Company from time to time has billing disputes with vendors in which amounts invoiced are not in accordance with the terms of their contracts.

In November 2015, Express Scripts filed suit against the Company in Delaware Superior Court, Newcastle County, asserting claims for breach of contract, breach of the implied covenant of good faith and fair dealing, unjust enrichment, and declaratory relief arising from the parties' 2012 Preferred Savings Grid Rebate Program Agreement. The Company filed a counter-claim against Express Scripts for breach of contract, breach of the implied covenant of good faith and fair dealing, and declaratory relief arising from Express Scripts' breach of the rebate agreement. In September 2016, the Company entered into a settlement agreement and mutual release with Express Scripts pursuant to which the Company and Express Scripts were released from any and all claims relating to the litigation without admitting any fault or wrongdoing and the Company agreed to pay Express Scripts $65.0 million. The settlement amount will be paid to Express Scripts in installments, with 50 percent of the installment paid in the fourth quarter of 2016, 25 percent due in the first quarter of 2017 and 25 percent due in the second quarter of 2017. The full amount of this settlement has been accounted for as a reduction of "net sales" in the consolidated statements of comprehensive loss for the year ended December 31, 2016.

In November 2015, the Company received a subpoena from the U.S. Attorney's Office for the Southern District of New York requesting documents and information related to its patient access programs and other aspects of its marketing and commercialization activities. The Company is unable to predict how long this investigation will continue or its outcome, but it has incurred and anticipates that it may continue to incur significant costs in connection with the investigation, regardless of the outcome. The Company may also become subject to similar investigations by other governmental agencies. The investigation by the U.S. Attorney's Office and any additional investigations of the Company's patient access programs and sales and marketing activities may result in damages, fines, penalties or other administrative sanctions against the Company.

Indemnification

In the normal course of business, the Company enters into contracts and agreements that contain a variety of representations and warranties and provide for general indemnifications. The Company's exposure under these agreements is unknown because it involves claims that may be made against the Company in the future, but have not yet been made. In connection with the federal securities class action litigation (described in Note 16 below), the Company has received notice from the Underwriter Defendants (as defined below) of their intention to seek indemnification and has received, but not yet paid, several invoices from the Underwriter Defendants. The Company may record charges in the future as a result of these indemnification obligations.

In accordance with its memorandum and articles of association, the Company has indemnification obligations to its officers and directors for certain events or occurrences, subject to certain limits, while they are serving at the Company's request in such capacity. Additionally, the Company has entered into, and intends to continue to enter into, separate indemnification agreements with its directors and executive officers. These agreements, among other things, require the Company to indemnify its directors and executive officers for certain expenses, including attorneys' fees, judgments, fines and settlement amounts incurred by a director or executive officer in any action or proceeding arising out of their services as one of the Company's directors or executive officers, or any of the Company's subsidiaries or any other company or enterprise to which the person provides services at the Company's request. In connection with the federal securities class action litigation (described in Note 16 below), the Company has paid legal fees and costs on behalf of itself and the current and former officers and directors of the Company who are named as defendants in that litigation. The Company also has a director and officer insurance policy that enables it to recover a portion of any amounts paid for future potential claims. Certain of the Company's officers and directors had also entered into separate indemnification agreements with HPI prior to the Vidara Merger.

NOTE 16 – LEGAL PROCEEDINGS

On July 15, 2013, the Company received a Paragraph IV Patent Certification from Watson Laboratories, Inc.—Florida, known as Actavis Laboratories FL, Inc. ("Actavis FL"), advising that Actavis FL had filed an Abbreviated New Drug Application ("ANDA") with the FDA for a generic version of RAYOS, containing up to 5 mg of prednisone. On August 26, 2013, the Company, together with Jagotec, filed suit in the United States District Court for the District of New Jersey against Actavis FL, Actavis Pharma, Inc., Andrx Corp., and Actavis, Inc. seeking an injunction to prevent the approval of the ANDA.

On October 1, 2015, the Company's subsidiary Horizon Pharma Switzerland GmbH, as well as Jagotec, entered into a license and settlement agreement (the "Actavis settlement agreement") with Actavis FL relating to the Company's and Jagotec's patent infringement litigation against Actavis FL. In accordance with legal requirements, the Company, Jagotec and Actavis FL agreed to submit the Actavis settlement agreement to the U.S. Federal Trade Commission ("FTC") and the U.S. Department of Justice ("DOJ") for review. The parties submitted the Actavis settlement agreement to the FTC and DOJ for review and no issues were raised by either. The parties agreed to file stipulations of dismissal with the court regarding the litigation and the court entered the stipulation and closed the case on December 4, 2015. The Actavis settlement agreement provides for a full settlement and release by each party of all claims that relate to the litigation or under the patents with respect to Actavis FL's generic version of RAYOS tablets.

Under the Actavis settlement agreement, the Company and Jagotec granted Actavis FL a non-exclusive license to manufacture and commercialize Actavis FL's generic version of RAYOS tablets in the United States after the generic entry date (as defined below) and to take steps necessary to develop inventory of, and prepare to commercialize, Actavis FL's generic version of RAYOS tablets during certain limited periods prior to the generic entry date. The Company and Jagotec also agreed that during the 180 days after the generic entry date, the license granted to Actavis FL would be exclusive with respect to any third-party generic version of RAYOS tablets.

Under the Actavis settlement agreement, the generic entry date is December 23, 2022; however, Actavis FL may be able to enter the market earlier under certain circumstances. Such events relate to the resolution of any other third-party RAYOS patent litigation, the entry of other generic versions of RAYOS tablets or certain substantial reductions in RAYOS prescriptions over specified periods of time.

The Company and Jagotec also agreed not to sue or assert any claim against Actavis FL for infringement of any patent or patent application owned or controlled by the Company or Jagotec during the term of the Actavis settlement agreement based on Actavis FL's generic version of RAYOS tablets in the United States. In turn, Actavis FL agreed not to challenge the validity or enforceability of the licensed patents.

If the Company or Jagotec enter into any similar agreements with other parties with respect to generic versions of RAYOS tablets, the Company and Jagotec agreed to amend the Actavis settlement agreement to provide Actavis FL with terms that are no less favorable than those provided to such other parties with respect to the license terms, generic entry date, permitted pre-market activities and notice provisions.

On November 13, 2014, the Company received a Paragraph IV Patent Certification from Watson Laboratories, Inc. ("Watson Laboratories") advising that Watson Laboratories had filed an ANDA with the FDA for a generic version of PENNSAID 2%. On December 23, 2014, the Company filed suit in the United States District Court for the District of New Jersey against Watson Laboratories, Actavis, Inc., and Actavis plc (collectively "Actavis") seeking an injunction to prevent the approval of the ANDA. Since then, Watson Laboratories, Inc. changed its name to Actavis Laboratories UT, Inc., and remains the current holder of the ANDA. The lawsuit alleged that Actavis has infringed U.S. Patent Nos. 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164, and 8,871,809 by filing an ANDA seeking approval from the FDA to market a generic version of PENNSAID 2% prior to the expiration of certain of the Company's patents listed in the FDA's Orange Book ("Orange Book"). The commencement of the patent infringement lawsuit stays, or bars, FDA approval of Actavis' ANDA for 30 months or until an earlier district court decision that the subject patents are not infringed or are invalid.

On June 30, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Actavis for patent infringement of U.S. Patent No. 9,066,913. On August 11, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Actavis for patent infringement of U.S. Patent No. 9,101,591. On September 17, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Actavis for patent infringement of U.S. Patent No. 9,132,110. All three patents, U.S. Patent Nos. 9,066,913, 9,101,591, and 9,132,110 are listed in the Orange Book and have claims that cover PENNSAID 2%. These three cases have since been consolidated with the case filed against Actavis on December 23, 2014.

On October 27, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Actavis for patent infringement of U.S. Patent Nos. 9,168,304 and 9,168,305. On February 5, 2016, the Company filed suit in the United States District Court for the District of New Jersey against Actavis for patent infringement of U.S. Patent No. 9,220,784. All three patents, U.S. Patent Nos. 9,168,304, 9,168,305, and 9,220,784 are listed in the Orange Book and have claims that cover PENNSAID 2%. These two cases have since been consolidated with the cases filed against Actavis on December 23, 2014, June 30, 2015, August 11, 2015, and September 17, 2015. A trial date for these actions has been set for March 21, 2017.

On August 18, 2016, the Company filed suit in the United States District Court for the District of New Jersey against Actavis for patent infringement of U.S. Patent Nos. 9,339,551, 9,339,552, 9,370,501, and 9,375,412. All four patents, U.S. Patent Nos. 9,339,551, 9,339,552, 9,370,501, and 9,375,412, are listed in the Orange Book and have claims that cover PENNSAID 2%. This case is still pending, but has been stayed pending resolution of the trial in the above consolidated actions.

The Company received from Actavis a Paragraph IV Patent Certification Notice Letter dated September 27, 2016, against Orange Book listed U.S. Patent Nos. 9,415,029, advising that Actavis had filed an ANDA with the FDA for a generic version of PENNSAID 2%.

On December 2, 2014, the Company received a Paragraph IV Patent Certification against Orange Book listed U.S. Patent Nos. 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164, and 8,741,956 from Paddock Laboratories, LLC ("Paddock") advising that Paddock had filed an ANDA with the FDA for a generic version of PENNSAID 2%. On January 9, 2015, the Company received from Paddock another Paragraph IV Patent Certification against newly Orange Book listed U.S. Patent No. 8,871,809. On January 13, 2015 and January 14, 2015, the Company filed suits in the United States District Court for the District of New Jersey and the United States District Court for the District of Delaware, respectively, against Paddock seeking an injunction to prevent the approval of the ANDA. The lawsuits alleged that Paddock has infringed U.S. Patent Nos. 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164, and 8,871,809 by filing an ANDA seeking approval from the FDA to market generic versions of PENNSAID 2% prior to the expiration of certain of the Company's patents listed in the Orange Book.

On May 6, 2015, the Company entered into a settlement and license agreement (the "Perrigo settlement agreement") with Perrigo Company plc and its subsidiary Paddock (collectively, "Perrigo"), relating to the Company's patent infringement litigation against Perrigo. The Perrigo settlement agreement provides for a full settlement and release by both the Company and Perrigo of all claims that were or could have been asserted in the litigation and that arise out of the issues that were the subject of the litigation or Perrigo's generic version of PENNSAID 2%. The Perrigo settlement agreement also contemplated the filing of a joint stipulation of dismissal by the parties. This stipulation of dismissal was entered by the district court on May 13, 2015.

Under the Perrigo settlement agreement, the Company granted Perrigo a non-exclusive license to manufacture and commercialize Perrigo's generic version of PENNSAID 2% in the United States after the license effective date (as defined below) and to take steps necessary to develop inventory of, and prepare to commercialize, Perrigo's generic version of PENNSAID 2% during certain limited periods prior to the license effective date.

Under the Perrigo settlement agreement, the license effective date is January 10, 2029; however, Perrigo may be able to enter the market earlier under certain circumstances. Such events relate to the resolution of any other third-party PENNSAID 2% patent litigation, the entry of other third-party generic versions of PENNSAID 2% or certain substantial reductions in the Company's PENNSAID 2% shipments over specified periods of time.

Under the Perrigo settlement agreement, the Company also agreed not to sue or assert any claim against Perrigo for infringement of any patent or patent application owned or controlled by the Company during the term of the license granted in the Perrigo settlement agreement based on the manufacture, use, sale, offer for sale, or importation of Perrigo's generic version of PENNSAID 2% in the United States.

In certain circumstances following the entry of other third-party generic versions of PENNSAID 2%, the Company may be required to supply Perrigo PENNSAID 2% as its authorized distributor of generic PENNSAID 2%, with the Company receiving specified percentages of any net sales by Perrigo. The Company also agreed that if it enters into any similar agreements with other parties with respect to generic versions of PENNSAID 2%, the Company will amend the Perrigo settlement agreement to provide Perrigo with terms that are no less favorable than those provided to such other parties.

On February 2, 2015, the Company received a Paragraph IV Patent Certification against Orange Book listed U.S. Patent Nos. 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164, 8,741,956, and 8,871,809 from Taro Pharmaceuticals USA, Inc. and Taro Pharmaceutical Industries, Ltd. (collectively, "Taro") advising that Taro had filed an ANDA with the FDA for a generic version of PENNSAID 2%. On March 13, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Taro seeking an injunction to prevent the approval of the ANDA.

On September 9, 2015, certain subsidiaries of the Company (the "Horizon Subsidiaries") entered into a settlement and license agreement with Taro (the "Taro settlement agreement") relating to the Horizon Subsidiaries' patent infringement litigation against Taro. In accordance with legal requirements, the Horizon Subsidiaries and Taro submitted the Taro settlement agreement to the FTC and DOJ for review, and no issues have been raised by the FTC and DOJ. The Horizon Subsidiaries and Taro have also filed stipulations of dismissal with the courts regarding the litigation, with these dismissals being entered by the district court on November 3, 2015. The Taro settlement agreement provides for a full settlement and release by both us and Taro of all claims that were or could have been asserted in the Litigation and that arise out of the issues that were subject of the litigation or Taro's generic version of PENNSAID 2%.

Under the Taro settlement agreement, the Horizon Subsidiaries granted Taro a non-exclusive license to manufacture and commercialize Taro's generic version of PENNSAID 2% in the United States after the license effective date (as defined below) and to take steps necessary to develop inventory of, and prepare to commercialize, Taro's generic version of PENNSAID 2% during certain limited periods prior to the license effective date.

Under the Taro settlement agreement, the license effective date is January 10, 2029; however, Taro may be able to enter the market earlier under certain circumstances. Such events relate to the resolution of any other third-party PENNSAID 2% patent litigation, the entry of other third-party generic versions of PENNSAID 2% or certain substantial reductions in the Company's PENNSAID 2% shipments over specified periods of time.

Under the Taro settlement agreement, the Horizon Subsidiaries also agreed not to sue or assert any claim against Taro for infringement of any patent or patent application owned or controlled by the Horizon Subsidiaries during the term of the license granted in the Taro settlement agreement based on the manufacture, use, sale, offer for sale, or importation of Taro's generic version of PENNSAID 2% in the United States.

The Horizon Subsidiaries also agreed that if they enter into any similar agreements with other parties with respect to generic versions of PENNSAID 2%, the Horizon Subsidiaries will amend the Taro settlement agreement to provide Taro with terms that are no less favorable than those provided to the other parties.

On March 18, 2015, the Company received a Paragraph IV Patent Certification against Orange Book listed U.S. Patent Nos. 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164, 8,741,956, and 8,871,809 from Lupin Limited advising that Lupin Limited had filed an ANDA with the FDA for generic version of PENNSAID 2%. On April 30, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Lupin Limited and Lupin Pharmaceuticals Inc. (collectively, "Lupin"), seeking an injunction to prevent the approval of the ANDA. The lawsuit alleges that Lupin has infringed U.S. Patent Nos. 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164, and 8,871,809 by filing an ANDA seeking approval from the FDA to market generic versions of PENNSAID 2% prior to the expiration of certain of the Company's patents listed in the Orange Book. The commencement of the patent infringement lawsuit stays, or bars, FDA approval of Lupin's ANDA for 30 months or until an earlier district court decision that the subject patents are not infringed or are invalid.

On June 30, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Lupin for patent infringement of U.S. Patent No. 9,066,913. On August 11, 2015, the Company filed an amended complaint in the United States District Court for the District of New Jersey against Lupin that added U.S. Patent No. 9,101,591 to the litigation with respect to U.S. Patent No. 9,066,913. On September 17, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Lupin for patent infringement of U.S. Patent No. 9,132,110. All three patents, U.S. Patent Nos. 9,066,913, 9,101,591, and 9,132,110 are listed in the Orange Book and have claims that cover PENNSAID 2%.

On October 27, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Lupin for patent infringement of U.S. Patent Nos. 9,168,304 and 9,168,305. On February 5, 2016, the Company filed suit in the United States District Court for the District of New Jersey against Lupin for patent infringement of U.S. Patent No. 9,220,784. On August 18, 2016, the Company filed suit in the United States District Court for the District of New Jersey against Lupin for patent infringement of U.S. Patent Nos. 9,339,551, 9,339,552, 9,370,501, and 9,375,412. All seven patents, U.S. Patent Nos. 9,168,304, 9,168,305, 9,220,784, 9,339,551, 9,339,552, 9,370,501, and 9,375,412 are listed in the Orange Book and have claims that cover PENNSAID 2%. All of the infringement actions brought against Lupin remain pending. The court has not yet set a trial date for the Lupin actions.

The Company received from Teligent, Inc., formerly known as IGI Laboratories, Inc. ("Teligent"), a Paragraph IV Patent Certification dated March 24, 2015 against Orange Book listed U.S. Patent Nos. 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164, 8,741,956, and 8,871,809 advising that Teligent had filed an ANDA with the FDA for a generic version of PENNSAID 2%. On May 21, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Teligent seeking an injunction to prevent the approval of the ANDA. The lawsuit alleged that Teligent has infringed U.S. Patent Nos. 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164, and 8,871,809 by filing an ANDA seeking approval from the FDA to market generic versions of PENNSAID 2% prior to the expiration of certain of the Company's patents listed in the Orange Book. The commencement of the patent infringement lawsuit stays, or bars, FDA approval of Teligent's ANDA for 30 months or until an earlier district court decision that the subject patents are not infringed or are invalid.

On June 30, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Teligent for patent infringement of U.S. Patent No. 9,066,913. On August 11, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Teligent for patent infringement of U.S. Patent No. 9,101,591. On September 17, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Teligent for patent infringement of U.S. Patent No. 9,132,110. All three patents, U.S. Patent Nos. 9,066,913, 9,101,591, and 9,132,110 are listed in the Orange Book and have claims that cover PENNSAID 2%.

On October 27, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Teligent for patent infringement of U.S. Patent Nos. 9,168,304 and 9,168,305. On February 5, 2016, the Company filed suit in the United States District Court for the District of New Jersey against Teligent for patent infringement of U.S. Patent No. 9,220,784. All three patents, U.S. Patent Nos. 9,168,304, 9,168,305, and 9,220,784 are listed in the Orange Book and have claims that cover PENNSAID 2%.

The Company entered into a settlement and license agreement with Teligent (the "Teligent settlement agreement"), effective May 9, 2016, relating to the patent infringement litigation against Teligent. In accordance with legal requirements, the Company and Teligent submitted the Teligent settlement agreement to the FTC and DOJ for review, and no issues have been raised by the FTC and DOJ. The Company and Teligent have also filed stipulations of dismissal with the district court regarding the litigation, with these dismissals having been entered by the district court on May 2, 2016. The Teligent settlement agreement provides for a full settlement and release by both the Company and Teligent of all claims that were or could have been asserted in the litigation and that arise out of the issues that were subject of the litigation or Teligent's generic version of PENNSAID 2%.

Under the Teligent settlement agreement, the Company granted Teligent a non-exclusive license to manufacture and commercialize Teligent's generic version of PENNSAID 2% in the United States after the license effective date (as defined below) and to take steps necessary to develop inventory of, and prepare to commercialize, Teligent's generic version of PENNSAID 2% during certain limited periods prior to the license effective date.

Under the Teligent settlement agreement, the license effective date is January 10, 2029; however, Teligent may be able to enter the market earlier under certain circumstances. Such events relate to the resolution of any other third-party PENNSAID 2% patent litigation, the entry of other third-party generic versions of PENNSAID 2% or certain substantial reductions in the Company's PENNSAID 2% shipments over specified periods of time.

Under the Teligent settlement agreement, the Company also agreed not to sue or assert any claim against Teligent for infringement of any patent or patent application owned or controlled by the Company during the term of the license granted in the Teligent settlement agreement based on the manufacture, use, sale, offer for sale, or importation of Teligent's generic version of PENNSAID 2% in the United States.

In certain circumstances following the entry of other third-party generic versions of PENNSAID 2%, the Company may be required to supply Teligent PENNSAID 2% as an authorized distributor of generic PENNSAID 2%, with the Company receiving specified percentages of any net sales by Teligent. The Company also agreed that if it enters into any similar agreements with other parties with respect to generic versions of PENNSAID 2%, the Company will amend the Teligent settlement agreement to provide Teligent with terms that are no less favorable than those provided to the other parties.

The Company received from Amneal Pharmaceuticals LLC ("Amneal") a Paragraph IV Patent Certification dated April 2, 2015 against Orange Book listed U.S. Patent Nos. 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164, 8,741,956, and 8,871,809 advising that Amneal had filed an ANDA with the FDA for a generic version of PENNSAID 2%. On May 15, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Amneal seeking an injunction to prevent the approval of the ANDA. The lawsuit alleged that Amneal has infringed U.S. Patent Nos. 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164, and 8,871,809 by filing an ANDA seeking approval from the FDA to market generic versions of PENNSAID 2% prior to the expiration of certain of the Company's patents listed in the Orange Book. The commencement of the patent infringement lawsuit stays, or bars, FDA approval of Amneal's ANDA for 30 months or until an earlier district court decision that the subject patents are not infringed or are invalid.

On June 30, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Amneal for patent infringement of U.S. Patent No. 9,066,913. On August 11, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Amneal for patent infringement of U.S. Patent No. 9,101,591. On September 17, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Amneal for patent infringement of U.S. Patent No. 9,132,110. All three patents, U.S. Patent Nos. 9,066,913, 9,101,591, and 9,132,110 are listed in the Orange Book and have claims that cover PENNSAID 2%.

On October 27, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Amneal for patent infringement of U.S. Patent Nos. 9,168,304 and 9,168,305. On February 5, 2016, the Company filed suit in the United States District Court for the District of New Jersey against Amneal for patent infringement of U.S. Patent No. 9,220,784. All three patents, U.S. Patent Nos. 9,168,304, 9,168,305, and 9,220,784 are listed in the Orange Book and have claims that cover PENNSAID 2%.

On April 18, 2016, the Company entered into a settlement and license agreement (the "Amneal settlement agreement") with Amneal relating to the Company's patent infringement litigation against Amneal. In accordance with legal requirements, the Company and Amneal submitted the Amneal settlement agreement to the FTC and DOJ for review, and no issues have been raised by the FTC and DOJ. The Company and Amneal have also filed a stipulation of dismissal with the court regarding the litigation. The Amneal settlement agreement provides for a full settlement and release by both the Company and Amneal of all claims that were or could have been asserted in the litigation and that arise out of the issues that were the subject of the litigation or Amneal's generic version of PENNSAID 2%.

Under the Amneal settlement agreement, the Company granted Amneal a non-exclusive license to manufacture and commercialize Amneal's generic version of PENNSAID 2% in the United States after the license effective date (as defined below) and to take steps necessary to develop inventory of, and prepare to commercialize, Amneal's generic version of PENNSAID 2% during certain limited periods prior to the license effective date.

Under the Amneal settlement agreement, the license effective date is January 10, 2029; however, Amneal may be able to enter the market earlier under certain circumstances. Such events relate to the resolution of any other third-party PENNSAID 2% patent litigation or the entry of other third-party generic versions of PENNSAID 2%.

Under the Amneal settlement agreement, the Company also agreed not to sue or assert any claim against Amneal for infringement of any patent or patent application owned or controlled by the Company during the term of the license granted in Amneal settlement agreement based on the manufacture, use, sale, offer for sale, or importation of Amneal's generic version of PENNSAID 2% in the United States.

In certain circumstances following the entry of other third-party generic versions of PENNSAID 2%, the Company may be required to supply Amneal PENNSAID 2% as a non-exclusive, authorized distributor of generic PENNSAID 2%, with the Company receiving specified percentages of any net sales by Amneal. The Company also agreed that if it enters into any similar agreements with other parties with respect to generic versions of PENNSAID 2%, the Company will amend the Amneal settlement agreement to provide Amneal with terms that are no less favorable than those provided to the other parties.

The Company received from Apotex Inc. ("Apotex") a Paragraph IV Patent Certification Notice Letter dated April 1, 2016, against Orange Book listed U.S. Patent Nos. 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164, 8,741,956, 8,871,809, 9,066,913, 9,101,591, 9,132,110, 9,168,304, 9,168,305 and 9,220,784 advising that Apotex had filed an ANDA with the FDA for a generic version of PENNSAID 2%. The Company also received from Apotex a second Paragraph IV Patent Certification Notice Letter dated June 30, 2016, against Orange Book listed U.S. Patent Nos. 9,339,551 and 9,339,552, advising that Apotex had filed an ANDA with the FDA for a generic version of PENNSAID 2%. The Company also received from Apotex a third Paragraph IV Patent Certification Notice Letter dated September 21, 2016, against Orange Book listed U.S. Patent No. 9,415,029, advising that Apotex had filed an ANDA with the FDA for a generic version of PENNSAID 2%.

Currently, patent litigation is pending in the United States District Court for the District of New Jersey against three generic companies intending to market VIMOVO prior to the expiration of certain of the Company's patents listed in the Orange Book. These cases are in the United States District Court for the District of New Jersey. They are collectively known as the VIMOVO cases, and involve the following sets of defendants: (i) Dr. Reddy's Laboratories Inc. and Dr. Reddy's Laboratories Ltd. (collectively, "Dr. Reddy's"); (ii) Lupin Ltd. and Lupin Pharmaceuticals Inc. (collectively, "Lupin"); and (iii) Mylan Pharmaceuticals Inc., Mylan Laboratories Limited, and Mylan Inc. (collectively, "Mylan").Patent litigation in the United States District Court for the District of New Jersey against a fourth generic company, Actavis Laboratories FL., Inc. and Actavis Pharma, Inc. (collectively, "Actavis Pharma"), was dismissed on January 10, 2017 after the court granted Actavis' motion to compel enforcement of a settlement agreement. On February 3, 2017, the Company appealed this dismissal decision to the Court of Appeals for the Federal Circuit. Patent litigation in the United States District Court for the District of New Jersey against a fifth generic company, Anchen Pharmaceuticals Inc. ("Anchen"), was dismissed on June 9, 2014 after Anchen recertified under Paragraph III. The Company understands that Dr. Reddy's has entered into a settlement with AstraZeneca with respect to patent rights directed to Nexium for the commercialization of VIMOVO, and that according to the settlement agreement, Dr. Reddy's is now able to commercialize VIMOVO under AstraZeneca's Nexium patent rights. The settlement agreement, however, has no effect on the Aralez VIMOVO patents, which are still the subject of patent litigations. As part of the Company's acquisition of the U.S. rights to VIMOVO, the Company has taken over and is responsible for the patent litigations that include the Aralez patents licensed to the Company under the amended and restated collaboration and license agreement for the United States with Aralez.

The VIMOVO cases were filed on April 21, 2011, July 25, 2011, October 28, 2011, January 4, 2013, May 10, 2013, June 28, 2013, October 23, 2013, May 13, 2015 and November 24, 2015 and collectively include allegations of infringement of U.S. Patent Nos. 6,926,907, 8,557,285, 8,852,636, and 8,858,996 (the "'996 patent"). On June 18, 2015, the Company amended the complaints to add a charge of infringement of U.S. Patent No. 8,865,190 (the "'190 patent"). On January 7, 2016, Actavis Pharma asserted a counterclaim for declaratory judgment of invalidity and non-infringement of U.S. Patent No. 8,945,621 (the "'621 patent"). On January 25, 2016, the Company filed a new case against Actavis Pharma including allegations of infringement of U.S. Patent Nos. 9,161,920 and 9,198,888. This case was subsequently consolidated with the Actavis Pharma case involving the '996 patent, the '190 patent and U.S. Patent No. 8,852,636. On February 10, 2016, the Company amended the complaints against Dr. Reddy's, Lupin, and Mylan to add charges of infringement of U.S. Patent Nos. 9,161,920 and 9,198,888. On February 19, 2016, Mylan asserted a counterclaim for declaratory judgment of invalidity and non-infringement of U.S. Patent No. 9,220,698. On August 11, 2016, the Company filed new complaints asserting the '621 patent and U.S. Patent Nos. 9,220,698, and 9,345,695 against the defendants. On December 6, 2016, the Company asserted U.S. Patent No. 9,393,208 (the "'208 patent") against Lupin, Mylan, and Actavis in amended complaints, and against Dr. Reddy's in a new complaint.

"Case I" consists of the cases asserting U.S. Patent Nos. 8,557,285 and 6,926,907. "Case II" consists of the cases asserting the '996 patent, the '190 patent and U.S. Patent Nos. 8,852,636, 9,161,920, and 9,198,888. "Case III" consists of the cases asserting U.S. Patent Nos. 8,945,621, 9,220,698, 9,345,695, and the '208 patent against Lupin and Mylan, and the case asserting U.S. Patent Nos. 8,945,621, 9,220,698, and 9,345,695 against Dr. Reddy's. "Case IV" consists of the case asserting the '208 patent against Dr. Reddy's.

The Case I cases have been consolidated for discovery. The court has issued a claim construction order for Case I and set a trial date for January 12, 2017. On May 12, 2016, the court granted Dr. Reddy's motion for summary judgment of non-infringement of U.S. Patent No. 6,926,907 with respect to one of Dr. Reddy's two ANDAs.

The Case II cases have been consolidated for discovery. The court has not issued a claim construction order in Case II. On August 23, 2016, the court entered an order denying Mylan's motion to consolidate Case I with Case II.

On October 14, 2016, defendant Dr. Reddy's filed a motion to dismiss all counts in Case III and a motion for summary judgment relevant to Cases I, II, and III. No briefing schedule for defendant Dr. Reddy's motion to dismiss has been set. Briefing for defendant Dr. Reddy's motion for summary judgment was included in the parties' trial briefing.

On December 19, 2016, defendant Actavis filed a motion to compel enforcement of settlement agreement related to Cases I, II, and III. On December 22, 2016, a hearing before Magistrate Judge Arpert was held on defendant Actavis' motion. On December 22, 2016, Magistrate Judge Arpert entered a report and recommendation that Actavis' motion to compel the enforcement of settlement be granted. On December 30, 2016, the Honorable Judge Mary Cooper order the adoption of the report and recommendation. On January 10, 2017, an order of dismissal was entered for all claims in Cases I, II and III. The Company filed a Notice of Appeal with the district court on February 9, 2017.

On December 20, 2016, an initial case management conference was held for Case III (the cases asserting U.S. Patent Nos. 8,557,285, 945,621, 9,220,698, 9,345,695 and 9,393,208 against Lupin and Mylan, and the case asserting the U.S. Patent Nos. 8,945,621, 9,220,698 and 9,345,695 against Dr. Reddy's).

On January 12, 2017, a six-day bench trial commenced against defendants Dr. Reddy's and Mylan before Honorable Judge Mary Cooper in the District of New Jersey for Case I. The patents at issue in this trial included two Orange Book listed patents: U.S. Patent Nos. 6,926,907 and 8,557,285. Defendant Lupin formerly entered into a stay pending the entry of judgment in Case I. Currently, closing arguments and post-trial filings are not scheduled.

On January 19, 2017, the court entered a scheduling order for Case II and Case III. This scheduling order requires, *inter alia*, disclosure of asserted claims by January 31, 2017. A trial date for Cases II and III has not yet been set.

The Company understands the cases arise from Paragraph IV Patent Certification notice letters providing notice of the filing of ANDAs with the FDA seeking regulatory approval to market generic versions of VIMOVO before the expiration of the patents-in-suit. The Company understands the Dr. Reddy's notice letters were dated March 11, 2011, November 20, 2012 and April 20, 2015; the Lupin notice letters were dated June 10, 2011, March 12, 2014 and July 26, 2016; the Mylan notice letters were dated May 16, 2013, February 9, 2015, January 26, 2016, February 26, 2016, July 19, 2016 and September 22, 2016; the Actavis Pharma notice letters were dated March 29, 2013, November 5, 2013, May 29, 2015, October 9, 2015, December 10, 2015, March 1, 2016, April 6, 2016, July 22, 2016 and September 8, 2016; and the Anchen notice letter was dated September 16, 2011.

On February 24, 2015, Dr. Reddy's filed a Petition for inter partes review ("IPR") of U.S. Patent No. 8,557,285, one of the patents in litigation in the above referenced VIMOVO cases. On October 9, 2015, the United States Patent and Trademark Office (the "U.S. PTO") denied such Petition for IPR.

On May 21, 2015, the Coalition for Affordable Drugs VII LLC ("Coalition for Affordable Drugs") filed a Petition for IPR of U.S. Patent No. 6,926,907, one of the patents in litigation in the above referenced VIMOVO cases. On December 8, 2015, the U.S. PTO denied such Petition for IPR.

On June 5, 2015, the Coalition for Affordable Drugs filed another Petition for IPR of the '996 patent, one of the patents in litigation in the above referenced VIMOVO cases. On December 17, 2015, the U.S. PTO denied such Petition for IPR.

On August 7, 2015, the Coalition for Affordable Drugs filed another Petition for IPR of U.S. Patent No. 8,852,636, one of the patents in litigation in the above referenced VIMOVO cases. On February 11, 2016, the U.S. PTO denied such Petition for IPR.

On August 12, 2015, the Coalition for Affordable Drugs filed another Petition for IPR of the '621 patent, one of the patents in litigation in the above referenced VIMOVO cases. On February 22, 2016, the Patent Trial and Appeal Board (the "PTAB") issued a decision to institute the IPR. The PTAB hearing for the '621 patent was held on November 16, 2016. The PTAB issued a final written decision finding the '621 patent valid on February 21, 2017.

On August 19, 2015, Lupin filed Petitions for IPR of the '996 patent, the '190 patent and U.S. Patent No. 8,852,636, all patents in litigation in the above referenced VIMOVO cases. On March 1, 2016, the PTAB issued decisions to institute the IPRs for the '996 patent" and the '190 patent. On March 1, 2016, the PTAB denied the Petition for IPR for U.S. Patent No. 8,852,636. The PTAB hearings for the '996 patent and '190 patent were both held on November 29, 2016. The PTAB must issue a final written decision on the IPRs of the '996 patent and the '190 patent no later than March 1, 2017.

On March 17, 2014, Hyperion received notice from Par Pharmaceutical, Inc. ("Par Pharmaceutical") that it had filed an ANDA with the FDA seeking approval for a generic version of the Company's medicine RAVICTI. The ANDA contained a Paragraph IV Patent Certification alleging that two of the patents covering RAVICTI, U.S. Patent No. 8,404,215, titled "Methods of therapeutic monitoring of nitrogen scavenging drugs," which expires in March 2032 (the "'215 patent"), and U.S. Patent No. 8,642,012, titled "Methods of treatment using ammonia scavenging drugs," which expires in September 2030 (the "'012 patent"), are invalid and/or will not be infringed by Par Pharmaceutical's manufacture, use or sale of the medicine for which the ANDA was submitted. Par Pharmaceutical did not challenge the validity, enforceability, or infringement of the Company's primary composition of matter patent for RAVICTI, U.S. Patent No. 5,968,979 titled "Triglycerides and ethyl esters of phenylalkanoic acid and phenylalkanoic acid useful in treatment of various disorders," which would have expired on February 7, 2015, but as to which Hyperion was granted an interim term of extension until February 7, 2016 and to which the U.S. PTO has granted a final term extension of 1,267 days, which extends the expiration date to July 28, 2018. Hyperion filed suit in the United States District Court for the Eastern District of Texas, Marshall Division, against Par Pharmaceutical on April 23, 2014 seeking an injunction to prevent the approval of Par Pharmaceutical's ANDA and/or to prevent Par Pharmaceutical from selling a generic version of RAVICTI, and the Company has taken over and is responsible for this patent litigation. On September 15, 2015, the Company received notice from Par Pharmaceutical that it had filed a Paragraph IV Patent Certification alleging that U.S. Patent No. 9,095,559 (the "'559 patent") is invalid and/or will not be infringed by Par Pharmaceutical's manufacture, use or sale of the medicine for which the ANDA was submitted. On March 14, 2016, the Company received notice from Par Pharmaceutical that it had filed a Paragraph IV Patent Certification alleging that U.S. Patent No. 9,254,278 (the "'278 patent") is invalid and/or will not be infringed by Par Pharmaceutical's manufacture, use or sale of the medicine for which the ANDA was submitted. On June 3, 2016, the Company received notice from Par Pharmaceutical that it had filed a Paragraph IV Patent Certification alleging that U.S. Patent No. 9,326,966 (the "'966 patent") is invalid and/or will not be infringed by Par Pharmaceutical's manufacture, use or sale of the medicine for which the ANDA was submitted. The Company filed suit in the United States District Court for the District of New Jersey against Par Pharmaceutical on June 30, 2016 ("the Par New Jersey action"), seeking an injunction to prevent the approval of Par Pharmaceutical's ANDA and/or to prevent Par Pharmaceutical from selling a generic version of RAVICTI. The lawsuit alleges that Par Pharmaceutical has infringed the '559 patent, the '278 patent and the '966 patent by filing an ANDA seeking approval from the FDA to market generic versions of RAVICTI prior to the expiration of the patents. The subject patents are listed in the Orange Book. The Par New Jersey action has been stayed pending the resolution of the PTAB's IPR of the '559 patent.

On April 29, 2015, Par Pharmaceutical filed Petitions for IPR of the '215 patent and the '012 patent. The PTAB issued decisions instituting such IPRs on November 4, 2015. On December 14, 2015, the District Court Judge Roy Payne issued a stay pending a final written decision from the PTAB with respect to the IPRs of the '215 patent and the '012 patent. On September 29, 2016, the PTAB issued a final written decision holding all the claims of the '215 patent unpatentable. The Company has not appealed the PTAB's decision concerning the '215 patent to the Federal Circuit. On November 3, 2016, the PTAB issued a final written decision holding all of the claims of the '012 patent patentable. On December 29, 2016, Par filed a notice of appeal with the Federal Circuit to appeal the final written decision of the PTAB concerning the patentability of the '012 patent.

On September 4, 2015, the Company received notice from Lupin of Lupin's Paragraph IV Patent Certification against the '215 patent and the '012 patent, advising that Lupin had filed an ANDA with the FDA for a generic version of RAVICTI. On November 6, 2015, the Company also received Notice of Lupin's Paragraph IV Patent Certification against the '559 patent. Lupin has not advised the Company as to the timing or status of the FDA's review of its filing. On October 19, 2015 the Company filed suit in the United States District Court for the District of New Jersey against Lupin seeking an injunction to prevent the approval of the ANDA. The lawsuit alleges that Lupin has infringed the '215 patent, the '012 patent and the '559 patent by filing an ANDA seeking approval from the FDA to market generic versions of RAVICTI prior to the expiration of the patents. The subject patents are listed in the Orange Book. On April 6, 2016, the Company filed an amended complaint in the United States District Court for the District of New Jersey against Lupin alleging that Lupin has infringed the '559 patent by filing an ANDA seeking approval from the FDA to market generic versions of RAVICTI prior to expiration of the '559 patent. The commencement of the patent infringement lawsuit stays, or bars, FDA approval of Lupin's ANDA for 30 months or until an earlier district court decision that the subject patents are not infringed or are invalid. On April 18, 2016, the Company received notice from Lupin of Lupin's Paragraph IV Patent Certification against the '278 patent. On July 6, 2016, the Company received notice from Lupin of Lupin's Paragraph IV Patent Certification against the '966 patent. The Company filed suit in the United States District Court for the District of New Jersey against Lupin on July 21, 2016, seeking an injunction to prevent the approval of Lupin's ANDA and/or to prevent Lupin from selling a generic version of RAVICTI. The lawsuit alleges that Lupin has infringed the '278 patent and the '966 patent by filing an ANDA seeking approval from the FDA to market generic versions of RAVICTI prior to the expiration of the patents. The subject patents are listed in the Orange Book. The Lupin New Jersey actions have been stayed pending the resolution of the PTAB's IPR of the '559 patent.

On April 1, 2016, Lupin filed a Petition to request an IPR of the '559 patent. On September 30, 2016, the PTAB issued a decision to institute the IPR for the '559 patent. The PTAB must issue a final written decision on the IPR of the '559 patent no later than September 30, 2017.

In November 2015, Express Scripts filed suit against the Company in Delaware Superior Court, Newcastle County, asserting claims for breach of contract, breach of the implied covenant of good faith and fair dealing, unjust enrichment, and declaratory relief arising from the parties' 2012 Preferred Savings Grid Rebate Program Agreement. The Company filed a counter-claim against Express Scripts for breach of contract, breach of the implied covenant of good faith and fair dealing, and declaratory relief arising from Express Scripts' breach of the rebate agreement. In September 2016, the Company entered into a settlement agreement and mutual release with Express Scripts pursuant to which the Company and Express Scripts were released from any and all claims relating to the litigation without admitting any fault or wrongdoing and the Company agreed to pay Express Scripts $65.0 million.

Beginning on March 8, 2016, two federal securities class action lawsuits (captioned Schaffer v. Horizon Pharma plc, et al., Case No. 16-cv-01763-JMF and Banie v. Horizon Pharma plc, et al., Case No. 16-cv-01789-JMF) were filed in the United States District Court for the Southern District of New York against the Company and certain of the Company's current and former officers (the "Officer Defendants"). On March 24, 2016, the court consolidated the two actions under Schaffer v. Horizon Pharma plc, et al. On June 3, 2016, the court appointed Locals 302 and 612 of the International Union of Operating Engineers-Employers Construction Industry Retirement Trust and the Carpenters Pension Trust Fund for Northern California as lead plaintiffs and Labaton Sucharow LLP as lead counsel. On July 25, 2016, lead plaintiffs and additional named plaintiff Automotive Industries Pension Trust Fund filed their consolidated complaint, which they subsequently amended on October 7, 2016, including additional current and former officers, the Company's Board of Directors (the "Director Defendants"), and underwriters involved with the Company's April 2015 public offering (the "Underwriter Defendants") as defendants. The plaintiffs allege that certain of the Company and the Officer Defendants violated sections 10(b) and 20(a) of the Securities Exchange Act of 1934, as amended, by making false and/or misleading statements about, among other things: (a) the Company's financial performance, (b) the Company's business prospects and drug-pricing practices, (c) the Company's sales and promotional practices, and (d) the Company's design, implementation, performance, and risks associated with the Company's Prescriptions-Made-Easy program. The plaintiffs allege that certain of the Company, the Director Defendants and the Underwriter Defendants violated sections 11, 12(a)(2) and 15 of the Securities Act of 1933, as amended, (the "Securities Act") in connection with the Company's April 2015 public offering. The plaintiffs seek, among other things, an award of damages allegedly sustained by plaintiffs and the putative class, including a reasonable allowance for costs and attorneys' fees. On November 14, 2016, all defendants moved to dismiss the plaintiffs' amended complaint. Plaintiffs' filed their opposition to the motion to dismiss on December 21, 2016. Briefing on the Motion to Dismiss was completed on January 27, 2017 and the parties await the Court's ruling.

Between October 5 and October 7, 2016, two complaints (captioned Lavrenov v. Raptor Pharmaceutical Corp., et al., Case No. 16-cv-00901, and Jordan v. Raptor Pharmaceutical Corp., et al., Case No. 16-cv-00913) were filed in the United States District Court for the District of Delaware. Both actions were filed against Raptor and each member of Raptor's board of directors. The Company and Misneach Corporation, a wholly owned subsidiary of the Company, were named as defendants in the Lavrenov action, but not the Jordan action. The actions were brought by purported stockholders of Raptor, on their own behalf and as a putative class of Raptor stockholders, and assert causes of action under Sections 14 and 20 of the Securities Exchange Act of 1934, as amended. The Lavrenov action also asserts breach of fiduciary duty and aiding and abetting claims under Delaware law. The complaints allege, among other things, that the process leading up to the Raptor acquisition was inadequate and that the Schedule 14D-9 filed by Raptor with the Securities and Exchange Commission (the "SEC") omits certain material information, which allegedly renders the information disclosed materially misleading. The complaints seek, among other things, to enjoin the Raptor acquisition, or in the event the Raptor acquisition is consummated, to recover money damages. On October 17, 2016, Raptor filed an amended Schedule 14D-9 with the SEC. Plaintiffs did not file a motion to preliminarily enjoin the Raptor acquisition, which was completed on October 25, 2016. On December 2, 2016, named plaintiffs dismissed both suits with prejudice as to named plaintiffs, and without prejudice to any other potential party. The Court has retained jurisdiction solely for the purpose of ruling upon plaintiffs' motion for attorney fees, in the event such a motion is filed.

NOTE 17 – DEBT AGREEMENTS

The Company's outstanding debt balances as of December 31, 2016 and 2015 consisted of the following (in thousands):

	As of December 31	
	2016	2015
2015 Term Loan Facility	$ 394,000	$ 398,000
2016 Incremental Loan Facility	375,000	—
2023 Senior Notes	475,000	475,000
2024 Senior Notes	300,000	—
Exchangeable Senior Notes	400,000	400,000
Total face value	1,944,000	1,273,000
Debt discount	(126,352)	(127,885)
Deferred financing fees	(10,155)	(8,359)
Total long-term debt	1,807,493	1,136,756
Less: current maturities	7,750	4,000
Long-term debt, net of current maturities	$ 1,799,743	$ 1,132,756

Scheduled maturities with respect to the Company's long-term debt are as follows (in thousands):

2017	$ 7,750
2018	7,750
2019	7,750
2020	7,750
2021	738,000
Thereafter	1,175,000
Total	$ 1,944,000

The Company adopted ASU No. 2015-03, *Interest-Imputation of Interest (Subtopic 835-30): Simplifying the Presentation of Debt Issuance Costs* on January 1, 2016. The amendments in this ASU require that debt issuance costs related to a recognized debt liability be presented in the balance sheet as a direct deduction from the carrying amount of that debt liability, consistent with debt discounts. See Note 2 for further details of the impact this adoption has had on the financial statements.

2015 Senior Secured Credit Facility

On May 7, 2015, HPI, the Company and certain of its subsidiaries entered into a credit agreement with Citibank, N.A., as administrative and collateral agent, and the lenders from time to time party thereto (as amended by the 2016 Amendment described below, the "credit agreement") providing for (i) the six-year $400.0 million term loan facility (the "2015 Term Loan Facility"); (ii) an uncommitted accordion facility subject to the satisfaction of certain financial and other conditions; and (iii) one or more uncommitted refinancing loan facilities with respect to loans thereunder (collectively the "2015 Senior Secured Credit Facility"). The initial borrower under the 2015 Term Loan Facility is HPI. The credit agreement allows for the Company and certain other subsidiaries of the Company to become borrowers under the accordion or refinancing facilities. Loans under the 2015 Term Loan Facility bear interest, at each borrower's option, at a rate equal to either the London Inter-Bank Offer Rate ("LIBOR"), plus an applicable margin of 3.5% per year (subject to a 1.0% LIBOR floor), or the adjusted base rate plus 2.5%. The adjusted base rate is defined as the greater of (a) LIBOR (using one-month interest period) plus 1%, (b) prime rate, (c) fed funds plus ½ of 1%, and (d) 2%. The Company borrowed the full $400.0 million available under the 2015 Term Loan Facility on May 7, 2015 as a LIBOR-based borrowing. In connection with the financing for the acquisition of Raptor, the credit agreement was amended to add a $375.0 million incremental loan facility and change the interest rate margins applicable to the 2015 Term Loan Facility, as further described below.

The obligations under the credit agreement and any swap obligations and cash management obligations owing to a lender (or an affiliate of a lender) thereunder are and will be guaranteed by the Company and each of the Company's existing and subsequently acquired or organized direct and indirect subsidiaries (other than certain immaterial subsidiaries, subsidiaries whose guarantee would result in material adverse tax consequences and subsidiaries whose guarantee is prohibited by applicable law). The obligations under the credit agreement and any such swap and cash management obligations are secured, subject to customary permitted liens and other agreed upon exceptions, by a perfected security interest in (i) all tangible and intangible assets of the borrowers and the guarantors, except for certain customary excluded assets, and (ii) all of the capital stock owned by the borrowers and guarantors thereunder (limited, in the case of the stock of certain non-U.S. subsidiaries of the borrowers, to 65% of the capital stock of such subsidiaries).

The borrowers are permitted to make voluntary prepayments at any time without payment of a premium. HPI is required to make mandatory prepayments of loans under the 2015 Term Loan Facility (without payment of a premium) with (a) net cash proceeds from certain non-ordinary course asset sales (subject to reinvestment rights and other exceptions), (b) casualty proceeds and condemnation awards (subject to reinvestment rights and other exceptions), (c) net cash proceeds from issuances of debt (other than certain permitted debt), and (d) beginning with the fiscal year ending December 31, 2016, 50% of the Company's excess cash flow (subject to decrease to 25% or 0% if the Company's first lien leverage ratio is less than 2.25:1 and 1.75:1, respectively). The loans under the 2015 Term Loan Facility will amortize in equal quarterly installments in an aggregate annual amount equal to 1% of the original principal amount thereof, with any remaining balance payable on the final maturity date of the loans under the 2015 Term Loan Facility.

The credit agreement contains customary representations and warranties and customary affirmative and negative covenants, including, among other things, restrictions on indebtedness, liens, investments, mergers, dispositions, prepayment of other indebtedness and dividends and other distributions, and customary events of default.

The Company was, as of December 31, 2016, and is currently in compliance with this credit agreement.

As of December 31, 2016, the fair value of the 2015 Term Loan Facility was approximately $394.0 million, categorized as a Level 2 instrument, as defined in Note 14.

2016 Amendment to Credit Agreement

On October 25, 2016, HPI and Horizon Pharma USA, Inc., a wholly owned subsidiary of the Company ("HPUSA") (together, in such capacity, the "Incremental Borrowers") entered into an amendment to the credit agreement (the "2016 Amendment") with Citibank, N.A., as administrative and collateral agent, and Bank of America, N.A., as the incremental B-1 lender thereunder, pursuant to which the Incremental Borrowers borrowed $375.0 million aggregate principal amount of loans (the "2016 Incremental Loan Facility"). The 2016 Incremental Loan Facility was incurred as a separate class of term loans under the credit agreement with the same terms as the loans under the 2015 Term Loan Facility, except as described below.

Loans under the 2016 Incremental Loan Facility bear interest, at each Incremental Borrowers' option, at a rate equal to either LIBOR plus an applicable margin of 4.50% per year (subject to a LIBOR floor of 1.0%), or the adjusted base rate plus 3.50%. The terms of the loans under the 2015 Term Loan Facility (the "2015 Loans") provided for an amendment such that the effective yield of the 2015 Loans would not be less than the effective yield of the loans under the 2016 Incremental Loan Facility (the "2016 Incremental Loans") minus 0.50%. Consequently, the issuance of the 2016 Incremental Loans resulted in an increase of the interest rate applicable to the 2015 Loans, as of October 25, 2016, to LIBOR plus 4.00%, subject to a LIBOR floor of 1.0% (an initial interest rate of 5.00%). Borrowers under the credit agreement are permitted to make voluntary prepayments of the loans under the credit agreement at any time without payment of a premium, except that with respect to the 2016 Incremental Loans, a 1% premium will apply to a repayment of the 2016 Incremental Loans in connection with a repricing of, or any amendment to the credit agreement in a repricing of, such loans effected on or prior to the date that is twelve months following October 25, 2016.

The Company was, as of December 31, 2016, and is currently in compliance with this credit agreement.

As of December 31, 2016, the fair value of the 2016 Incremental Loan Facility was approximately $378.8 million, categorized as a Level 2 instrument, as defined in Note 14.

2023 Senior Notes

On April 29, 2015, Horizon Pharma Financing Inc. ("Horizon Financing") a wholly owned subsidiary of the Company, completed a private placement of $475.0 million aggregate principal amount of 6.625% Senior Notes due 2023 (the "2023 Senior Notes") to certain investment banks acting as initial purchasers who subsequently resold the 2023 Senior Notes to qualified institutional buyers as defined in Rule 144A under the Securities Act, and in offshore transactions to non-U.S. persons in reliance on Regulation S under the Securities Act.

In connection with the closing of the Hyperion acquisition on May 7, 2015, Horizon Financing merged with and into HPI and, as a result, the 2023 Senior Notes became HPI's general unsecured senior obligations and the Company and all of the Company's direct and indirect subsidiaries that are guarantors under the 2015 Senior Secured Credit Facility fully and unconditionally guaranteed on a senior unsecured basis HPI's obligations under the 2023 Senior Notes.

The 2023 Senior Notes accrue interest at an annual rate of 6.625% payable semiannually in arrears on May 1 and November 1 of each year, beginning on November 1, 2015. The 2023 Senior Notes will mature on May 1, 2023, unless earlier exchanged, repurchased or redeemed.

Except as described below, the 2023 Senior Notes may not be redeemed before May 1, 2018. Thereafter, some or all of the 2023 Senior Notes may be redeemed at any time at specified redemption prices, plus accrued and unpaid interest to the redemption date. At any time prior to May 1, 2018, some or all of the 2023 Senior Notes may be redeemed at a price equal to 100% of the aggregate principal amount thereof, plus a make-whole premium and accrued and unpaid interest to the redemption date. Also prior to May 1, 2018, up to 35% of the aggregate principal amount of the 2023 Senior Notes may be redeemed at a redemption price of 106.625% of the aggregate principal amount thereof, plus accrued and unpaid interest, with the net proceeds of certain equity offerings. In addition, the 2023 Senior Notes may be redeemed in whole but not in part at a redemption price equal to 100% of the principal amount plus accrued and unpaid interest and additional amounts, if any, to, but excluding, the redemption date, if on the next date on which any amount would be payable in respect of the 2023 Senior Notes, HPI or any guarantor is or would be required to pay additional amounts as a result of certain tax-related events.

If the Company undergoes a change of control, HPI will be required to make an offer to purchase all of the 2023 Senior Notes at a price in cash equal to 101% of the aggregate principal amount thereof plus accrued and unpaid interest to, but not including, the repurchase date. If the Company or certain of its subsidiaries engages in certain asset sales, HPI will be required under certain circumstances to make an offer to purchase the 2023 Senior Notes at 100% of the principal amount thereof, plus accrued and unpaid interest to the repurchase date.

The indenture governing the 2023 Senior Notes contains covenants that limit the ability of the Company and its restricted subsidiaries to, among other things, pay dividends or distributions, repurchase equity, prepay junior debt and make certain investments, incur additional debt and issue certain preferred stock, incur liens on assets, engage in certain asset sales, merge, consolidate with or merge or sell all or substantially all of their assets, enter into transactions with affiliates, designate subsidiaries as unrestricted subsidiaries, and allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to the Company. Certain of the covenants will be suspended during any period in which the notes receive investment grade ratings. The indenture also includes customary events of default.

The Company was, as of December 31, 2016, and is currently in compliance with the indenture governing the 2023 Senior Notes.

As of December 31, 2016, the fair value of the 2023 Senior Notes was approximately $449.5 million, categorized as a Level 2 instrument, as defined in Note 14.

2024 Senior Notes

On October 25, 2016, HPI and HPUSA (together, the "2024 Issuers"), completed a private placement of $300.0 million aggregate principal amount of 2024 Senior Notes to certain investment banks acting as initial purchasers who subsequently resold the 2024 Senior Notes to qualified institutional buyers as defined in Rule 144A under the Securities Act.

The 2024 Senior Notes are the 2024 Issuers' general unsecured senior obligations and the Company and all of the Company's direct and indirect subsidiaries that are guarantors under the 2015 Senior Secured Credit Facility and the 2016 Incremental Loan Facility fully and unconditionally guaranteed on a senior unsecured basis the 2024 Issuers' obligations under the 2024 Senior Notes.

The 2024 Senior Notes accrue interest at an annual rate of 8.75% payable semiannually in arrears on May 1 and November 1 of each year, beginning on May 1, 2017. The 2024 Senior Notes will mature on November 1, 2024, unless earlier exchanged, repurchased or redeemed.

Except as described below, the 2024 Senior Notes may not be redeemed before November 1, 2019. Thereafter, some or all of the 2024 Senior Notes may be redeemed at any time at specified redemption prices, plus accrued and unpaid interest to the redemption date. At any time prior to November 1, 2019, some or all of the 2024 Senior Notes may be redeemed at a price equal to 100% of the aggregate principal amount thereof, plus a make-whole premium and accrued and unpaid interest to the redemption date. Also prior to November 1, 2019, up to 35% of the aggregate principal amount of the 2024 Senior Notes may be redeemed at a redemption price of 108.75% of the aggregate principal amount thereof, plus accrued and unpaid interest, with the net proceeds of certain equity offerings. In addition, the 2024 Senior Notes may be redeemed in whole but not in part at a redemption price equal to 100% of the principal amount plus accrued and unpaid interest and additional amounts, if any, to, but excluding, the redemption date, if on the next date on which any amount would be payable in respect of the 2024 Senior Notes, the 2024 Issuers or any guarantor is or would be required to pay additional amounts as a result of certain tax-related events.

If the Company undergoes a change of control, the 2024 Issuers will be required to make an offer to purchase all of the 2024 Senior Notes at a price in cash equal to 101% of the aggregate principal amount thereof plus accrued and unpaid interest to, but not including, the repurchase date. If the Company or certain of its subsidiaries engages in certain asset sales, the 2024 Issuers will be required under certain circumstances to make an offer to purchase the 2024 Senior Notes at 100% of the principal amount thereof, plus accrued and unpaid interest to the repurchase date.

The indenture governing the 2024 Senior Notes contains covenants that limit the ability of the Company and its restricted subsidiaries to, among other things, pay dividends or distributions, repurchase equity, prepay junior debt and make certain investments, incur additional debt and issue certain preferred stock, incur liens on assets, engage in certain asset sales, merge, consolidate with or merge or sell all or substantially all of their assets, enter into transactions with affiliates, designate subsidiaries as unrestricted subsidiaries, and allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to the Company. Certain of the covenants will be suspended during any period in which the notes receive investment grade ratings. The indenture also includes customary events of default.

The Company was, as of December 31, 2016, and is currently in compliance with the indenture governing the 2024 Senior Notes.

As of December 31, 2016, the fair value of the 2024 Senior Notes was approximately $301.5 million, categorized as a Level 2 instrument, as defined in Note 14.

Exchangeable Senior Notes

On March 13, 2015, Horizon Investment completed a private placement of $400.0 million aggregate principal amount of Exchangeable Senior Notes to several investment banks acting as initial purchasers who subsequently resold the Exchangeable Senior Notes to qualified institutional buyers as defined in Rule 144A under the Securities Act. The net proceeds from the offering of the Exchangeable Senior Notes were approximately $387.2 million, after deducting the initial purchasers' discount and offering expenses payable by Horizon Investment.

The Exchangeable Senior Notes are fully and unconditionally guaranteed, on a senior unsecured basis, by the Company (the "Guarantee"). The Exchangeable Senior Notes and the Guarantee are Horizon Investment's and the Company's senior unsecured obligations. The Exchangeable Senior Notes accrue interest at an annual rate of 2.50% payable semiannually in arrears on March 15 and September 15 of each year, beginning on September 15, 2015. The Exchangeable Senior Notes will mature on March 15, 2022, unless earlier exchanged, repurchased or redeemed. The initial exchange rate is 34.8979 ordinary shares of the Company per $1,000 principal amount of the Exchangeable Senior Notes (equivalent to an initial exchange price of approximately $28.66 per ordinary share). The exchange rate will be subject to adjustment in some events but will not be adjusted for any accrued and unpaid interest. In addition, following certain corporate events that occur prior to the maturity date or upon a tax redemption, Horizon Investment will increase the exchange rate for a holder who elects to exchange its Exchangeable Senior Notes in connection with such a corporate event or a tax redemption in certain circumstances.

Other than as described below, the Exchangeable Senior Notes may not be redeemed by the Company.

Issuer Redemptions:

Optional Redemption for Changes in the Tax Laws of a Relevant Taxing Jurisdiction: Horizon Investment may redeem the Exchangeable Senior Notes at its option, prior to March 15, 2022, in whole but not in part, in connection with certain tax-related events.

Provisional Redemption on or After March 20, 2019: On or after March 20, 2019, Horizon Investment may redeem for cash all or a portion of the Exchangeable Senior Notes if the last reported sale price of ordinary shares of the Company has been at least 130% of the exchange price then in effect for at least 20 trading days whether or not consecutive) during any 30 consecutive trading day period ending on, and including, the trading day immediately preceding the date on which Horizon Investment provide written notice of redemption. The redemption price will be equal to 100% of the principal amount of the Exchangeable Senior Notes to be redeemed, plus accrued and unpaid interest to, but not including, the redemption date; provided that if the redemption date occurs after a regular record date and on or prior to the corresponding interest payment date, Horizon Investment will pay the full amount of accrued and unpaid interest due on such interest payment date to the record holder of the Exchangeable Senior Notes on the regular record date corresponding to such interest payment date, and the redemption price payable to the holder who presents an Exchangeable Senior Note for redemption will be equal to 100% of the principal amount of such Exchangeable Senior Note.

Holder Exchange Rights:

Holders may exchange all or any portion of their Exchangeable Senior Notes at their option at any time prior to the close of business on the business day immediately preceding December 15, 2021 only upon satisfaction of one or more of the following conditions:

1. Exchange upon Satisfaction of Sale Price Condition – During any calendar quarter commencing after the calendar quarter ending on June 30, 2015 (and only during such calendar quarter), if the last reported sale price of ordinary shares of the Company for at least 20 trading days (whether or not consecutive) during the period of 30 consecutive trading days ending on the last trading day of the immediately preceding calendar quarter is greater than or equal to 130% of the applicable exchange price on each applicable trading day.
2. Exchange upon Satisfaction of Trading Price Condition – During the five business day period after any ten consecutive trading day period in which the trading price per $1,000 principal amount of Exchangeable Senior Notes for each trading day of such period was less than 98% of the product of the last reported sale price of ordinary shares of the Company and the applicable exchange rate on such trading day.
3. Exchange upon Notice of Redemption – Prior to the close of business on the business day immediately preceding December 15, 2021, if Horizon Investment provides a notice of redemption, at any time prior to the close of business on the second scheduled trading day immediately preceding the redemption date.

As of December 31, 2016, none of the above conditions had been satisfied and no exchange of Exchangeable Senior Notes had been triggered.

On or after December 15, 2021, a holder may exchange all or any portion of its Exchangeable Senior Notes at any time prior to the close of business on the second scheduled trading day immediately preceding the maturity date regardless of the foregoing conditions.

Upon exchange, Horizon Investment will settle exchanges of the Exchangeable Senior Notes by paying or causing to be delivered, as the case may be, cash, ordinary shares or a combination of cash and ordinary shares, at its election.

The Company recorded the Exchangeable Senior Notes under the guidance in Topic ASC 470-20, *Debt with Conversion and Other Options,* and separated them into a liability component and equity component. The carrying amount of the liability component of $268.9 million was determined by measuring the fair value of a similar liability that does not have an associated equity component. The carrying amount of the equity component of $119.1 million represented by the embedded conversion option was determined by deducting the fair value of the liability component of $268.9 million from the initial proceeds of $387.2 million ascribed to the convertible debt instrument as a whole. The initial debt discount of $131.1 million is being charged to interest expense over the life of the Exchangeable Senior Notes using the effective interest rate method.

As of December 31, 2016, the fair value of the Exchangeable Senior Notes was approximately $380.5 million, categorized as a Level 2 instrument, as defined in Note 14.

2014 Senior Secured Credit Facility

On June 17, 2014, the Company entered into a credit agreement with a group of lenders and Citibank, N.A., as administrative and collateral agent to provide the Company with $300.0 million in financing through a five-year senior secured credit facility (the "2014 Senior Secured Credit Facility"). Loans under the five-year $300.0 million term loan facility ("2014 Term Loan Facility") bore interest, at each borrower's option, at a rate equal to either the LIBOR, plus an applicable margin of 8.0% per year (subject to a 1.0% LIBOR floor), or the prime lending rate, plus an applicable margin equal to 7.0% per year. The Company borrowed the full $300.0 million available on the 2014 Term Loan Facility on September 19, 2014 as a LIBOR-based borrowing.

On May 7, 2015, the Company repaid the entire $300.0 million outstanding amount under the 2014 Senior Secured Credit Facility in connection with the closing of the Hyperion acquisition and recognized a $56.8 million loss on debt extinguishment as a result of the early repayment.

Convertible Senior Notes

On November 22, 2013, the Company issued $150.0 million aggregate principal amount of Convertible Senior Notes and received net proceeds of $143.6 million, after deducting fees and expenses of $6.4 million.

During 2015, the Company entered into separate, privately-negotiated conversion agreements with certain holders of the Convertible Senior Notes ("2015 Conversions") which were on substantially the same terms as prior conversion agreements entered into by the Company. Under the 2015 Conversions, the applicable holders agreed to convert an aggregate principal amount of $61.0 million of Convertible Senior Notes held by them and the Company agreed to settle such conversions by issuing an aggregate of 11,368,921 ordinary shares. In addition, pursuant to such conversion agreements, the Company made an aggregate cash payment of $10.0 million to the applicable holders for additional exchange consideration and $0.9 million for accrued and unpaid interest, and recognized a non-cash charge of $10.1 million related to the extinguishment of debt as a result of the note conversions. The number of shares issued equaled the number of shares based on the underlying conversion option. The aggregate cash payments to the holders for additional exchange consideration were recorded as part of the extinguishment loss. Following the closings under the 2015 Conversions, there were no Convertible Senior Notes remaining outstanding.

NOTE 18 – SHAREHOLDERS' EQUITY

During the year ended December 31, 2016, the Company issued an aggregate of:

- 666,984 ordinary shares in net settlement of vested restricted stock units;

- 581,840 ordinary shares in connection with the exercise of stock options and received $3.9 million in proceeds;
- 513,659 ordinary shares pursuant to employee stock purchase plans and received $6.5 million in proceeds; and
- 13,584 ordinary shares in net settlement of vested performance stock units;

During the year ended December 31, 2016, the Company issued an aggregate of 1,750 ordinary shares upon the cash exercise of warrants and the Company received proceeds of $8,000 representing the aggregate exercise price for such warrants. In addition, warrants to purchase an aggregate of 207,110 ordinary shares of the Company were exercised in cashless exercises, resulting in the issuance of 161,259 ordinary shares. As of December 31, 2016, there were outstanding warrants to purchase 1,372,660 ordinary shares of the Company.

During the year ended December 31, 2016, the Company made payments of $5.5 million for employee withholding taxes relating to share-based awards.

In May 2016, the Company's board of directors authorized a share repurchase program pursuant to which the Company may repurchase up to 5,000,000 of its ordinary shares. The timing and amount of repurchases, including whether the Company decides to repurchase any shares pursuant to the authorization, will depend on a variety of factors, including the price of the Company's ordinary shares, alternative investment opportunities, the Company's cash resources, restrictions under the Company's credit agreement, and market conditions. As of December 31, 2016, the Company had not purchased any of its ordinary shares under this repurchase program.

NOTE 19 – EQUITY INCENTIVE PLANS

Employee Stock Purchase Plan

2014 Employee Stock Purchase Plan. On May 17, 2014, HPI's board of directors adopted the 2014 Employee Stock Purchase Plan (the "2014 ESPP"). On September 18, 2014, at a special meeting of the stockholders of HPI (the "Special Meeting"), HPI's stockholders approved the 2014 ESPP. Upon consummation of the Vidara Merger, the Company assumed the 2014 ESPP, which serves as the successor to the Company's 2011 Employee Stock Purchase Plan. As described below, effective as of May 3, 2016, the number of ordinary shares authorized for issuance under the 2014 ESPP was reduced by 5,000,000 shares.

As of December 31, 2016, an aggregate of 3,824,400 ordinary shares were authorized and available for future issuance under the 2014 ESPP.

Share-Based Compensation Plans

2005 Stock Plan. In October 2005, HPI adopted the 2005 Stock Plan (the "2005 Plan"). Upon the signing of the underwriting agreement related to HPI's initial public offering, on July 28, 2011, no further option grants were made under the 2005 Plan. All stock awards granted under the 2005 Plan prior to July 28, 2011 continue to be governed by the terms of the 2005 Plan. Upon consummation of the Vidara Merger, the Company assumed the 2005 Plan.

2011 Equity Incentive Plan. In July 2010, HPI's board of directors adopted the 2011 Equity Incentive Plan (the "2011 EIP"). In June 2011, HPI's stockholders approved the 2011 EIP, and it became effective upon the signing of the underwriting agreement related to HPI's initial public offering on July 28, 2011. Upon consummation of the Vidara Merger, the Company assumed the 2011 EIP, and upon the effectiveness of the Horizon Pharma Public Limited Company 2014 Equity Incentive Plan (the "2014 EIP"), no additional stock awards were or will be made under the 2011 Plan, although all outstanding stock awards granted under the 2011 Plan continue to be governed by the terms of the 2011 Plan.

2014 Equity Incentive Plan and 2014 Non-Employee Equity Plan. On May 17, 2014, HPI's board of directors adopted the 2014 EIP and the Horizon Pharma Public Limited Company 2014 Non-Employee Equity Plan (the "2014 Non-Employee Equity Plan"). At the Special Meeting, HPI's stockholders approved the 2014 EIP and 2014 Non-Employee Equity Plan. Upon consummation of the Vidara Merger, the Company assumed the 2014 EIP and 2014 Non-Employee Equity Plan, which serve as successors to the 2011 EIP.

The 2014 EIP provides for the grant of incentive and nonstatutory stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards, performance awards and other stock awards that may be settled in cash, shares or other property to the employees of the Company (or a subsidiary company). The number of ordinary shares of the Company that were initially authorized for issuance under the 2014 EIP was no more than 22,052,130, which number consisted of (i) 15,500,000 ordinary shares of the Company; plus (ii) the number of shares available for issuance pursuant to the grant of future awards under the 2011 EIP; plus (iii) any shares subject to outstanding stock awards granted under the 2011 EIP and the 2005 Plan that expire or terminate for any reason prior to exercise or settlement or are forfeited, redeemed or repurchased because of the failure to meet a contingency or condition required to vest such shares; less (iv) 10,000,000 shares, which is the additional number of shares which were previously approved as an increase to the share reserve of the 2011 EIP. On March 23, 2015, the compensation committee of the Company's board of directors approved amending the 2014 EIP subject to shareholder approval to, among other things, increase the aggregate number of shares authorized for issuance under the 2014 EIP by 14,000,000 shares. On May 6, 2015, the shareholders of the Company approved the amendment to the 2014 EIP. On February 25, 2016, the compensation committee of the Company's board of directors approved, subject to shareholder approval, amending the 2014 EIP to, among other things, increase the aggregate number of shares authorized for issuance under the 2014 EIP beyond those remaining available for future grant under the 2014 EIP by 6,000,000 shares and also approved a reduction in the number of shares authorized under the Company's 2014 Non-Employee Equity Plan and 2014 ESPP by 1,000,000 shares and 5,000,000 shares, respectively, contingent on shareholder approval of the amendment to the 2014 EIP. On May 3, 2016, the shareholders of the Company approved the amendment to the 2014 EIP. The Company's board of directors has authority to suspend or terminate the 2014 EIP at any time.

The 2014 Non-Employee Equity Plan provides for the grant of nonstatutory stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards and other forms of stock awards that may be settled in cash, shares or other property to the non-employee directors and consultants of the Company (or a subsidiary company). The total number of ordinary shares of the Company that were initially authorized for issuance under the 2014 Non-Employee Equity Plan is 2,500,000. As described above, effective as of May 3, 2016, the number of ordinary shares authorized for issuance under the 2014 Non-Employee Equity Plan was reduced by 1,000,000 shares. The Company's board of directors has authority to suspend or terminate the 2014 Non-Employee Equity Plan at any time.

As of December 31, 2016, an aggregate of 6,952,414 and 963,567 ordinary shares were authorized and available for future grants under the 2014 EIP and 2014 Non-Employee Equity Plan, respectively.

Stock Options

The following table summarizes stock option activity during the year ended December 31, 2016:

	Options	Weighted Average Exercise Price	Weighted Average Contractual Term Remaining (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2015	13,385,791	$ 17.73		
Granted	2,057,247	17.90		
Exercised	(581,840)	6.73		
Forfeited	(1,139,933)	18.49		
Expired	(93,746)	15.99		
Outstanding as of December 31, 2016	13,627,519	$ 18.17	7.60	$ 35,157
Exercisable and fully vested as of December 31, 2016	7,021,797	$ 15.65	6.79	30,017

Stock options typically have a contractual term of ten years from grant date.

The following table summarizes the Company's outstanding stock options at December 31, 2016:

	Options Outstanding			Options Exercisable and Fully Vested		
Exercise Price Ranges	Number of options outstanding	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (in years)	Number Exercisable	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (in years)
$2.01 - $4.00	880,261	$ 2.65	6.10	832,503	$ 2.64	6.07
$4.01 - $8.00	1,278,964	6.29	5.56	1,128,647	6.13	5.37
$8.01 - $12.00	866,586	9.14	6.50	610,226	9.20	6.10
$12.01 - $17.00	2,271,218	14.28	7.42	1,350,199	13.87	6.62
$17.01 - $22.00	2,148,781	18.77	8.81	352,362	19.25	8.03
$22.01 - $28.00	3,580,450	22.31	8.23	1,552,310	22.30	8.23
$28.01 - $36.00	2,601,259	29.48	7.74	1,195,550	29.30	6.96
	13,627,519	$ 18.17	7.60	7,021,797	$ 15.65	6.79

During the years ended December 31, 2016, 2015 and 2014, the Company granted stock options to purchase an aggregate of 2,057,247, 8,010,638 and 3,902,836 ordinary shares (or prior to the Vidara Merger, shares of HPI common stock), respectively, with a weighted average grant date fair value of $17.90, $23.92 and $10.71, respectively.

The total intrinsic value of the options exercised during the years ended December 31, 2016, 2015 and 2014 was $6.9 million, $15.6 million, and $3.9 million, respectively. The total fair value of stock options vested during the years ended December 31, 2016, 2015 and 2014 was $55.6 million, $11.4 million, and $8.2 million, respectively.

The fair value of each stock option award is estimated on the date of grant using the Black-Scholes option pricing model. The determination of the fair value of each stock option is affected by the Company's share price on the date of grant, as well as assumptions regarding a number of highly complex and subjective variables. These variables include, but are not limited to, the Company's expected share price volatility over the expected life of the awards and actual and projected stock option exercise behavior. The weighted average fair value per share of stock option awards granted during the years ended December 31, 2016, 2015 and 2014, and assumptions used to value stock options, are as follows:

	For the Years Ended December 31,		
	2016	2015	2014
Dividend yield	—	—	—
Risk-free interest rate	1.3%-2.2%	1.3% - 2.2%	1.6% - 2.1%
Weighted average volatility	73.2%	77.1%	83.1%
Expected life (in years)	6.02	6.07	6.11
Weighted average grant date fair value per share of options granted	$ 11.58	$ 16.07	$ 8.88

Dividend yields

The Company has never paid dividends and does not anticipate paying any dividends in the near future. Additionally, the 2015 Senior Secured Credit Facility, as amended by the 2016 Amendment, as well as the 2023 Senior Notes and the 2024 Senior Notes (each described in Note 17 above), contain covenants that restrict the Company from issuing dividends.

Risk-Free Interest Rate

The Company determined the risk-free interest rate by using a weighted average assumption equivalent to the expected term based on the U.S. Treasury constant maturity rate as of the date of grant.

Volatility

The Company used an average historical share price volatility of comparable companies to be representative of future share price volatility, as the Company did not have sufficient trading history for its ordinary shares.

Expected Term

Given the Company's limited historical exercise behavior, the expected term of options granted was determined using the "simplified" method since the Company does not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term. Under this approach, the expected term is presumed to be the average of the vesting term and the contractual life of the option.

Forfeitures

As share-based compensation expense recognized in the consolidated statements of comprehensive (loss) income is based on awards ultimately expected to vest, it has been reduced for estimated forfeitures based on actual forfeiture experience, analysis of employee turnover and other factors. ASC Topic 718, *Compensation-Stock Compensation* ("ASC 718") requires forfeitures to be estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates.

Restricted Stock Units

The following table summarizes restricted stock unit activity for the year ended December 31, 2016:

	Number of Units	Weighted Average Grant-Date Fair Value Per Units
Outstanding as of December 31, 2015	3,361,746	$ 18.71
Granted	1,384,104	17.07
Vested	(970,197)	17.38
Forfeited	(407,782)	18.42
Outstanding as of December 31, 2016	3,367,871	$ 18.45

The grant-date fair value of restricted stock units is the closing price of the Company's shares on the date of grant.

During the years ended December 31, 2016, 2015 and 2014, the Company granted 1,384,104, 2,361,948 and 1,312,722 restricted stock units to acquire shares of the Company's ordinary shares (or prior to the Vidara Merger, shares of HPI common stock) to its employees and non-executive directors, respectively, with a weighted average grant date fair value of $17.07, $23.36 and $10.55, respectively. The restricted stock units vest over a four-year period on each anniversary of the vesting commencement date. The Company accounts for the restricted stock units as equity-settled awards in accordance with ASC 718. The total fair value of restricted stock units vested during the years ended December 31, 2016, 2015 and 2014 was $16.2 million, $9.0 million and $3.4 million, respectively.

Performance Stock Unit Awards

The following table summarizes performance stock unit awards ("PSUs") activity for the year ended December 31, 2016:

	Number of Units	Weighted Average Grant-Date Fair Value Per Unit	Average Illiquidity Discount	Recorded Weighted Average Fair Value Per Unit
Outstanding as of December 31, 2015	13,049,000			
Granted	260,000	$ 7.99	8.2%	$ 7.34
Vested	(20,000)	18.97	0.0%	18.97
Forfeited	(1,243,344)	14.68	10.9%	13.08
Outstanding as of December 31, 2016	12,045,656			

In January 2016, the compensation committee of the Company's board of directors (the "Committee") approved the grant of 260,000 PSUs to certain members of the Company's senior leadership team.

In March 2015, the Committee approved the grant of 10,604,000 PSUs to certain members of the Company's executive committee, senior leadership team and other key employees. 7,998,000 of these PSUs were granted subject to shareholder approval of certain amendments of the 2014 EIP, which occurred on May 6, 2015. In May 2015, the Committee granted 1,264,000 PSUs to new and promoted key employees. In the third and fourth quarters of 2015, the Committee granted 1,120,000 PSUs to a new member of the Company's executive committee and key employees and 388,000 PSUs to non-executive committee members, respectively.

In 2014, the Company granted 25,000 PSUs. All other outstanding PSUs were granted in 2015 and 2016 and may vest if the Company's total compounded annual shareholder rate of return ("TSR") over three performance measurement periods summarized below equals or exceeds a minimum of 15%.

Vesting Tranche	Percent of Total PSU Award	Beginning of Performance Measurement Period	End of Performance Measurement Period	Length of Performance Measurement Period (Years)
Tranche One	33.3%	March 23, 2015	December 22, 2017	2.75
Tranche Two	33.3%	March 23, 2015	March 22, 2018	3.00
Tranche Three	33.3%	March 23, 2015	June 22, 2018	3.25

These outstanding PSUs granted in 2015 and 2016 may vest in amounts ranging from 25% to 100% based on the achievement of the following TSR over the three performance periods:

TSR Achieved	Vesting Amount
15%	25%
30%	50%
45%	75%
60%	100%

The TSR will be based on the volume weighted average trading price ("VWAP") of the Company's ordinary shares over the 20 trading days ending on the last day of each of the three performance measurement periods versus the VWAP of the Company's ordinary shares over the twenty trading days ended March 23, 2015 of $21.50. The PSUs are subject to a post vesting holding period of one year for 50% of the PSUs and two years for 50% of the PSUs for those who were members of the executive committee at the date of grant, and one year for 50% of the PSUs for all who were not executive committee members at the date of grant.

The Company accounts for the PSUs as equity-settled awards in accordance with ASC 718. Because the value of the PSUs is dependent upon the attainment of a level of TSR, it requires the impact of the market condition to be considered when estimating the fair value of the PSUs. As a result, the Monte Carlo model is applied and the most significant valuation assumptions used include:

	For the Years Ended December 31,		
	2016	2015	2014
Valuation date stock price	$ 17.72 - 21.07	$ 16.81 - 35.06	$ —
Expected volatility	76.8% - 77.6%	64.6% - 72.3%	—%
Risk-free rate	1.0% - 1.2%	1.0% - 1.1%	—%

The average estimated fair value of each outstanding PSU granted under the 2014 EIP is as follows (allocated between groupings based on grant-date classification):

	Number of Units	Weighted Average Fair Value Per Unit	Average Illiquidity Discount	Recorded Weighted Average Fair Value Per Unit
Executive committee members	8,889,656	$ 15.15	18.9%	$ 12.29
Non-executive committee members	3,131,000	13.55	7.3%	12.56
	12,020,656	$ 14.74	16.1%	$ 12.36

For the year ended December 31, 2016, the Company recorded $48.6 million of expense related to PSUs.

Cash Long-Term Incentive Program

On November 5, 2014, the Committee approved a performance cash long-term incentive program for the members of the Company's executive committee and executive leadership team, including its executive officers (the "Cash Bonus Program"). Participants in the Cash Bonus Program will be eligible for a specified cash bonus. The Cash Bonus Program pool funding of approximately $16.0 million was determined based on the Company's actual TSR over the period from November 5, 2014 to May 6, 2015, and the bonus will be earned and payable only if the TSR for the period from November 5, 2014 to November 4, 2017 is greater than 15%. The portion of the total bonus pool payable to individual participants is based on allocations established by the Company's compensation committee. Participants must remain employed by the Company through November 4, 2017 unless a participant's earlier departure from employment is due to death, disability, termination without cause or a change in control transaction. Bonus payments under the Cash Bonus Program, if any, will be made after November 4, 2017.

The Company accounts for the Cash Bonus Program under the liability method in accordance with ASC 718. Because vesting of the bonus pool is dependent upon the attainment of a VWAP of $18.37 or higher over the 20 trading days ending November 4, 2017, the Cash Bonus Program will be considered to be subject to a "market condition" for the purposes of ASC 718. ASC 718 requires the impact of the market condition to be considered when estimating the fair value of the bonus pool. As a result, the Monte Carlo simulation model is applied and the fair value is revalued at each reporting period. As of December 31, 2016 and December 31, 2015, the estimated fair value was $4.8 million and $6.0 million, respectively. For the years ended December 31, 2016 and 2015, the Company recorded $1.1 million and $2.2 million, respectively, of expense related to the Cash Bonus Program. The most significant valuation assumptions used include:

	For the Years Ended December 31,		
	2016	2015	2014
Valuation date stock price	$ 16.18	$ 21.67	$ 12.89
Expected volatility	74.7%	74.8%	71.8%
Risk-free rate	0.78%	1.00%	1.03%

Share-Based Compensation Expense

The following table summarizes share-based compensation expense included in the Company's consolidated statements of comprehensive (loss) income for the years ended December 31, 2016, 2015 and 2014 (in thousands):

	For the Years Ended December 31,		
	2016	2015	2014
Share-based compensation expense:			
Cost of goods sold	$ 26	$ —	$ —
Research and development	9,413	6,590	1,515
Sales and marketing	26,215	23,062	4,174
General and administrative	78,490	56,134	7,509
Total share-based compensation expense	$ 114,144	$ 85,786	$ 13,198

For the year ended December 31, 2016, no income tax benefit was recognized relating to share-based compensation expense. As of December 31, 2016, the Company estimates that pre-tax unrecognized compensation expense of $199.6 million for all unvested share-based awards, including both stock options and restricted stock units, will be recognized through the fourth quarter of 2020. The Company expects to satisfy the exercise of stock options and future distribution of shares for restricted stock units and PSUs by issuing new ordinary shares which have been reserved under the 2014 EIP.

NOTE 20 – INCOME TAXES

The Company's (loss) income before benefit for income taxes by jurisdiction for the years ended December 31, 2016, 2015 and 2014 is as follows (in thousands):

	For the Years Ended December 31,		
	2016	2015	2014
Ireland	$ (27,955)	$ (10,746)	$ 22,164
United States	(165,476)	(198,442)	(275,080)
Other foreign	(34,654)	76,476	(16,771)
Loss before benefit for income taxes	$ (228,085)	$ (132,712)	$ (269,687)

The components of the benefit for income taxes were as follows for the years ended December 31, 2016, 2015 and 2014 (in thousands):

	For the Years Ended December 31,		
	2016	2015	2014
Current provision			
Ireland	$ 1,187	$ 1,924	$ —
U.S. - Federal and State	10,491	6,355	815
Other foreign	679	328	55
Total current provision	12,357	8,607	870
Deferred benefit			
Ireland	$ (2,054)	$ (5,623)	$ —
U.S. - Federal and State	(69,073)	(175,228)	(3,860)
Other foreign	(2,481)	—	(3,094)
Total deferred benefit	(73,608)	(180,851)	(6,954)
Total benefit for income taxes	$ (61,251)	$ (172,244)	$ (6,084)

Total benefit for income taxes was $61.3 million, $172.2 million and $6.1 million for the years ended December 31, 2016, 2015 and 2014, respectively. The current tax provision of $12.4 million for the year ended December 31, 2016 was primarily attributable to U.S. state income tax liabilities and the U.S. Federal alternative minimum tax liabilities. The deferred tax benefit of $73.6 million for the year ended December 31, 2016 resulted primarily from the benefit recognized from the mix of income and losses incurred in various tax jurisdictions and the benefit recognized from the change in the U.S. state effective tax rate.

A reconciliation between the Irish income tax statutory rate to the Company's effective tax rate for 2016, 2015 and 2014 is as follows (in thousands):

	For the Years Ended December 31,		
	2016	2015	2014
Irish income tax at statutory rate (12.5%)	$ (28,510)	$ (16,586)	$ (33,711)
Bargain purchase gain	—	—	(5,542)
Transaction costs	3,447	3,109	5,402
Excise tax	—	—	3,911
Share-based compensation	7,125	3,776	1,460
Foreign tax rate differential	(1,893)	(30,348)	(64,675)
Change in valuation allowance	(6,117)	(106,834)	7,360
Derivative liability	—	—	75,248
Notional interest deduction	(35,075)	(22,848)	(2,149)
Interest expense on convertible debt inducements	—	(1,218)	(4,789)
Book loss on debt extinguishment	—	6,396	10,286
Uncertain tax positions	2,837	3,012	(491)
Change in U.S. state effective tax rate	(17,246)	(9,061)	—
Disallowed interest	2,620	2,139	—
Disqualified compensation expense	2,555	3,949	30
Tax charges on intragroup profit	2,154	(9,955)	—
U.S. state income taxes	8,579	1,002	272
U.S. federal and state tax credits	(3,613)	—	—
Other, net	1,886	1,223	1,304
Benefit for income taxes	$ (61,251)	$ (172,244)	$ (6,084)
Effective income tax rate	26.9%	129.8%	2.3%

The overall effective tax rate benefit for 2016 of 26.9% was a higher benefit rate than the Irish statutory rate of 12.5% primarily due to the notional interest deduction, the benefit realized in the change in U.S. state effective tax rate, and the change in valuation allowance. The net benefit to income taxes is partially offset by the increase in stock based compensation not deductible for tax purposes and the increase in U.S. state income taxes.

The overall effective tax rate benefit for 2015 of 129.8% was a higher benefit rate than the Irish statutory rate of 12.5% primarily due to the release of valuation allowances in the United States following the acquisition of Hyperion in that year, the benefit realized on the foreign rate differential and the benefit realized on the notional interest deduction.

The decrease in the effective tax rate in 2016 compared to 2015 was primarily due to the one-time benefit recognized in 2015 for the release in valuation allowance.

During the year ended December 31, 2014, the Company released a portion of its valuation allowances as a result of the Vidara Merger. In connection with the Vidara Merger, the Company recorded additional deferred tax liabilities related to certain acquired assets. Accordingly, the Company recorded a net benefit for income taxes of $3.0 million for the release of its valuation allowances during the third quarter of 2014. In addition, the Company eliminated its deferred tax liability of $3.0 million at its Swiss subsidiary related to the intercompany sale of intellectual property in the fourth quarter of 2014.

The increase in the effective tax rate benefit in 2015 compared to 2014 was largely attributable to the 2015 release of valuation allowances in the United States and the benefit realized on losses tax effected at a higher statutory rate than the Irish statutory rate of 12.5%.

The Company accounts for income taxes based upon an asset and liability approach. Deferred tax assets and liabilities represent the future tax consequences of the differences between the financial statement carrying amounts of assets and liabilities versus the tax basis of assets and liabilities. Under this method, deferred tax assets are recognized for future deductible temporary differences and operating loss and tax credit carryforwards. Deferred tax liabilities are recognized for future taxable temporary differences. Deferred tax assets are reduced by a valuation allowance when, in the opinion of management, it is more likely than not that some portion or all of the deferred tax assets will not be realized. The impact of tax rate changes on deferred tax assets and liabilities is recognized in the period in which the change is enacted.

The tax effects of the temporary differences and net operating losses that give rise to significant portions of deferred tax assets and liabilities, before jurisdictional netting, are as follows (in thousands):

	As of December 31,	
	2016	2015
Deferred tax assets:		
Net operating loss carryforwards	$ 99,004	$ 95,401
Capital loss carryforwards	4,631	14,843
Alternative minimum tax credit	5,922	3,157
U.S. federal and state credits	48,758	25,739
Accrued compensation	65,733	39,951
Accruals and reserves	20,179	5,829
Contingent royalties	68,628	41,544
Intercompany interest	54,703	51,919
Other	—	3,813
Total deferred tax assets	367,558	282,196
Valuation allowance	(32,532)	(31,310)
Deferred tax assets, net of valuation allowance	335,026	250,886
Deferred tax liabilities:		
Inventories	$ 13,077	$ —
Debt discount	23,050	26,424
Intangible assets	593,057	335,584
Other	1,499	—
Total deferred tax liabilities	630,683	362,008
Net deferred income tax liability	$ 295,657	$ 111,122

As of December 31, 2016, the Company had net operating loss carryforwards of approximately $179.5 million for U.S. federal, $293.0 million for various states and $176.2 million for non-U.S. losses. These net operating losses include the net operating losses acquired in the acquisition of Raptor and are available to reduce future taxable income, if any, in the jurisdiction in which the net operating losses have been generated. Net operating loss carryforwards for U.S. federal income tax purposes have a twenty-year carryforward life and the earliest layers will begin to expire in 2019. U.S. state net operating losses started to expire in 2016 for the earliest net operating loss layers. Swiss net operating loss carryovers have a seven-year carryforward life and a portion of the earliest layer will begin to expire in 2017 for lack of sufficient taxable income to fully absorb the available carryover loss. Irish net operating losses are carried forward indefinitely and therefore have no expiration. Utilization of the U.S. net operating loss carryforwards may be subject to annual limitations as prescribed by federal and state statutory provisions. The imposition of the annual limitations may result in the expiration of net operating loss carryforwards in acceleration of the carryforward period allowed under statute.

Utilization of certain net operating loss carryforwards in the United States is subject to an annual limitation due to ownership change limitations provided by Sections 382 and 383 of the Internal Revenue Code. The Company is limited under the annual limitation of $14.7 million for 2017 and $7.7 million from the year 2018 until 2028 on certain net operating losses generated before an August 2, 2012 ownership change date. We continue to carryforward the annual limitation related to Hyperion of $50.0 million resulting from the last ownership change in 2014. Further, as a result of the acquisition of Raptor, its acquired net operating losses are subject to certain annual limitations for federal and state purposes. The U.S. federal net operating loss carryforward limitation is cumulative such that any use of the carryforwards below the limitation in a particular tax year will result in a corresponding increase in the limitation for the subsequent tax year.

At December 31, 2016, the Company had $61.8 million and $3.7 million of U.S. federal and state income tax credits, respectively, to reduce future tax liabilities. These tax credits include the tax credits acquired resulting from the acquisition of Raptor. The federal income tax credits consisted primarily of orphan drug credits, research and development credits and alternative minimum tax credits. The U.S. state income tax credits consisted primarily of California research and development credits and the Illinois Economic Development for a Growing Economy (“EDGE”) tax credit. Both the U.S. federal orphan drug credits and research and development credits have a twenty-year carryforward life. The U.S. federal orphan drug credits will begin to expire in 2027 and the U.S. federal research and development credits will begin to expire in 2025. The U.S. federal alternative minimum tax credit and California research and development credits have indefinite lives and therefore are not subject to expiration. The Illinois EDGE credit has a five-year carryforward life following the year of generation and will begin to expire in 2019.

For the year ended December 31, 2016, the Company had $1.6 million of excess tax benefits from share-based compensation. Under the with-and-without approach, there is no benefit recognized as a result of share-based compensation deductions and the tax benefit of the $0.5 million of excess tax benefit is not recognized in the balance sheet.

A reconciliation of the beginning and ending amounts of valuation allowances for the years ended December 31, 2016, 2015 and 2014 is as follows (in thousands):

Valuation allowances at December 31, 2013	$	(128,422)
Decrease for 2014 activity		17,166
Release of valuation allowances		6,478
Additions to valuation allowances due to acquisitions		(6,777)
Valuation allowances at December 31, 2014	$	(111,555)
Increase for 2015 activity		(37,569)
Release of valuation allowances		117,814
Valuation allowances at December 31, 2015	$	(31,310)
Increase for 2016 activity		(14,636)
Release of valuation allowances		15,056
Additions to valuation allowances due to acquisitions		(1,642)
Valuation allowances at December 31, 2016	$	(32,532)

Deferred tax valuation allowances increased by $1.2 million during the year ended December 31, 2016, and decreased by $80.2 million and $16.9 million during the years ended December 31, 2015 and 2014, respectively. For the year ended December 31, 2016, the increase in valuation allowances resulted primarily from the valuation allowances acquired from the acquisition of Raptor as well as activity resulting from certain deferred tax assets for which the Company determined that the deferred tax benefits may not be realized in the foreseeable future. The net increase in valuation allowance is partially offset by the release of valuation allowances resulting from the utilization of U.S. Federal capital loss carryforwards which were established in the year ended December 31, 2015. For the year ended December 31, 2015, the increase in valuation allowances resulted from capital loss carryforwards generated by the restructure of the Company's Swiss subsidiary, and a capital loss recognized on the sale of long-term investments. As capital losses can only be offset by capital gains, and capital losses can only be carried forward for five years, the Company believes that the benefit of the capital losses may not be realized in the foreseeable future.

No provision has been made for income taxes on undistributed earnings of subsidiaries because it is the Company's intention to indefinitely reinvest undistributed earnings of its subsidiaries. In the event of the distribution of those earnings in the form of dividends, a sale of the subsidiaries, or certain other transactions, the Company may be liable for income taxes. The unremitted earnings of the Company as of December 31, 2016 were $280.9 million, and the Company estimates tax on unremitted earnings to be $16.7 million.

The Company is required to recognize the financial statement effects of a tax position when it is more likely than not, based on the technical merits, that the position will be sustained upon examination. The Company accounts for the uncertainty in income taxes by utilizing a comprehensive model for the recognition, measurement, presentation and disclosure in financial statements of any uncertain tax positions that have been taken, or are expected to be taken, on an income tax return. The changes in the Company's uncertain income tax positions for the years ended December 31, 2016, 2015 and 2014, excluding interest and penalties, consisted of the following (in thousands):

	For the Years Ended December 31,	
	2016	2015
Beginning balance – uncertain tax positions	$ 9,812	$ 775
Tax positions in the year:		
Additions	471	2,604
Acquired uncertain tax positions	5,362	6,433
Tax positions related to prior years:		
Additions	2,102	—
Ending balance – uncertain tax positions	$ 17,747	$ 9,812

For the year ended December 31, 2016, the increase in uncertain tax positions primarily resulted from the acquired uncertain tax positions related to the acquisition of Raptor. In the Company's consolidated balance sheet, uncertain tax positions of $7.7 million were included in other long-term liabilities and an additional $10.7 million was offset against deferred tax assets.

Penalties of $0.1 million and interest of $0.6 million are included in the balance of the uncertain tax positions at December 31, 2016, and there were penalties of $0.1 million and interest of $0.3 million included in the balance of uncertain tax positions at December 31, 2015. The Company classifies interest and penalties with respect to income tax liabilities as a component of income tax expense. The Company assessed that its liability for uncertain tax positions will not significantly change within the next twelve months. If these uncertain tax positions are released, the impact on the Company's tax provision would be a benefit of $18.4 million, including interest and penalties.

The Company files income tax returns in Ireland, in the United States for federal and various states, as well as in certain other non-U.S. jurisdictions. At December 31, 2016, all open tax years in U.S. federal and certain state jurisdictions date back to 2005 due to the taxing authorities' ability to adjust operating loss carryforwards. In Ireland the statute of limitations expires five years from the end of the tax year or four years from the time a tax return is filed, whichever is later. Therefore the earliest year open to examination is 2012 with the lapse of statute occurring in 2017. No changes in settled tax years have occurred to date. The Company is not currently under any income tax examinations.

NOTE 21 – EMPLOYEE BENEFIT PLANS

The Company sponsors a defined contribution 401(k) retirement savings plan covering all of its U.S. employees, whereby an eligible employee may elect to contribute a portion of his or her salary on a pre-tax basis, subject to applicable federal limitations. The Company is not required to make any discretionary matching of employee contributions. Beginning in 2014, the Company made a matching contribution generally equal to 50% of each employee's elective contribution to the plan of up to six percent of the employee's eligible pay with a 20% graded vesting over five years. Beginning in 2017, the Company will make a matching contribution equal to 100% of each employee's elective contribution to the plan of up to 3% of the employee's eligible pay, and 50% for the next 2% of the employee's eligible pay. The full amount of this employer contribution will be immediately vested in the plan. For the years ended December 31, 2016, 2015 and 2014, the Company recorded defined contribution expense of $2.7 million, $2.1 million and $0.8 million, respectively.

The Company's wholly owned subsidiary, Horizon Pharma Switzerland GmbH, sponsors a defined benefit savings plan covering all of its employees in Switzerland. The Company's wholly owned subsidiaries sponsor defined contribution plans for its employees in Germany, the Netherlands, Belgium, Denmark, Sweden, Norway and the United Kingdom. For the years ended December 31, 2016, 2015 and 2014, the Company recognized immaterial expenses under these plans.

The Company's wholly owned subsidiary, Horizon Pharma Services Limited, sponsors a defined contribution plan covering all of its employees in Ireland. For the years ended December 31, 2016 and 2015, the Company recognized expenses of $0.4 million and $0.2 million, respectively, under this plan. No expense was recorded in 2014, as the entity became part of the consolidated group as a result of the Vidara Merger in September 2014.

The Company has a non-qualified deferred compensation plan for executives, which was established in April 2015. The deferred compensation plan obligations are payable in cash upon retirement, termination of employment and/or certain other times in a lump-sum distribution or in installments, as elected by the participant in accordance with the plan. As of December 31, 2016 and 2015, the deferred compensation plan liabilities totaled $3.1 million and $0.8 million, respectively, and are included in "other long-term liabilities" in the consolidated balance sheet. The Company held funds of approximately $3.1 million and $0.8 million in an irrevocable grantor's rabbi trust as of December 31, 2016 and 2015, respectively, related to this plan. Rabbi trust assets are classified as available-for-sale marketable securities and are included in "other current assets" in the consolidated balance sheets. Unrealized gains and losses on these marketable securities are included in "other income" in the consolidated statements of comprehensive (loss) income.

NOTE 22 – SELECTED QUARTERLY FINANCIAL INFORMATION (UNAUDITED)

The following table provides a summary of selected financial results of operations by quarter for the years ended December 31, 2016 and 2015 (in thousands, except per share data):

2016	First	Second	Third	Fourth
Net sales	$ 204,690	$ 257,378	$ 208,702	$ 310,350
Gross profit	127,457	176,252	123,541	160,598
Operating (loss) income	(27,204)	31,467	(21,322)	(130,108)
Net (loss) income	(45,406)	14,984	(5,870)	(130,542)
Net (loss) income per ordinary share - basic	$ (0.28)	$ 0.09	$ (0.04)	$ (0.81)
Net (loss) income per ordinary share - diluted	(0.28)	0.09	(0.04)	(0.81)

2015	First	Second	Third	Fourth
Net sales	$ 113,141	$ 172,821	$ 226,544	$ 244,538
Gross profit	84,288	110,995	165,294	176,965
Operating income (loss)	4,764	(33,173)	45,732	38,049
Net (loss) income	(19,553)	31,814	3,277	23,994
Net (loss) income per ordinary share - basic	$ (0.16)	$ 0.21	$ 0.02	$ 0.15
Net (loss) income per ordinary share - diluted	(0.16)	0.20	0.02	0.15

HORIZON PHARMA PLC

SCHEDULE II – VALUATION AND QUALIFYING ACCOUNTS

For Each of the Three Fiscal Years Ended December 31, 2016, 2015 and 2014:

Valuation and Qualifying Accounts (in thousands)	Balance at beginning of period	Acquisitions	Additions Charged to costs and expenses	Deductions from reserves	Balance at end of period
Year ended December 31, 2016:					
Allowance for discounts and returns	$ 14,964	$ 1,234	$ 81,089	$ (75,371)	$ 21,916
Allowance for slow moving and obsolete inventory	1,001	—	1,092	(782)	1,311
Deferred tax asset valuation allowances	31,310	1,642	14,636	(15,056)	32,532
Year ended December 31, 2015:					
Allowance for discounts and returns	4,483	236	55,702	(45,457)	14,964
Allowance for slow moving and obsolete inventory	842	—	1,189	(1,030)	1,001
Deferred tax asset valuation allowances	111,555	—	37,569	(117,814)	31,310
Year ended December 31, 2014:					
Allowance for discounts and returns	431	—	18,254	(14,202)	4,483
Allowance for slow moving and obsolete inventory	365	—	1,195	(718)	842
Deferred tax asset valuation allowances	128,422	6,777	—	(23,644)	111,555

INDEX TO EXHIBITS

Exhibit Number	Description of Document
2.1(15)	Transaction Agreement and Plan of Merger, dated March 18, 2014, by and among Horizon Pharma, Inc., Vidara Therapeutics Holdings LLC, Vidara Therapeutics International Ltd. (now known as Horizon Pharma Public Limited Company), Hamilton Holdings (USA), Inc. and Hamilton Merger Sub, Inc.†
2.2(17)	First Amendment to Transaction Agreement and Plan of Merger, dated June 12, 2014, by and between Horizon Pharma, Inc. and Vidara Therapeutics Holdings LLC.
2.3(25)	Agreement and Plan of Merger, dated March 29, 2015, by and among Horizon Pharma, Inc., Ghrian Acquisition Inc. and Hyperion Therapeutics, Inc.†
2.4**(26)	Agreement and Plan of Merger, dated December 10, 2015, by and among Horizon Pharma USA, Inc., HZNP Limited, Criostail LLC, Crealta Holdings LLC and the other parties thereto.††
2.5(4)	Agreement and Plan of Merger, dated September 12, 2016, by and among Horizon Pharma Public Limited Company, Misneach Corporation and Raptor Pharmaceutical Corp.†
3.1(21)	Memorandum and Articles of Association of Horizon Pharma Public Limited Company, as amended.
4.1(3)***	Form of Warrant issued by Horizon Pharma, Inc. pursuant to the Securities Purchase Agreement, dated February 28, 2012, by and among Horizon Pharma, Inc. and the Purchasers and Warrant Holders listed therein.
4.2(6)***	Form of Warrant issued by Horizon Pharma, Inc. in Public Offering of Units.
4.3(24)	Indenture, dated March 13, 2015, by and among Horizon Pharma Public Limited Company, Horizon Pharma Investment Limited and U.S. Bank National Association.
4.4(24)	Form of 2.50% Exchangeable Senior Note due 2022 (included in Exhibit 4.3).
4.5(19)	Indenture, dated April 29, 2015, by and between Horizon Pharma Financing Inc. and U.S. Bank National Association.
4.6(19)	Form of 6.625% Senior Note due 2023 (included in Exhibit 4.5).
4.7(18)	First Supplemental Indenture, dated May 7, 2015, by and among Horizon Pharma Public Limited Company, certain subsidiaries of Horizon Pharma Public Limited Company and U.S. Bank National Association.
4.8(27)	Indenture, dated October 25, 2016, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and U.S. Bank National Association, as trustee.
4.9(27)	Form of 8.75% Senior Note due 2024 (included in Exhibit 4.8).
10.1(20)	Form of Indemnification Agreement entered into by and between Horizon Pharma Public Limited Company and certain of its directors, officers and employees.
10.2(20)	Form of Indemnification Agreement entered into by and between Horizon Pharma, Inc. and certain directors, officers and employees of Horizon Pharma Public Limited Company.
10.3+(26)	Horizon Pharma Public Limited Company Non-Employee Director Compensation Policy, as amended.
10.4+(1)***	Horizon Pharma, Inc. 2005 Stock Plan and Form of Stock Option Agreement thereunder.
10.5+(11)***	Horizon Pharma, Inc. 2011 Equity Incentive Plan, as amended, and Form of Option Agreement and Form of Stock Option Grant Notice thereunder.
10.6+(1)***	Horizon Pharma, Inc. 2011 Employee Stock Purchase Plan and Form of Offering Document thereunder.
10.7+(7)	Horizon Pharma Public Limited Company 2014 Equity Incentive Plan, as amended, and Form of Option Agreement, Form of Stock Option Grant Notice, Form of Restricted Stock Unit Agreement and Form of Restricted Stock Unit Grant Notice thereunder.

Exhibit Number	Description of Document
10.8+(7)	Horizon Pharma Public Limited Company 2014 Non-Employee Equity Plan, as amended, and Form of Option Agreement, Form of Stock Option Grant Notice, Form of Restricted Stock Unit Agreement and Form of Restricted Stock Unit Grant Notice thereunder.
10.9+(7)	Horizon Pharma Public Limited Company 2014 Employee Share Purchase Plan, as amended.
10.10*(1)	Development and License Agreement, dated August 20, 2004, by and among Horizon Pharma Switzerland GmbH (formerly known as Horizon Pharma AG), Jagotec AG and Vectura Group plc (as successor in interest to SkyePharma AG).
10.11*(1)	Amendment to Development and License Agreement, dated August 3, 2007, by and among Horizon Pharma Switzerland GmbH (formerly known as Horizon Pharma AG), Jagotec AG and Vectura Group plc (as successor in interest to SkyePharma AG).
10.12*(1)	Manufacturing and Supply Agreement, dated August 3, 2007, by and between Horizon Pharma Ireland Limited (as successor in interest to Horizon Pharma Switzerland GmbH (formerly known as Horizon Pharma AG)) and Jagotec AG.
10.13+(1)	Form of Employee Proprietary Information and Inventions Agreement.
10.14+(1)	Amended and Restated Executive Employment Agreement, dated July 27, 2010, by and between Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Timothy P. Walbert.
10.15+(1)	Amended and Restated Executive Employment Agreement, dated July 27, 2010, by and between Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Jeffrey W. Sherman, M.D. FACP.
10.16*(1)	Amendment to Manufacturing and Supply Agreement, dated March 4, 2011, by and between Horizon Pharma Switzerland GmbH (formerly known as Horizon Pharma AG) and Jagotec AG.
10.17*(1)	Manufacturing and Supply Agreement, dated May 25, 2011, by and between Horizon Pharma USA, Inc. and Sanofi-Aventis U.S. LLC.
10.18*(1)	Sales Contract, dated July 1, 2010, by and between Horizon Pharma USA, Inc. and BASF Corporation.
10.19*(10)	Amendment to Manufacturing and Supply Agreement, effective as of September 25, 2013, by and between Horizon Pharma USA, Inc. and S anofi-Aventis U.S. LLC.
10.20+(5)	Amended and Restated Severance Benefit Plan Dated March 1, 2012.
10.21*(10)	License Agreement, dated August 21, 2013, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc., Par Pharmaceutical Companies, Inc. and Par Pharmaceutical, Inc.
10.22*(16)	License Agreement, dated November 22, 2013, by and between Horizon Pharma USA, Inc. and AstraZeneca AB.
10.23*(16)	Amended and Restated Collaboration and License Agreement for the United States, dated November 18, 2013, by and between Horizon Pharma USA, Inc. and Aralez Pharmaceuticals Inc. (as successor in interest to Pozen Inc.).
10.24*(14)	Amendment No. 1 to Amended and Restated Collaboration and License Agreement for the United States, dated November 18, 2013, by and between Horizon Pharma USA, Inc. and Aralez Pharmaceuticals Inc. (as successor in interest to Pozen Inc.).
10.25*(14)	Letter Agreement, dated November 18, 2013, by and among Horizon Pharma USA, Inc., AstraZeneca AB and Aralez Pharmaceuticals Inc. (as successor in interest to Pozen Inc.).
10.26*(16)	Master Manufacturing Services Agreement, dated October 31, 2013, by and between Horizon Pharma, Inc. and Patheon Pharmaceuticals, Inc.
10.27+(13)	First Amendment to Amended and Restated Executive Employment Agreement, dated January 16, 2014, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Timothy P. Walbert.
10.28+(13)	First Amendment to Amended and Restated Executive Employment Agreement, dated January 16, 2014, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Jeffrey W. Sherman, M.D., FACP.

Exhibit Number	Description of Document
10.29+(14)	Executive Employment Agreement, effective March 5, 2014, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Robert F. Carey.
10.30+(17)	Executive Employment Agreement, effective June 23, 2014, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Paul W. Hoelscher.
10.31*(23)	Supply Agreement, dated October 17, 2014, by and between Horizon Pharma Ireland Limited and Nuvo Research Inc.
10.32(22)	Lease, dated November 4, 2014, by and among Horizon Pharma Public Limited Company, Horizon Pharma Services Limited and John Ronan and Castle Cove Property Developments Limited.
10.33**(22)	Consolidated Supply Agreement, dated July 31, 2013, by and between Vidara Therapeutics Research Limited and Boehringer Ingelheim RCV GmbH & Co KG.
10.34**(22)	License Agreement for Interferon Gamma, dated May 5, 1998, by and between Genentech, Inc. and Connetics Corporation.
10.35(22)	Amendment No. 1 to License Agreement for Interferon Gamma, dated December 28, 1998, by and between Genentech, Inc. and Connetics Corporation.
10.36**(22)	Amendment No. 2 to License Agreement for Interferon Gamma, dated January 15, 1999, by and between Genentech, Inc. and Connetics Corporation.
10.37**(22)	Amendment No. 3 to License Agreement for Interferon Gamma, dated April 27, 1999, by and between Genentech, Inc. and Connetics Corporation.
10.38(22)	Consent to Assignment Agreement, dated June 23, 2000 (Amendment No. 4), by and among Genentech, Inc., Connetics Corporation and InterMune Pharmaceuticals, Inc.
10.39(22)	Amendment No. 5 to License Agreement for Interferon Gamma, dated January 25, 2001, by and between Genentech, Inc. and InterMune Pharmaceuticals, Inc.
10.40**(22)	Amendment No. 6 to License Agreement for Interferon Gamma, dated February 27, 2006, by and between Genentech, Inc. and InterMune, Inc.
10.41**(22)	Amendment No. 7 to License Agreement for Interferon Gamma, dated December 17, 2013, by and between Genentech, Inc. and Vidara Therapeutics International Public Limited Company.
10.42+(22)	Consulting Agreement, dated March 18, 2014 between Horizon Pharma USA, Inc. and Virinder Nohria.
10.43+(22)	Executive Employment Agreement, effective September 18, 2014, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Barry Moze.
10.44+(22)	Horizon Pharma Public Limited Company Cash Long Term Incentive Program.
10.45+(2)	Horizon Pharma, Inc. Deferred Compensation Plan.
10.46+(2)	Horizon Pharma Public Limited Company Equity Long Term Incentive Program.
10.47+(2)	Executive Employment Agreement, dated May 7, 2015, by and among Horizon Pharma Inc., Horizon Pharma USA, Inc. and Brian Beeler.
10.48(18)	Credit Agreement, dated May 7, 2015, by and among Horizon Pharma, Inc., as borrower, Horizon Pharma Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent.
10.49*(9)	Confidential Settlement and License Agreement, dated May 6, 2015, by and among Horizon Pharma Ireland Limited, HZNP Limited, Horizon Pharma USA, Inc., Perrigo Company and Paddock Laboratories, LLC.
10.50**(12)	Amended and Restated Collaboration Agreement, dated March 22, 2012, by and among Hyperion Therapeutics, Inc. and Ucyclyd Pharma, Inc.
10.51**(12)	License Agreement, dated April 16, 1999, by and among Saul Brusilow, M.D., Brusilow Enterprises, Inc. and Medicis Pharmaceutical Corporation.

Exhibit Number	Description of Document
10.52**(12)	Settlement Agreement and First Amendment to License Agreement, dated August 21, 2007, by and among Saul Brusilow, M.D., Brusilow Enterprises, Inc., Medicis Pharmaceutical Corporation and Ucyclyd Pharma, Inc.
10.53+(28)	Horizon Pharma Public Limited Company Share Clog Program Trust Deed, as amended, and Form of Clog Letter.
10.54+(8)	Executive Employment Agreement, dated August 6, 2015, by and among Horizon Pharma Inc., Horizon Pharma USA, Inc. and George P. Hampton.
10.55**(8)	Confidential Settlement and License Agreement, dated September 9, 2015, by and among Horizon Pharma Ireland Limited, HZNP Limited, Horizon Pharma USA, Inc., Taro Pharmaceuticals USA, Inc. and Taro Pharmaceuticals Industries, Ltd.
10.56**(26)	License and Settlement Agreement, dated October 1, 2015, by and among Horizon Pharma Switzerland GmbH (formerly known as Horizon Pharma AG), Jagotec AG and Actavis Laboratories FL, Inc. (formerly known as Watson Laboratories, Inc.).
10.57**(26)	License Agreement, dated August 12, 1998, by and among Mountain View Pharmaceuticals, Inc., Duke University and Crealta Pharmaceuticals LLC (as successor in interest to Bio-Technology General Corporation), as amended November 12, 2001, August 30, 2010, March 12, 2014 and July 16, 2015.
10.58**(26)	Commercial Supply Agreement, dated March 20, 2007, by and between Crealta Pharmaceuticals LLC (as successor in interest to Savient Pharmaceuticals, Inc.) and Bio-Technology General (Israel) Ltd., as amended September 24, 2007, January 24, 2009, July 1, 2010 and March 21, 2012.
10.59**(26)	Supply Agreement, dated August 3, 2015, by and between NOF Corporation and Crealta Pharmaceuticals LLC.
10.60(26)	Sublease, dated August 21, 2015, by and between Solo Cup Operating Corporation and Horizon Pharma USA, Inc. and Sublease Consent and Recognition Agreement, dated October 2, 2015, by and among Lake Forest Landmark II, LLC, Solo Cup Operating Corporation and Horizon Pharma USA, Inc.
10.61**(12)	Asset Purchase Agreement, dated March 22, 2012, by and between Hyperion Therapeutics, Inc. and Ucyclyd Pharma, Inc.
10.62**(26)	Amendment No. 1 to Supply Agreement, dated February 4, 2016, by and between Horizon Pharma Ireland Limited and Nuvo Research Inc.
10.63**(26)	Commercial Supply Agreement, dated October 16, 2008, by and between Exelead, Inc. (formerly known as Sigma Tau PharmaSource, Inc. (as successor in interest to Enzon Pharmaceuticals, Inc.)) and Crealta Pharmaceuticals LLC (as successor in interest to Savient Pharmaceuticals, Inc.), as amended October 5, 2009, October 22, 2009 and July 29, 2014.
10.64	Amendment to Manufacturing and Supply Agreement, dated January 1, 2017, by and between Horizon Pharma Ireland Limited and Jagotec AG.
10.65*(28)	Amendment No. 2 to the Consolidated Supply Agreement, effective as of June 1, 2015, by and between Horizon Pharma Ireland Limited (as successor in interest to Vidara Therapeutics Research Limited) and Boehringer Ingelheim Biopharmaceuticals GmbH (as successor in interest to Boehringer Ingelheim RCV GmbH & Co KG).
10.66**(29)	Fifth Amendment to Commercial Supply Agreement, effective as of August 31, 2016, by and between Horizon Pharma Ireland Limited and Bio-Technology General (Israel) Ltd.
10.67(27)	Amendment No. 1, dated October 25, 2016, to Credit Agreement, dated May 7, 2015, by and among Horizon Pharma, Inc., as borrower, Horizon Pharma Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent.
10.68**(29)	Amended and Restated License Agreement, effective October 30, 2012, by and between The Regents of the University of California and Horizon Orphan LLC (as successor in interest to Raptor Therapeutics Inc.), as amended March 1, 2013 and December 16, 2013.

Exhibit Number	Description of Document
10.69**(29)	API Supply Agreement, dated November 3, 2010, by and among Cambrex Profarmaco Milano, Horizon Orphan LLC (as successor in interest to Raptor Therapeutics Inc.) and Horizon Pharma Europe B.V. (as successor in interest to Raptor Pharmaceuticals Europe B.V.), as amended April 9, 2013.
10.70**(29)	Manufacturing Services Agreement, dated November 15, 2010, by and among Patheon Pharmaceuticals Inc., Horizon Orphan LLC (as successor in interest to Raptor Therapeutics Inc.) and Horizon Pharma Europe B.V. (as successor in interest to Raptor Pharmaceuticals Europe B.V.), as amended April 5, 2012 and June 21, 2013.
10.71**(29)	Confidential Settlement Agreement and Mutual Release, dated September 26, 2016, by and between Horizon Pharma USA, Inc. and Express Scripts, Inc.
10.72+	Executive Employment Agreement, effective as of October 25, 2016, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and David A. Happel.
10.73+**	Transition Agreement, dated October 13, 2016, by and between Horizon Pharmaceutical LLC (as successor in interest to Raptor Pharmaceutical Corp.) and David A. Happel.
10.74**	Amendment No. 1 to Sales Contract, effective as of January 1, 2016, by and between Horizon Pharma USA, Inc. and BASF Corporation.
21.1	Subsidiaries of Horizon Pharma Public Limited Company.
23.1	Consent of PricewaterhouseCoopers LLP, independent registered public accounting firm.
24.1	Power of Attorney. Reference is made to the signature page hereto.
31.1	Certification of Principal Executive Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Exchange Act.
31.2	Certification of Principal Financial Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Exchange Act.
32.1	Certification of Principal Executive Officer pursuant to Rule 13a-14(b) or 15d-14(b) of the Exchange Act and 18 U.S.C. Section 1350.
32.2	Certification of Principal Financial Officer pursuant to Rule 13a-14(b) or 15d-14(b) of the Exchange Act and 18 U.S.C. Section 1350.
101.INS	XBRL Instance Document
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	XBRL Taxonomy Extension Label Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document

+ Indicates management contract or compensatory plan.

† Schedules have been omitted pursuant to Item 601(b)(2) of Regulation S-K. Horizon Pharma Public Limited Company undertakes to furnish supplemental copies of any of the omitted schedules upon request by the Securities and Exchange Commission.

†† Schedules have been omitted pursuant to Item 601(b)(2) of Regulation S-K. Horizon Pharma Public Limited Company undertakes to furnish supplemental copies of any of the omitted schedules upon request by the Securities and Exchange Commission; provided, however, that Horizon Pharma Public Limited Company may request confidential treatment pursuant to Rule 24b-2 of the Securities Exchange Act of 1934, as amended, for any schedule so furnished.

* Confidential treatment has been granted with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.

** Confidential treatment has been requested with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.

*** Indicates an instrument, agreement or compensatory arrangement or plan assumed by Horizon Pharma Public Limited Company in the merger and no longer binding on Horizon Pharma, Inc.

(1) Incorporated by reference to Horizon Pharma, Inc.'s Registration Statement on Form S-1 (No. 333-168504), as amended.

(2) Incorporated by reference to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on May 8, 2015.

(3) Incorporated by reference to Horizon Pharma, Inc.'s Current Report on Form 8-K, filed on March 1, 2012.

(4) Incorporated by reference to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on September 12, 2016.

(5) Incorporated by reference to Horizon Pharma, Inc.'s Annual Report on Form 10-K, filed on March 23, 2012.

(6) Incorporated by reference to Horizon Pharma, Inc.'s Current Report on Form 8-K, filed on September 20, 2012.

(7) Incorporated by reference to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on May 4, 2016.

(8) Incorporated by reference to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on November 6, 2015.

(9) Incorporated by reference to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2015.

(10) Incorporated by reference to Horizon Pharma, Inc.'s Quarterly Report on Form 10-Q, filed on November 8, 2013.

(11) Incorporated by reference to Horizon Pharma, Inc.'s Current Report on Form 8-K, filed on July 2, 2014.

(12) Incorporated by reference to Hyperion Therapeutics, Inc.'s Amendment No. 1 to the Registration Statement on Form S-1, filed on May 24, 2012.

(13) Incorporated by reference to Horizon Pharma, Inc.'s Current Report on Form 8-K, filed on January 16, 2014.

(14) Incorporated by reference to Horizon Pharma, Inc.'s Annual Report on Form 10-K, filed on March 13, 2014.

(15) Incorporated by reference to Horizon Pharma, Inc.'s Current Report on Form 8-K, filed on March 20, 2014.

(16) Incorporated by reference to Horizon Pharma, Inc.'s Amendment No.1 to Annual Report on Form 10-K, filed on May 23, 2014.

(17) Incorporated by reference to Horizon Pharma, Inc.'s Current Report on Form 8-K, filed on June 18, 2014.

(18) Incorporated by reference to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on May 11, 2015.

(19) Incorporated by reference to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on April 29, 2015.

(20) Incorporated by reference to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on September 19, 2014.

(21) Incorporated by reference to Horizon Pharma Public Limited Company's Registration Statement on Form S-8, filed on May 4, 2016.

(22) Incorporated by reference to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015.

(23) Incorporated by reference to Horizon Pharma Public Limited Company's Amendment No. 2 to Annual Report on Form 10-K, filed on April 10, 2015.

(24) Incorporated by reference to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on March 13, 2015.

(25) Incorporated by reference to Horizon Pharma Public Limited Company's Amendment No. 1 to Current Report on Form 8-K, filed on April 9, 2015.

(26) Incorporated by reference to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 29, 2016.

(27) Incorporated by reference to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on October 25, 2016.

(28) Incorporated by reference to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on August 8, 2016.

(29) Incorporated by reference to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on November 7, 2016.

Exhibit 10.64

AMENDMENT

THIS AMENDMENT ("Amendment") is entered into effective this first day of January 2017, ("Effective Date") by and between **Jagotec AG** ("**Skyepharma**") and **Horizon Pharma Ireland Limited** ("**Horizon**").

WHEREAS, Nitec Pharma AG and Skyepharma entered into that certain Manufacturing and Supply Agreement dated August 3, 2007 (the "Agreement");

WHEREAS, effective December 14, 2016, Horizon Pharma Switzerland GmbH, formerly Nitec Pharma AG, assigned the Agreement to Horizon Pharma Ireland Limited; and

WHEREAS, Horizon and Skyepharma mutually desire to amend the Agreement to reflect this assignment and to amend the term of the Agreement;

IT IS THEREFORE AGREED AS FOLLOWS:

1. Capitalized terms used herein and not otherwise defined herein shall have the same meanings as set forth in the Agreement.
2. All references to the company name "Nitec Pharma AG in the Agreement shall be replaced by the company name "Horizon Pharma Ireland Limited"
3. Section 10.1 shall be deleted and replaced to read:

   "This Agreement shall commence as of the Effective Date and shall continue in full force and effect until December 31, 2023 ("Minimum Term"). It shall thereafter be automatically extended on a yearly basis unless terminated by one Party by giving to the other at least (subject to the Section 10.2 below) twenty four (24) months' written notice to expire not before December 31, 2023."
4. As of the Amendment Effective Date, except as expressly set forth in this Amendment, all of the terms and conditions of the Agreement shall remain in full force and effect.

IN WITNESS WHEREOF, the parties hereto have executed this Amendment by their duly authorized representatives as of the Amendment Effective Date.

HORIZON PHARMA IRELAND LIMITED		**JAGOTEC AG**	
By:	/s/ David G. Kelly	By:	/s/ Susan Ferguson
Name:	David G. Kelly	Name:	Susan Ferguson
Title:	Director	Title:	Director

JAGOTEC AG

By: /s/ Gaelle Bohrer

Name: Gaelle Bohrer

Title: Director Commercial Quality

Exhibit 10.72

EXECUTIVE EMPLOYMENT AGREEMENT BY AND BETWEEN HORIZON PHARMA, INC., HORIZON PHARMA USA, INC. AND DAVID A. HAPPEL

This Executive Employment Agreement (hereinafter referred to as the ***"Agreement"***), is entered into by and between Horizon Pharma, Inc., a Delaware corporation, and its wholly owned subsidiary, Horizon Pharma USA, Inc., a Delaware corporation, each having a principal place of business at 150 S. Saunders Road, Lake Forest, IL 60045 (hereinafter referred to together as the ***"Company"***) and David A. Happel (hereinafter referred as to the ***"Executive"***). The terms of this Agreement shall be effective commencing October 25, 2016 (the "***Effective Date***").

RECITALS

WHEREAS, the Executive previously entered into an amended and restated employment agreement with Raptor Pharmaceuticals Corp. ("***Raptor***") on October 13, 2014 and a Change in Control Severance Agreement with Raptor dated March 8, 2016 (together, the "***Prior Agreement"***);

WHEREAS, the Company's parent entity, Horizon Pharma Public Limited Company ("***Horizon plc***") acquired Raptor on October 25, 2016, and Raptor became a wholly owned subsidiary of Horizon plc;

WHEREAS, the Company desires assurance of the continued association and services of the Executive in order to continue to retain the Executive's experience, skills, abilities, background and knowledge, and is willing to continue to engage the Executive's services on the terms and conditions set forth in this Agreement, which as of the Effective Date shall replace supersede in its entirety the terms of the Prior Agreement; and

WHEREAS, Executive desires to be in the employ of the Company, and is willing to accept such employment on the terms and conditions set forth in this Agreement and the letter agreement by and between the Executive and Raptor dated October 13, 2016 (the "***Transition Services Agreement***") the terms of which will continue in full force and effect following the Effective Date.

WHEREAS, nothing herein is intended to alter Executive's right to receive the retention bonus amount of $196,219 that was approved for Executive by Raptor's compensation committee in September 2016.

AGREEMENT

1. Employment.

1.1 Term. Executive's employment will be transferred from Raptor to the Company as of the Effective Date. The Company hereby agrees to employ the Executive, and the Executive hereby accepts employment by the Company, upon the terms and conditions set forth in this Agreement. Executive's employment shall be

governed under the terms set forth in this Agreement beginning on the Effective Date and shall continue until it is terminated pursuant to Section 4 herein (hereinafter referred to as the ***"Term"***).

1.2 Title. From and after the Effective Date the Executive will have the title of Executive Vice President, Global Orphan Business (such position held by Executive during such period is hereinafter referred to as ***"EVP GOB")*** and Executive shall continue to serve in such other capacity or capacities commensurate with his position as EVP GOB as the President and CEO of the Company may from time to time prescribe.

1.3 Duties. The Executive shall do and perform all services, acts or things necessary or advisable to manage and conduct the business of the Company and shall have the authority and responsibilities which are generally associated with the position of EVP GOB including being responsible for the Company's international operations and the U.S. orphan business unit. The Executive shall report to the President and CEO.

1.4 Policies and Practices. The employment relationship between the parties shall be governed by this Agreement and the policies and practices established by the Company and the Board of Directors (hereinafter referred to as the ***"Board"***). In the event that the terms of this Agreement differ from or are in conflict with the Company's policies or practices or the Company's Employee Handbook, this Agreement shall control.

1.5 Location. The Executive shall perform the services the Executive is required to perform pursuant to this Agreement in Novato California. The Company may from time to time require the Executive to travel temporarily to other locations outside of the Novato California area in connection with the Company's business.

2. Loyalty of Executive.

2.1 Loyalty. During the Executive's employment by the Company, the Executive shall devote the Executive's business energies, interest, abilities and productive time to the proper and efficient performance of Executive's duties under this Agreement. Subject to the prior written consent of the President and CEO, the Executive is permitted to serve on the board of directors of one other company, so long as the other company does not compete with the Company**.**

2.2 Exclusive Employment. Except with the prior written consent of the Chief Executive Officer, Executive shall not, during the term of this Agreement, undertake or engage in any other employment, occupation or business enterprise, other than ones in which Executive is a passive investor. Executive may engage in any civic and not-for-profit activities so long as such activities do not materially interfere with the performance of his duties hereunder or present a conflict of interest with the Company.

2.3 Agreement not to Participate in Company's Competitors. During the Term of this Agreement, the Executive agrees not to acquire, assume or participate in, directly or indirectly, any position, investment or interest known by Executive to be adverse or antagonistic to the Company, its business or prospects, financial or otherwise or in any company, person or entity that is, directly or indirectly, in competition with the business of the Company or any of its affiliates. Notwithstanding the foregoing,

Executive may invest and/or maintain investments in any public or private entity up to an amount of 2% of an entity's fully diluted shares and on a passive basis.

3. Compensation to Executive.

3.1 Base Salary. The Company shall pay the Executive a base salary at the initial annualized rate of five hundred thousand dollars ($500,000) per year, subject to standard deductions and withholdings, or such higher rate as may be determined from time to time by the Board or the compensation committee thereof (hereinafter referred to as the ***"Base Salary"***). Such Base Salary shall be paid in accordance with the Company's standard payroll practice. Payments of salary installments shall be made no less frequently than once per month. Executive's Base Salary will be reviewed annually each December and Executive shall be eligible to receive a salary increase (but not decrease) annually in an amount to be determined by the Board or the compensation committee thereof in its sole and exclusive discretion. Once increased, the new salary shall become the Base Salary for purposes of this Agreement and shall not be reduced without the Executive's written consent. Any material reduction in the Base Salary of the Executive, without his written consent, may be deemed Good Reason as set forth in and subject to Section 4.5.2 of this Agreement.

3.2 Discretionary Bonus. Executive's eligibility to receive a bonus for the 2016 calendar year will be governed by the terms of Transition Services Agreement. Provided the Executive meets the conditions stated in this Section 3.2, commencing with the 2017 calendar year the Executive shall be eligible for an annual discretionary bonus (hereinafter referred to as the ***"Bonus"***) with a target amount of fifty percent (50%) of the Executive's Base Salary, subject to standard deductions and withholdings, based on the Board's determination, in good faith, and based upon the Executive's individual achievement and company performance objectives as set by the Board or the compensation committee thereof, of whether the Executive has met such performance milestones as are established for the Executive by the Board or the compensation committee thereof, in good faith, in consultation with the Executive (hereinafter referred to as the ***"Performance Milestones"***). The Performance Milestones will be based on certain factors including, but not limited to, the Executive's performance and the Company's financial performance. The Executive's Bonus target will be reviewed annually and may be adjusted by the Board or the compensation committee thereof in its discretion, provided however, that the Bonus target may only be materially reduced upon Executive's written consent. The Executive must be employed on the date the Bonus is awarded to be eligible for the Bonus, subject to the termination provisions thereof. The Bonus shall be paid during the calendar year following the performance calendar year.

3.3 Horizon Retention Agreement. Concurrently with the execution of this Agreement, the Executive shall execute the Retention Agreement, a copy of which is attached as Exhibit D (the "***Horizon Retention Agreement***"). Subject to Executive's timely acceptance and execution of this Agreement and the Horizon Retention Agreement, Executive will be eligible to earn a retention bonus on the terms and conditions set forth in the Horizon Retention Agreement.

3.4 Equity Awards.

3.4.1 Equity Grants. Subject to Executive's timely acceptance and execution of this Agreement, on the Effective Date the Executive was granted the following equity awards pursuant to and subject to the terms of the Horizon Pharma Public Limited Company 2014 Equity Incentive Plan ("***2014 Equity Incentive Plan***") and its form of stock option and restricted stock unit award agreements, in the forms provided to Executive concurrently with this Agreement (collectively the "***Equity Plan Documents***") and compliance with applicable securities laws:

(i) Option. A stock option to purchase up to 50,674 ordinary shares of Horizon plc (the "***Option***"). The Option has an exercise price equal to the fair market value of Horizon plc's ordinary shares on the applicable date of grant, which is October 25, 2016. The Option will be an incentive stock option to the maximum extent permitted by applicable tax laws. Any portion of the Option that does not qualify as an incentive stock option will be a nonstatutory stock option. Subject to Executive's continued provision of services to the Company through the applicable vesting dates, the Option shall vest as follows: 25% of the total number of shares subject to the Option shall vest on the first anniversary of the date of grant (the "***Vesting Commencement Date***") and 1/36 of the remaining number of shares subject to the Option shall vest on each monthly anniversary thereafter so that the Option would fully vest on the four (4) year anniversary of the Vesting Commencement Date subject to Executive's continued services with the Company through such date.

(ii) Restricted Stock Unit Award. A restricted stock unit award in respect of 31,813 ordinary shares of Horizon plc (the "***RSU Award***"). Subject to Executive's continued provision of services to the Company through the applicable vesting dates, the RSU Award shall vest as follows: 25% of the total number of units subject to the RSU Award shall vest on the first anniversary of the Vesting Commencement Date, and thereafter 25% of the total number of units subject to the RSU Award shall vest on each anniversary thereafter, so that the RSU Award would fully vest on the fourth anniversary of the Vesting Commencement Date, subject to Executive's continued services with the Company through such date.

3.4.2 Legal Review. Upon the Executive's submission of appropriate itemized proof and verification of reasonable and customary legal fees incurred by the Executive in obtaining legal advice associated with the review, preparation, approval, and execution of this Agreement, the Company shall pay for up to $10,000.00 of such legal fees subject to receipt of appropriate proof and verification of such legal fees no later than sixty (60) days of receipt of an invoice for legal services from the Executive and/or his attorneys. To be eligible for reimbursement, the invoice must be submitted no later than ninety (90) days after the legal fees are incurred.

3.5 Changes to Compensation. The Executive's compensation may be changed from time to time by mutual agreement of the Executive and the Company. In the event that the Executive's base salary is materially decreased without his written consent, said decrease will be Good Reason for the Executive to terminate the Agreement as set forth in and subject to Section 4.5.2 of this Agreement.

3.6 Taxes. All amounts paid under this Agreement to the Executive by the Company will be paid less applicable tax withholdings and any other withholdings required by law or authorized by the Executive.

3.7 Benefits. The Executive shall, in accordance with Company policy and the terms of the applicable plan documents, be eligible to participate in benefits under any executive benefit plan or arrangement which may be in effect from time to time and made available to the Company's executives or key management employees, provided, however, that the Executive shall be entitled to at least four (4) weeks of paid vacation annually.

4. Termination.

4.1 Termination by the Company. The Executive's employment with the Company may be terminated only under the following conditions:

4.1.1 Termination for Death or Disability. The Executive's employment with the Company shall terminate effective upon the date of the Executive's death or "Complete Disability" (as defined in Section 4.5.1), provided, however, that this Section 4.1.1 shall in no way limit the Company's obligations to provide such reasonable accommodations to the Executive and/or his heirs as may be required by law.

4.1.2 Termination by the Company For Cause. The Company may terminate the Executive's employment under this Agreement for "Cause" (as defined in Section 4.5.3) by delivery of written notice to the Executive specifying the Cause or Causes relied upon for such termination, provided that such notice is delivered within two (2) months following the occurrence or discovery of any event or events constituting "Cause". Any notice of termination given pursuant to this Section 4.1.2 shall effect termination as of the date of the notice or such date as specified in the notice. The Executive shall have the right to appear before the CEO before any termination for Cause becomes effective and binding upon the Executive.

4.1.3 Termination by the Company Without Cause. The Company may terminate the Executive's employment under this Agreement at any time and for any reason or no reason subject to the requirements set out in Section 4.4 of this Agreement. Such termination shall be effective on the date the Executive is so informed or as otherwise specified by the Company, pursuant to notice requirements set forth in Section 6 of this Agreement.

4.2 Termination By The Executive. The Executive may terminate his employment with the Company at any time and for any reason or no reason, including, but not limited, to the following conditions:

4.2.1 Good Reason. The Executive may terminate his employment under this Agreement for "Good Reason" (as defined below in Section 4.5.2) by delivery of written notice to the Company specifying the Good Reason relied upon by the Executive for such termination in accordance with the requirements of such section.

4.2.2 Without Good Reason. The Executive may terminate the Executive's employment hereunder for other than Good Reason upon thirty (30) days written notice to the Company.

4.3 Termination by Mutual Agreement of the Parties. The Executive's employment pursuant to this Agreement may be terminated at any time upon a mutual agreement in writing of the parties. Any such termination of employment shall have the consequences specified in such mutual agreement.

4.4 Compensation to Executive Upon Termination. In connection with any termination of the Executive's employment for any reason, the Executive or the Executive's estate, as applicable, shall be entitled to any amounts payable to the Executive or the Executive's beneficiaries subject to and accordance with the terms of the Company's employee welfare benefit plans or policies (excluding any severance pay).

4.4.1 Death or Complete Disability. If the Executive's employment shall be terminated by death or Complete Disability as provided in Section 4.1.1, the Company shall pay to Executive, and/or Executive's heirs, all earned but unpaid Base Salary, any earned but unpaid discretionary bonuses for any prior period at such time as bonuses would have been paid if the Executive remained employed, all accrued but unpaid business expenses, and all accrued but unused vacation time earned through the date of termination at the rate in effect at the time of termination (hereinafter referred to as the ***"Accrued Amounts"***), less standard deductions and withholdings. The Executive shall also be eligible to receive a pro-rated bonus for the year of termination, as determined by the Board or the Compensation Committee of the Board based on actual performance and the period of the year he was employed (hereinafter referred to as the ***"Pro-rata Bonus"***), less standard deductions and withholdings, to be paid as a lump sum within thirty (30) days after the date of termination.

4.4.2 With Cause or Without Good Reason. If the Executive's employment shall be terminated by the Company for Cause, or if the Executive terminates employment hereunder without Good Reason, the Company shall pay the Executive's Base Salary, accrued but unpaid business expenses and accrued and unused vacation benefits earned through the date of termination at the rate in effect at the time of termination, less standard deductions and withholdings.

4.4.3 Without Cause or For Good Reason.

(i) Not in Connection With a Change in Control. If the Company terminates the Executive's employment without Cause or the Executive terminates his employment for Good Reason, and Section 4.4.3(ii) below does not apply, the Company shall pay the Accrued Amounts subject to standard deductions and withholdings, to be paid as a lump sum no later than thirty (30) days after the date of termination. In addition, subject to the limitations stated in this Agreement and upon the Executive's furnishing to the Company an executed waiver and release of claims (the form of which is attached hereto as Exhibit A) (the "***Release***") within the applicable time period set forth therein, but in no event later than forty-five days following termination of employment and permitting such Release to become effective in accordance with its terms (the "***Release Effective Date***"), and subject to Executive entering into no later than the Release Effective Date a non-competition agreement to be effective during the

Severance Period (as defined below), substantially similar to Section 2.3, and continuing to abide by its terms during the Severance Period, the Executive shall be entitled to:

(a) the equivalent of the Executive's Base Salary in effect at the time of termination will continue to be paid for a period of twelve (12) months following the date of termination (hereinafter referred to as the "***Severance Period***"), less standard deductions and withholdings, to be paid during the Severance Period according to the Company's regular payroll practices, subject to any delay in payment required by Section 4.6 in connection with the Release Effective Date; and

(b) in the event the Executive timely elects continued coverage under COBRA, the Company will continue to pay the same portion of Executive's COBRA health insurance premium as the percentage of health insurance premiums that it paid during the Executive's employment, including any amounts that Company paid for benefits to the qualifying family members of the Executive, following the date of termination up until the earlier of either (i) the last day of the Severance Period or, (ii) the date on which the Executive begins full-time employment with another company or business entity which offers comparable health insurance coverage to the Executive (such period, the "***COBRA Payment Period***"). Notwithstanding the foregoing, if the Company determines, in its sole discretion, that the Company cannot provide the COBRA premium benefits without potentially incurring financial costs or penalties under applicable law (including, without limitation, Section 2716 of the Public Health Service Act), the Company shall in lieu thereof pay Executive a taxable cash amount, which payment shall be made regardless of whether the Executive or his qualifying family members elect COBRA continuation coverage (the "***Health Care Benefit Payment***"). The Health Care Benefit Payment shall be paid in monthly or bi-weekly installments on the same schedule that the COBRA premiums would otherwise have been paid to the insurer. The Health Care Benefit Payment shall be equal to the amount that the Company otherwise would have paid for COBRA insurance premiums (which amount shall be calculated based on the premium for the first month of coverage), and shall be paid until the expiration of the COBRA Payment Period.

(ii) In Connection With a Change in Control. If the Company (or its successor) terminates the Executive's employment without Cause or the Executive terminates his employment for Good Reason within the period commencing ninety (90) days immediately prior to a Change in Control of the Company and ending eighteen (18) months immediately following a Change in Control of the Company (as defined in Section 4.5.4 of this Agreement), the Executive shall receive the Accrued Amounts subject to standard deductions and withholdings, to be paid as a lump sum no later than thirty (30) days after the date of termination. In addition, subject to the limitations stated in this Agreement and upon the Executive's furnishing to the Company (or its successor) an executed Release within the applicable time period set forth therein, but in no event later than forty-five days following termination of employment and permitting such Release to become effective in accordance with its terms, and subject to Executive entering into no later than the Release Effective Date a non-competition agreement to be effective during the Severance Period, substantially similar to Section 2.3, and continuing to abide by its terms during the Severance Period, then in lieu of (and not additional to) the benefits provided pursuant to Section 4.4.3(i) above, the

Executive shall be entitled to:

(a) the equivalent of the Executive's Base Salary in effect at the time of termination will continue to be paid during the Severance Period, less standard deductions and withholdings, to be paid during the Severance Period according to the Company's regular payroll practices, subject to any delay in payment required by Section 4.6 in connection with the Release Effective Date;

(b) Executive's target Bonus in effect at the time of termination, or if none, the last target Bonus in effect for Executive, less standard deductions and withholdings, to be paid in a lump sum within ten (10) days following the later of (i) the Release Effective Date, or (ii) the effective date of the Change in Control; and

(c) in the event the Executive timely elects continued coverage under COBRA, the Company will continue to pay the same portion of Executive's COBRA health insurance premium as the percentage of health insurance premiums that it paid during the Executive's employment, including any amounts that Company paid for benefits to the qualifying family members of the Executive, following the date of termination until the expiration of the COBRA Payment Period. Notwithstanding the foregoing, if the Company determines, in its sole discretion, that the Company cannot provide the COBRA premium benefits without potentially incurring financial costs or penalties under applicable law (including, without limitation, Section 2716 of the Public Health Service Act), the Company shall in lieu thereof pay Executive the Health Care Benefit Payment, which payment shall be made regardless of whether the Executive or his qualifying family members elect COBRA continuation coverage. The Health Care Benefit Payment shall be paid in monthly or bi-weekly installments on the same schedule that the COBRA premiums would otherwise have been paid to the insurer. The Health Care Benefit Payment shall be equal to the amount that the Company otherwise would have paid for COBRA insurance premiums (which amount shall be calculated based on the premium for the first month of coverage), and shall be paid until the expiration of the COBRA Payment Period.

(iii) No Duplication of Benefits. For the avoidance of doubt, in no event will Executive be entitled to benefits under Section 4.4.3(i) and Section 4.4.3(ii). If Executive commences to receive benefits under Section 4.4.3(i) due to a qualifying termination prior to a Change in Control and thereafter becomes entitled to benefits under Section 4.4.3(ii), any benefits previously provided to Executive under Section 4.4.3(i) shall offset the benefits to be provided to Executive under Section 4.4.3(ii) and shall be deemed to have been provided to Executive pursuant to Section 4.4.3(ii).

4.4.4 Equity Award Acceleration.

(i) In Connection With a Change in Control. In the event that the Executive's employment is terminated without Cause or for Good Reason within the ninety (90) days immediately preceding or during the eighteen (18) months immediately following a Change in Control of the Company (as defined in Section 4.5.4 of this Agreement), the vesting of the Option, the RSU Award and any other time-based vesting Company equity awards granted to Executive shall be fully accelerated such that

on the effective date of such termination (or, if later, the date of the Change in Control) one hundred percent (100%) of the equity award shares granted to Executive prior to such termination shall be fully vested and immediately exercisable, if applicable, by the Executive.

(ii) Release and Waiver. Any equity vesting acceleration pursuant to this Section 4.4.4 shall be conditioned upon and subject to the Executive's delivery to the Company of a fully effective Release in accordance with the terms specified by Section 4.4.3 hereof and such vesting acceleration benefit shall be in addition to the benefits provided by Section 4.4.3 hereof.

4.5 Definitions. For purposes of this Agreement, the following terms shall have the following meanings:

4.5.1 Complete Disability. ***"Complete Disability"*** shall mean the inability of the Executive to perform the Executive's duties under this Agreement, whether with or without reasonable accommodation, because the Executive has become permanently disabled within the meaning of any policy of disability income insurance covering employees of the Company then in force. In the event the Company has no policy of disability income insurance covering employees of the Company in force when the Executive becomes disabled, the term "Complete Disability" shall mean the inability of the Executive to perform the Executive's duties under this Agreement, whether with or without reasonable accommodation, by reason of any incapacity, physical or mental, which the Board, based upon medical advice or an opinion provided by a licensed physician, determines to have incapacitated the Executive from satisfactorily performing all of the Executive's usual services for the Company, with or without reasonable accommodation, for a period of at least one hundred eighty (180) days during any twelve (12) month period that need not be consecutive.

4.5.2 Good Reason. ***"Good Reason"*** for the Executive to terminate the Executive's employment hereunder shall mean the occurrence of any of the following events without the Executive's consent:

(i) a material reduction in the Executive's duties, authority, or responsibilities relative to the duties, authority, or responsibilities in effect immediately prior to such reduction, including by way of example, having the same title, duties, authority and responsibilities at a subsidiary level following a Change in Control;

(ii) the relocation of the Executive's primary work location to a point more than fifty (50) miles from the Executive's current work location set forth in Section 1.5 that requires a material increase in Executive's one-way driving distance;

(iii) a material reduction by the Company of the Executive's base salary or annual target Bonus opportunity, without the written consent of the Executive, as initially set forth herein or as the same may be increased from time to time pursuant to this Agreement; and

(iv) a material breach by the Company of Section 1.2 of this Agreement.

Provided, however that, such termination by the Executive shall only be deemed for Good Reason pursuant to the foregoing definition if (i) the Company is given written notice from the Executive within sixty (60) days following the first occurrence of the condition that he considers to constitute Good Reason describing the condition and the Company fails to satisfactorily remedy such condition within thirty (30) days following such written notice, and (ii) the Executive terminates employment within thirty (30) days following the end of the period within which the Company was entitled to remedy the condition constituting Good Reason but failed to do so.

4.5.3 Cause. ***"Cause"*** for the Company to terminate Executive's employment hereunder shall mean the occurrence of any of the following events, as determined reasonably and in good faith by the Board or a committee designated by the Board:

(i) the Executive's gross negligence or willful failure to substantially perform his duties and responsibilities to the Company or willful and deliberate violation of a Company policy;

(ii) the Executive's conviction of a felony or the Executive's commission of any act of fraud, embezzlement or dishonesty against the Company or involving moral turpitude that is likely to inflict or has inflicted material injury on the business of the Company, to be determined by the sole discretion of the Company;

(iii) the Executive's unauthorized use or disclosure of any proprietary information or trade secrets of the Company or any other party that the Executive owes an obligation of nondisclosure as a result of the Executive's relationship with the Company; and

(iv) the Executive's willful and deliberate breach of the obligations under this Agreement that causes material injury to the business of the Company.

4.5.4 Change in Control. For purposes of this Agreement, ***"Change in Control"*** means: (i) a sale of all or substantially all of the assets of the Company; (ii) a merger or consolidation in which the Company is not the surviving entity and in which the holders of the Company's outstanding voting stock immediately prior to such transaction own, immediately after such transaction, securities representing less than fifty percent (50%) of the voting power of the entity surviving such transaction or, where the surviving entity is a wholly-owned subsidiary of another entity, the surviving entity's parent; (iii) a reverse merger in which the Company is the surviving entity but the shares of Common Stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities of the surviving entity's parent, cash or otherwise, and in which the holders of the Company's outstanding voting stock immediately prior to such transaction own, immediately after such transaction, securities representing less than fifty percent (50%) of the voting power of the Company or, where the Company is a wholly-owned subsidiary of another entity, the Company's parent; or (iv) an acquisition by any person, entity or group (excluding any employee benefit plan, or related trust, sponsored or maintained by the Company or subsidiary of the Company or other entity controlled by the Company) of the beneficial

ownership of securities of the Company representing at least seventy-five percent (75%) of the combined voting power entitled to vote in the election of Directors; provided, however, that nothing in this paragraph shall apply to a sale of assets, merger or other transaction effected exclusively for the purpose of changing the domicile of the Company.

4.6 Application of Internal Revenue Code Section 409A. Notwithstanding anything to the contrary set forth herein, any payments and benefits provided under this Agreement (the ***"Severance Benefits"***) that constitute "deferred compensation" within the meaning of Section 409A of the Internal Revenue Code of 1986, as amended (the ***"Code"***) and the regulations and other guidance thereunder and any state law of similar effect (collectively ***"Section 409A"***) shall not commence in connection with Executive's termination of employment unless and until Executive has also incurred a "separation from service" (as such term is defined in Treasury Regulation Section 1.409A-1(h) (***"Separation From Service"***), unless the Company reasonably determines that such amounts may be provided to Executive without causing Executive to incur the additional 20% tax under Section 409A.

It is intended that each installment of the Severance Benefits payments provided for in this Agreement is a separate "payment" for purposes of Treasury Regulation Section 1.409A-2(b)(2)(i). For the avoidance of doubt, it is intended that payments of the Severance Benefits set forth in this Agreement satisfy, to the greatest extent possible, the exemptions from the application of Section 409A provided under Treasury Regulation Sections 1.409A-1(b)(4), 1.409A-1(b)(5) and 1.409A-1(b)(9). However, if the Company (or, if applicable, the successor entity thereto) determines that the Severance Benefits constitute "deferred compensation" under Section 409A and Executive is, on the termination of service, a "specified employee" of the Company or any successor entity thereto, as such term is defined in Section 409A(a)(2)(B)(i) of the Code, then, solely to the extent necessary to avoid the incurrence of the adverse personal tax consequences under Section 409A, the timing of the Severance Benefit payments shall be delayed until the earlier to occur of: (i) the date that is six months and one day after Executive's Separation From Service, or (ii) the date of Executive's death (such applicable date, the ***"Specified Employee Initial Payment Date"***), the Company (or the successor entity thereto, as applicable) shall (A) pay to Executive a lump sum amount equal to the sum of the Severance Benefit payments that Executive would otherwise have received through the Specified Employee Initial Payment Date if the commencement of the payment of the Severance Benefits had not been so delayed pursuant to this Section and (B) commence paying the balance of the Severance Benefits in accordance with the applicable payment schedules set forth in this Agreement.

Notwithstanding anything to the contrary set forth herein, Executive shall receive the Severance Benefits described above, if and only if Executive duly executes and returns to the Company within the applicable time period set forth therein, but in no event more than forty-five days following Separation From Service, the Company's standard form of release of claims in favor of the Company (attached to this Agreement as Exhibit A) (the "***Release***") and permits the release of claims contained therein to become effective in accordance with its terms (such latest permitted date, the **"*Release Deadline*"**). If the severance benefits are not covered by one or more exemptions from the application of Section 409A and the Release could become effective in the calendar year following the calendar year in which Executive separates from service, the Release will not be deemed effective any earlier than the Release Deadline. Notwithstanding any other payment schedule set forth in this Agreement, none of the Severance Benefits will be paid or otherwise delivered prior to the effective date (or deemed effective date) of the Release. Except to the extent that payments may be delayed until the Specified Employee Initial Payment Date pursuant to the preceding paragraph, on the first regular payroll pay day following the effective date of the Release, the Company will pay Executive the Severance Benefits Executive would otherwise have received under the Agreement on or prior to such date but for the delay in payment related to the effectiveness of the Release, with the balance of the Severance Benefits being paid as originally scheduled.

The severance benefits are intended to qualify for an exemption from application of Section 409A or comply with its requirements to the extent necessary to avoid adverse personal tax consequences under Section 409A, and any ambiguities herein shall be interpreted accordingly.

4.7 Application of Internal Revenue Code Section 280G. If any payment or benefit Executive would receive pursuant to a Change in Control from the Company or otherwise (***"Payment"***) would (i) constitute a "parachute payment" within the meaning of Section 280G of the Code, and (ii) but for this sentence, be subject to the excise tax imposed by Section 4999 of the Code (the ***"Excise Tax"***), then such Payment shall be equal to the Reduced Amount. The "Reduced Amount" shall be either (x) the largest portion of the Payment that would result in no portion of the Payment being subject to the Excise Tax or (y) the largest portion, up to and including the total, of the Payment, whichever amount, after taking into account all applicable federal, state and local employment taxes, income taxes, and the Excise Tax (all computed at the highest applicable marginal rate), results in Executive's receipt, on an after-tax basis, of the greater economic benefit notwithstanding that all or some portion of the Payment may be subject to the Excise Tax. If a reduction in payments or benefits constituting "parachute payments" is necessary so that the Payment equals the Reduced Amount, reduction shall occur in the manner that results in the greatest economic benefit for Executive. If more than one method of reduction will result in the same economic benefit, the items so reduced will be reduced pro rata.

In the event it is subsequently determined by the Internal Revenue Service that some portion of the Reduced Amount as determined pursuant to clause (x) in the preceding paragraph is subject to the Excise Tax, Executive agrees to promptly return to

the Company a sufficient amount of the Payment so that no portion of the Reduced Amount is subject to the Excise Tax. For the avoidance of doubt, if the Reduced Amount is determined pursuant to clause (y) in the preceding paragraph, Executive will have no obligation to return any portion of the Payment pursuant to the preceding sentence.

Unless Executive and the Company agree on an alternative accounting firm, the accounting firm engaged by the Company for general tax compliance purposes as of the day prior to the effective date of the Change in Control shall perform the foregoing calculations. If the accounting firm so engaged by the Company is serving as accountant or auditor for the individual, entity or group effecting the Change in Control, the Company shall appoint a nationally recognized accounting firm to make the determinations required hereunder. The Company shall bear all expenses with respect to the determinations by such accounting firm required to be made hereunder.

The Company shall use commercially reasonable efforts to cause the accounting firm engaged to make the determinations hereunder to provide its calculations, together with detailed supporting documentation, to Executive and the Company within fifteen (15) calendar days after the date on which Executive's right to a Payment is triggered (if requested at that time by Executive or the Company) or such other time as requested by Executive or the Company.

4.8 Indemnification Agreements. Concurrently with the execution of this Agreement, the Company and the Executive shall enter into indemnification agreements, copies of which are attached hereto as Exhibit B-1 and Exhibit B-2.

4.9 Confidential Information and Invention Assignment Agreement. Concurrently with the execution of this Agreement, the Executive shall execute the Company's Confidential Information and Invention Assignment Agreement, a copy of which is attached as Exhibit C.

4.10 No Mitigation or Offset. The Executive shall not be required to seek or accept other employment, or otherwise to mitigate damages, as a condition to receipt of the Severance Benefits, and the Severance Benefits shall not be offset by any amounts received by the Executive from any other source, except to the extent that the Executive's rights to the benefits described in Sections 4.4.3(i)(b) or 4.4.3(ii)(c), as applicable, are terminated by reason of the Executive obtaining full-time employment with another company or business entity which offers comparable health insurance coverage.

5. Assignment and Binding Effect.

This Agreement shall be binding upon the Executive and the Company and inure to the benefit of the Executive and the Executive's heirs, executors, personal representatives, assigns, administrators and legal representatives. Because of the unique and personal nature of the Executive's duties under this Agreement, neither this Agreement nor obligations under this Agreement shall be assignable by the Executive. This Agreement shall be binding upon and inure to the benefit of the Company and its successors, assigns and legal representatives, provided that the Agreement may only be assigned to an acquirer of all or substantially all of the Company's assets. Any such

successor of the Company will be deemed substituted for the Company under the terms of this Agreement for all purposes. For this purpose, "successor" means any person, firm, corporation or other business entity which at any time, whether by purchase, merger or otherwise, directly or indirectly acquires all or substantially all of the assets or business of the Company.

6. Notice.

For the purposes of this Agreement, notices, demands, and all other forms of communication provided for in this Agreement shall be in writing and shall be deemed to have been duly given when delivered or (unless otherwise specified) mailed by registered mail, return receipt requested, postage prepaid, or by confirmed facsimile, addressed as set forth below, or to such other address as any party may have furnished to the other in writing in accordance herewith, except that notices of address shall be effective only upon receipt, as follows:

If to the Company:

Horizon Pharma, Inc.
150 S. Saunders Road
Lake Forest, IL 60045
Attention: Timothy P. Walbert, Chairman, President & CEO
Fax: 847-572-1372

If to the Executive:

David A. Happel
2362 Caballo Ranchero Drive
Diablo, CA 94528

Any such written notice shall be deemed given on the earlier of the date on which such notice is personally delivered or five (5) days after its deposit in the United States mail as specified above. Either Party may change its address for notices by giving written notice to the other Party in the manner specified in this section.

7. Choice of Law.

This Agreement shall be governed by the laws of the State of Illinois, without regard to any conflicts of law principals thereof that would call for the application of the laws of any other jurisdiction. The parties consent to the exclusive jurisdiction and venue of the federal court in the Northern District of Illinois, and state courts located in the state of Illinois, county of Cook. Nothing in this Section 7 limits the rights of the parties to seek appeal of a decision of an Illinois court outside of Illinois that has proper jurisdiction over the decision of a court sitting in Illinois.

8. Integration.

This Agreement, including Exhibit A, Exhibit B, Exhibit C, Exhibit D, the 2014 Equity Incentive Plan, and the Transition Services Agreement contains the complete, final and exclusive agreement of the parties relating to the terms and conditions of the Executive's employment and the termination of Executive's employment, and supersedes all prior and contemporaneous oral and written employment agreements or arrangements between the parties, including but not limited to the Prior Agreement. By executing this Agreement, Executive hereby agrees that Executive's Prior Agreement is terminated and superseded in its entirety by this Agreement as of the Effective Date and that Executive waives any right that Executive may have and/or is not entitled to severance benefits under the Prior Agreement.

9. Amendment.

This Agreement cannot be amended or modified except by a written agreement signed by the Executive and the Company.

10. Waiver.

No term, covenant or condition of this Agreement or any breach thereof shall be deemed waived, except with the written consent of the party against whom the wavier is claimed, and any waiver or any such term, covenant, condition or breach shall not be deemed to be a waiver of any preceding or succeeding breach of the same or any other term, covenant, condition or breach.

11. Severability.

The finding by a court of competent jurisdiction of the unenforceability, invalidity or illegality of any provision of this Agreement shall not render any other provision of this Agreement unenforceable, invalid or illegal. Such court shall have the authority to modify or replace the invalid or unenforceable term or provision with a valid and enforceable term or provision, which most accurately represents the parties' intention with respect to the invalid, unenforceable, or illegal term or provision.

12. Interpretation; Construction.

The headings set forth in this Agreement are for convenience of reference only and shall not be used in interpreting this Agreement. This Agreement has been drafted and negotiated by legal counsel representing the Company and the Executive. The parties acknowledge that each party and its counsel has reviewed and revised, or had an opportunity to review and revise, this Agreement, and any rule of construction to the effect that any ambiguities are to be resolved against the drafting party shall not be employed in the interpretation of this Agreement.

13. Execution by Facsimile Signatures and in Counterparts.

The parties agree that facsimile signatures shall have the same force and effect as original signatures. This Agreement may be executed in one or more counterparts, each

of which shall be deemed an original but all of which together shall constitute one and the same instrument.

14. Survival.

The provisions of this Agreement, and of all other agreements referenced herein, shall survive the termination of this Agreement, and of the Executive's employment by the Company for any reason, to the extent necessary to enable the parties to enforce their respective rights hereunder.

[Remainder of Page Intentionally Left Blank]

IN WITNESS WHEREFORE, the parties have signed this Agreement on the date first written above.

COMPANY:

HORIZON PHARMA, INC.
HORIZON PHARMA USA, INC.

By:
Title: Chairman, President & CEO
Print Name: Timothy P. Walbert

/s/ Timothy P. Walbert

Signature:

As authorized agent of the Company

November 4, 2016

Date

EXECUTIVE:

David A. Happel

/s/ David A. Happel
David A. Happel, individually

November 4, 2016

Date

EXHIBIT A

RELEASE AND WAIVER OF CLAIMS

In consideration of the payments and other benefits set forth in Section 4.4 of the Executive Employment Agreement dated October 25, 2016, (the ***"Employment Agreement"***), to which this form is attached, I, David A. Happel, hereby furnish Horizon Pharma, Inc. and Horizon Pharma USA, Inc. (together the ***"Company"***), with the following release and waiver (***"Release and Waiver"***).

In exchange for the consideration provided to me by the Employment Agreement that I am not otherwise entitled to receive, I hereby generally and completely release the Company and its directors, officers, employees, shareholders, partners, agents, attorneys, predecessors, successors, parent and subsidiary entities, insurers, Affiliates, and assigns from any and all claims, liabilities and obligations, both known and unknown, that arise out of or are in any way related to events, acts, conduct, or omissions occurring relating to my employment or the termination thereof prior to my signing this Release and Waiver. This general release includes, but is not limited to: (1) all claims arising out of or in any way related to my employment with the Company or the termination of that employment; (2) all claims related to my compensation or benefits from the Company, including, but not limited to, salary, bonuses, commissions, vacation pay, expense reimbursements, severance pay, fringe benefits, stock, stock options, or any other ownership interests in the Company; (3) all claims for breach of contract, wrongful termination, and breach of the implied covenant of good faith and fair dealing; (4) all tort claims, including, but not limited to, claims for fraud, defamation, emotional distress, and discharge in violation of public policy; and (5) all federal, state, and local statutory claims, including, but not limited to, claims for discrimination, harassment, retaliation, attorneys' fees, or other claims arising under the federal Civil Rights Act of 1964 (as amended), the federal Americans with Disabilities Act of 1990, the federal Age Discrimination in Employment Act of 1967 (as amended) (***"ADEA"***), the California Labor Code (as amended), the California Family Rights Act, and the California Fair Employment and Housing Act (as amended). Notwithstanding the foregoing, this Release and Waiver, shall not release or waive my rights: to indemnification under the articles and bylaws of the Company or applicable law; to payments under Sections of the Employment Agreement; under any provision of the Employment Agreement that survives the termination of that agreement; under any applicable workers' compensation statute; under any option, restricted share or other agreement concerning any equity interest in the Company; as a shareholder of the Company or any other right that is not waivable under applicable law.

I acknowledge that, among other rights, I am waiving and releasing any rights I may have under ADEA, that this Release and Waiver is knowing and voluntary, and

that the consideration given for this Release and Waiver is in addition to anything of value to which I was already entitled as an executive of the Company. If I am 40 years of age or older upon execution of this Release and Waiver, I further acknowledge that I have been advised, as required by the Older Workers Benefit Protection Act, that: (a) the release and waiver granted herein does not relate to claims under the ADEA which may arise after this Release and Waiver is executed; (b) I should consult with an attorney prior to executing this Release and Waiver; and (c) I have twenty-one (21) days from the date of termination of my employment with the Company in which to consider this Release and Waiver (although I may choose voluntarily to execute this Release and Waiver earlier); (d) I have seven (7) days following the execution of this Release and Waiver to revoke my consent to this Release and Waiver; and (e) this Release and Waiver shall not be effective until the seven (7) day revocation period has expired unexercised. If I am less than 40 years of age upon execution of this Release and Waiver, I acknowledge that I have the right to consult with an attorney prior to executing this Release and Waiver (although I may choose voluntarily not to do so); and (c) I have five (5) days from the date of termination of my employment with the Company in which to consider this Release and Waiver (although I may choose voluntarily to execute this Release and Waiver earlier).

I acknowledge my continuing obligations under my Confidential Information and Inventions Agreement dated , . Pursuant to the Confidential Information and Inventions Agreement I understand that among other things, I must not use or disclose any confidential or proprietary information of the Company and I must immediately return all Company property and documents (including all embodiments of proprietary information) and all copies thereof in my possession or control. I understand and agree that my right to the payments and other benefits I am receiving in exchange for my agreement to the terms of this Release and Waiver is contingent upon my continued compliance with my Confidential Information and Inventions Agreement.

This Release and Waiver, including my Confidential Information and Inventions Agreement dated , , constitutes the complete, final and exclusive embodiment of the entire agreement between the Company and me with regard to the subject matter hereof. I am not relying on any promise or representation by the Company that is not expressly stated herein. This Release and Waiver may only be modified by a writing signed by both me and a duly authorized officer of the Company.

Date:

By:

David A. Happel

EXHIBIT D

HORIZON RETENTION AGREEMENT

October 28, 2016

David Happel

RE: Retention Agreement

Dear David:

As you know, Horizon Pharma PLC (***"Horizon"***) and Misneach Corporation have executed an Agreement and Plan of Merger (the "***Merger Agreement***") with Raptor Pharmaceutical Corp. ("***Raptor***"), pursuant to which Raptor has become a wholly-owned subsidiary of Horizon effective as of October 25, 2016 (the "***Merger Closing Date***"). In connection with the closing of this transaction, your employment was transferred from Raptor to Horizon Pharma, Inc., a Delaware corporation, and its wholly owned subsidiary, Horizon Pharma USA, Inc., a Delaware corporation, (together "the ***Company***") as of October 25, 2016. Certain capitalized terms used in this Retention Agreement have the meanings set forth in Section III below.

I. Eligibility for Retention Bonus

As you know, under your Transition Services Agreement with Raptor dated October 13, 2016 you are eligible to earn a retention bonus of $335,000 subject to your continued employment through May 15, 2017 (the "***Initial Retention Date***") and the other terms and conditions set forth in the Transition Services Agreement, which remains in full force and effect. As an incentive for you to continue to contribute your efforts, talents and services to the Company and its Affiliates for the period following the Initial Retention Date through and including the Earn Date (as defined below) Horizon is pleased to announce your eligibility to earn a one-time retention bonus in the aggregate amount of 150% of your annual base salary (**$750,000)** (the "***Retention Bonus***"), less applicable taxes and withholdings, pursuant to the terms and conditions set forth in this Retention Agreement.

In order to earn the Retention Bonus, you must remain employed by the Company or any other Affiliate (together, the "***Horizon Employer***") regularly working at least 30 hours per week and in good performance standing for the period following the Initial Retention Date through and including November 1, 2017 (the "***Earn Date***"). The period from the Initial Retention Date through and including the Earn Date is the "***Retention Bonus Period.***" If earned, the Retention Bonus will be paid in a lump sum by the Company or its Affiliate, less applicable taxes and withholdings, on the first administratively practicable payroll pay date after the Earn Date.

II. Employment Termination

Notwithstanding the foregoing, if during the Retention Bonus Period, the Horizon Employer terminates your employment without Cause, or your employment with the Horizon Employer is terminated due to your death or Disability (as defined below), you will be eligible for the following benefits, subject to your satisfaction of the additional conditions specified below:

- If the Horizon Employer terminates your employment without Cause during the Retention Bonus Period, you will be eligible for the full amount of the Retention Bonus.
- If your employment with the Horizon Employer is terminated due to your death or Disability during the Retention Bonus Period, you will be eligible for a pro-rata portion of the Retention

Bonus, with such pro-rata portion determined by dividing the number of days you were actually employed by the Horizon Employer during the Retention Bonus Period by the total number of days in the Retention Bonus Period (the "***Pro-Rata Retention Bonus***").

In order to earn the full Retention Bonus or Pro-Rata Retention Bonus in connection with your employment termination, you (or your estate or legal guardian, if applicable) must execute and deliver to Horizon a general release of all known and unknown claims in a form acceptable to Horizon (the "***Release***"), and such Release must become effective in accordance with its terms, but in no event later than sixty (60) days following your employment termination date. If earned, such bonus payment will be paid in a lump sum by the Horizon Employer or its Affiliate, less applicable taxes and withholdings, on the first administratively practicable payroll pay date after the Release becomes effective.

For the avoidance of doubt, if prior to expiration of the Retention Bonus Period: (i) you provide notice of your employment resignation, or actually sever the employment relationship by resignation (for any reason, including retirement), or (ii) the Horizon Employer terminates your employment for Cause; then you will not be eligible for and will not earn the full Retention Bonus or any Pro-Rata Retention Bonus. Under no circumstances will you be eligible to receive both the full Retention Bonus and a Pro-Rata Retention Bonus.

III. Definitions

For purposes of this Retention Agreement, ***"Affiliates"*** means Horizon Pharma plc and each of its majority owned subsidiaries and ***"Affiliate"*** means any of the Affiliates.

For purposes of this Retention Agreement, "***Cause***" means the occurrence of any one or more of the following: **(i)** your conviction of, or plea of no contest with respect to, any felony, or of any misdemeanor involving dishonesty or moral turpitude; **(ii)** your participation in a fraud or act of dishonesty (or an attempted fraud or act of dishonesty) that results in (or could result in) material harm to the Horizon Employer or any Affiliate, including but not limited to material harm to reputational interests; **(iii)** your violation of a fiduciary duty owed to the Horizon Employer or any Affiliate; **(iv)** your material breach of any fully executed agreement between you and the Horizon Employer or any Affiliate; **(v)** persistent, unsatisfactory performance or neglect of your job duties, which is not cured within ten (10) business days after you are provided written notice by the Horizon Employer (*provided, that,* such written notice and opportunity to cure are not required if your performance or neglect is not reasonably susceptible to being cured); or **(vi)** your gross misconduct or material failure to comply with a written instruction of the Horizon Employer or any Affiliate.

For purposes of this Retention Agreement, "***Disability***" means you are eligible for long-term disability benefits under the Horizon Employer's long-term disability benefit plan.

IV. IRS Code Section 409A

It is intended that any bonus amount payable under this Retention Agreement satisfies, to the greatest extent possible, the exemption from the application of Section 409A of the Internal Revenue Code of 1986, as amended (the "***Code***") provided under Treasury Regulations Section 1.409A-1(b)(4) and in all cases will be paid not later than March 15 of the year following the year in which your right to such amount became vested. To the extent that such bonus is deferred compensation under Section 409A of the Code, and is not otherwise exempt from the application of Section 409A, then, if the period during which you may consider and sign the Release spans two calendar years, the payment of such bonus will not be made to you until the later calendar year.

V. Miscellaneous

The Retention Agreement is intended to provide a financial incentive to you and is not intended to confer any rights to continued employment upon you. Nothing in this Retention Agreement is intended to alter your at-will employment relationship with the Horizon Employer, and your employment remains terminable by either you or the Horizon Employer with or without Cause or advanced notice. This Agreement also does not change or modify any other benefits that you may be eligible to receive from the Horizon Employer.

This Retention Agreement is the complete, final and exclusive embodiment of the entire agreement between you and Horizon with regard to the Retention Bonus and Pro-Rata Retention Bonus, and it supersedes and replaces any other agreements (whether written or unwritten) you may have with the Horizon Employer concerning these matters. This Retention Agreement is entered into without reliance on any promise or representation (written or unwritten), other than those expressly contained herein, and it supersedes any other such promises, warranties or representations. The terms of this Retention Agreement may not be modified or amended except in a written agreement signed by you and a duly authorized officer of Horizon.

Please sign and return this agreement to Keith Swenson on or before November 4, 2016.

Sincerely,

/s/ Timothy P. Walbert
Timothy P. Walbert
Chairman, President & CEO

ACKNOWLEDGMENT AND ACCEPTANCE

Accepted and Agreed:

David Happel

/s/ David Happel
Signature

11/04/16
Date

Exhibit 10.73

*****Text Omitted and Filed Separately with the Securities and Exchange Commission. Confidential Treatment Requested Under 17 C.F.R. Sections 200.80(b)(4) and 240.24b-2.**

October 13, 2016

David A. Happel

CONFIDENTIAL

Dear Mr. Happel,

As you are aware, on September 12, 2016, Raptor Pharmaceutical Corp. (the "Company") entered into a definitive agreement to be acquired by Horizon Pharma plc. ("Parent"). We expect the acquisition to close by the end of October of this year (the date the acquisition closes, the "Closing").

We are committed to a seamless and smooth transition and in order to promote these goals, we have adopted a transition services program pursuant to which you are eligible to earn a retention bonus for your continued service from the Closing through December 31, 2016 (or earlier termination by the Company or Horizon without Cause), subject to certain conditions described in more detail below. As a participant in the program, you will be eligible to earn and receive an amount equal to $128,000 (the "2016 Retention Bonus"), less any applicable state, federal and local income taxes as well as any applicable employment or excise taxes, subject to your continued employment with the Company through December 31, 2016 (or earlier termination by the Company or Horizon without Cause) and your compliance with the terms of this letter agreement.

As a condition to your participation in this program and eligibility to earn the 2016 Retention Bonus and in consideration therewith, you hereby expressly waive any right that you may have to be paid the target amount of your 2016 performance bonus under the Company's 2016 bonus program at the Closing. You will instead have the opportunity to earn a 2016 performance bonus under the Company's 2016 bonus program (the "2016 Performance Bonus") subject to your continued employment with the Company through December 31, 2016 (or earlier termination by the Company or Horizon without Cause) and your compliance with the terms of this letter agreement. If earned, the amount of your 2016 Performance Bonus awarded to you will be equal to the lesser of: (i) your target 2016 bonus amount, and (ii) the amount of 2016 bonus determined pursuant to the applicable performance criteria previously established for the Company's 2016 bonus program for you, as specified on the attached Exhibit A, based on the actual performance levels attained through December 31, 2016, as determined by Parent in its sole discretion. In no event will you be eligible to earn more than your target 2016 bonus amount as specified on the attached Exhibit A. Parent's determination of your actual 2016 Performance Bonus amount awarded to you will be final and binding. Your 2016 Performance Bonus will be paid to you less any applicable state, federal and local income taxes as well as any applicable employment or excise taxes.

If you satisfy this continued service requirement through December 31 , 2016 (the "2016 Transition Period End Date") or are earlier terminated by the Company or Horizon without Cause, and comply with the terms of this letter agreement, your 2016 Retention Bonus will be payable in a lump-sum on the first regular payroll in January 2017. If you satisfy this continued service requirement through the 2016 Transition Period End Date or are earlier terminated by the Company or Horizon without Cause, and comply with the terms of this letter agreement, your 2016 Performance Bonus will be payable in a lump-sum as soon as practicable following the determination by Parent' of the applicable level of attainment of the performance goals, but in no event will be paid later than March 15, 2017.

We have also adopted an additional transition services bonus program pursuant to which you are eligible to earn an additional bonus for your continued service from January 1, 2017 through May 15, 2017 (the "2017 Transition Period End Date"), subject to certain conditions described in more detail below. As a participant in this program, you will be eligible to earn and receive an additional amount equal to $335,000 (the "2017 Retention Bonus"), less any applicable state, federal and local income taxes as well as any applicable employment or excise taxes, subject to your continued employment with the Company through the 2017 Transition Period End Date or earlier termination by the Company or Horizon without Cause and your compliance with the terms of this letter agreement. If earned, your 2017 Retention Bonus will be paid to you in a single lump sum on the first regular payroll following the 2017 Transition Period End Date. You will not be eligible to receive the 2017 Retention Bonus if your employment terminates prior to the 2017 Transition Period End Date due to your resignation for any reason, death or disability (within the meaning of Section 22(e) of the Code).

The period from the Closing through the 2017 Transition Period End Date (or, if earlier, the date of your termination by the Company or Horizon without Cause) is the "Transition Period." During the Transition Period you shall continue to provide services in your area of expertise and responsibility including as related to the following goals: assisting with the Quinsair launch in Canada and preparation for U.S. and assisting in Procysbi and Quinsair commercial transition outside the U.S. and Procybi in the U.S. (your "Responsibilities"). You agree to continue to devote your best efforts and substantially all of your business time and attention to the business of the Company during this period and keep the Company regularly apprised of your activities in order to facilitate this process.

If, after the Closing but prior to the 2017 Transition Period End Date, (1) your employment with the Company is terminated by the Company or Horizon for reasons other than for Cause, or (2) the Company or Horizon provides you with written direction not to devote all of your business time and attention to the business of the Company during this period, then if any payment or benefit you receive in connection with the acquisition or otherwise ("Payment") would (A) constitute a "parachute payment" within the meaning of Section 280G of the Code, and (B) as such, is subject to the excise tax imposed by Section 4999 of the Code (the "Excise Tax"), then the Company shall pay to you an additional cash amount (the "Gross-Up Payment") with respect to each such Payment. The amount of each Gross-Up Payment shall be sufficient that, after paying (A) any Excise Tax on the Payment, (B) any federal, state or local income or employment taxes and Excise Tax on the Gross-Up Payment, and (C) any interest and penalties imposed in respect of the Excise Tax, you will retain an amount equal to the full amount of the Payment. Any Gross-Up Payment, as determined in accordance with this letter agreement, shall be paid by the Company to you at the same time withholding taxes for the related excise tax is due. You will not be eligible to receive the Gross-Up

Payment if your employment terminates prior to the 2017 Transition Period End Date due to your resignation for any reason, death or disability (within the meaning of Section 22(e) of the Code).

If you are not entitled to a Gross-Up Payment and any payment or benefit you would receive from the Company or otherwise pursuant to the acquisition of the Company by Parent ("Payment") would (i) constitute a "parachute payment" within the meaning of Section 280G of the Code, and (ii) but for this sentence, be subject to the excise tax imposed by Section 4999 of the Code (the "Excise Tax"), then such Payment shall be equal to the Reduced Amount. The "Reduced Amount" shall be either (x) the largest portion of the Payment that would result in no portion of the Payment being subject to the Excise Tax or (y) the largest portion, up to and including the total, of the Payment, whichever amount, after taking into account all applicable federal, state and local employment taxes, income taxes, and the Excise Tax (all computed at the highest applicable marginal rate), results in your receipt, on an after-tax basis, of the greater economic benefit notwithstanding that all or some portion of the Payment may be subject to the Excise Tax. If a reduction in payments or benefits constituting "parachute payments" is necessary so that the Payment equals the Reduced Amount, reduction shall occur in the following order: (1) reduction of cash payments; (2) cancellation of accelerated vesting of equity awards other than stock options; (3) cancellation of accelerated vesting of stock options; and (4) reduction of other benefits payable to you.

If you are not entitled to a Gross-Up Payment and it is subsequently determined by the U.S. Internal Revenue Service that some portion of the Reduced Amount as determined pursuant to clause (x) in the preceding paragraph is subject to the Excise Tax, you agree to promptly return to the Company a sufficient amount of the Payment so that no portion of the Reduced Amount is subject to the Excise Tax. For the avoidance of doubt, if the Reduced Amount is determined pursuant to clause (y) in the preceding paragraph, you will have no obligation to return any portion of the Payment pursuant to the preceding sentence.

For the avoidance of doubt, the benefits provided by this letter agreement shall not be in lieu of or in any way amend any rights to base salary, severance or other benefits under your employment agreement or change in control severance agreement with the Company. You hereby reaffirm your commitment to remain in compliance with the Employee Invention Assignment and Confidentiality Agreement entered into between you and the Company (the "Confidentiality Agreement"). You acknowledge and agree that the benefits described in this letter agreement are subject to all of the terms and conditions set forth above, including your agreement to remain in compliance with the Confidentiality Agreement and that if you fail to do so, any right you may have to receive the bonuses and other benefits described in this letter will be forfeited. Please indicate your acceptance of and agreement to, the terms and conditions of this letter agreement by signing and returning a copy of this letter agreement to Justin Ford.

Yours sincerely,

Julie Anne Smith
President and CEO
Raptor Pharmaceutical Corp.

Acknowledged, agreed and accepted:

/s/ David A. Happel
David A. Happel
Date: 10/13/16

APPENDIX

"*Cause*" means (i) your commission of a felony or other crime involving moral turpitude; (ii) any willful act or acts of dishonesty, embezzlement or fraud you undertake that are intended to result in substantial gain or personal enrichment for you, your family or any third party at the expense of the Company or Horizon; (iii) your commission of any willful act of gross misconduct which is materially and demonstrably injurious to the Company or Horizon; (iv) your material breach of the letter agreement to which this Appendix is attached, your employment, severance or other similar written agreement with the Company or the Confidentiality Agreement, (v) your unauthorized use or disclosure of any proprietary information or trade secrets of the Company, Horizon or any other party that you owe an obligation of nondisclosure as a result of your relationship with the Company; and/or (vi) your gross negligence or willful failure to substantially perform your Responsibilities to the Company or willful and deliberate violation of a material Company policy. For the avoidance of doubt, the termination of your employment as a result of your death or your inability to perform the essential functions of your job due to permanent disability (within the meaning of Section 22(e) of the Internal Revenue Code of 1986, as amended) will not be deemed to constitute a termination without Cause.

EXHIBIT A

2016 BONUS PERFORMANCE CRITERIA

Target 2016 Bonus Amount: $156,975

Horizon will determine the level of attainment of the corporate goals and your individual performance level and applicable amount of 2016 bonus payments in accordance with the following criteria, which are set forth in Raptor's proxy statement and are consistent with the Raptor Compensation Committee's stated policy and historical practice:

- After evaluation of performance, achievement scores may be awarded which recognize partial performance of a goal or recognize additional score points for exceptional performance due to unanticipated challenges or superior performance.
- Awards can vary to up to 125% of the target percentage based on assessment of achievement above the targeted levels, of meaningful additional goals or sustained superior performance in the conduct of duties and responsibilities in the employee's position.

In determining your 2016 bonus award, corporate goals are weighted at 80% and your individual 2016 performance is weighted at 20%.

The corporate goals established for the 2016 bonus program are:

Weight	2016 Corporate Goals
30%	Achieve WW net sales revenue of $120M
15%	Launch QUINSAIR in Europe by 1st half of 2016
20%	Acceptance of QUINSAIR NDA for CF in the U.S.
15%	End 2016 with sufficient cash to provide planned funded runway through June 30, 2018
20%	Advance pipeline by achieving certain internal and external development. a) 10% First patient dosed for MP-376 P2 in BE; b) 10% Generate data from clinical and/or non-clinical studies to inform dose selection, advance discussions with FDA and EMA regarding the full development plan including the pivotal Phase 3 HD study and make substantial progress to partner or out-license the RP-103 HD program.

The individual goals established for the 2016 bonus program are:

Weight	2016 Individual Goals
35%	[…***…]
20%	[…***…]
25%	[…***…]

*****Confidential Treatment Requested**

10%	[…***…]
5%	[…***…]
5%	[…***…]

Horizon's determination of your 2016 bonus award will be final and binding on you and all other parties. Regardless of performance levels, in no event are you eligible to be awarded more than your Target 2016 Bonus Amount.

*****Confidential Treatment Requested**

*****Text Omitted and Filed Separately
with the Securities and Exchange Commission.
Confidential Treatment Requested
Under 17 C.F.R. Sections 200.80(b)(4)
and 240.24b-2.**

AMENDMENT NO. 1 TO SALES CONTRACT

This AMENDMENT NO. 1 ("Amendment") is to that certain Sales Contract, dated as of July 1, 2010 ("Contract"), by and between Horizon Pharma USA, Inc. ("Buyer") and BASF Corporation ("BASF" or "Seller"). Capitalized terms used and not defined herein shall have the respective meanings assigned to such terms in the Contract. This Amendment shall be effective as of January 1, 2016 (the "Amendment Effective Date").

Recitals:

WHEREAS, Buyer and BASF previously negotiated the Contract; and

WHEREAS, pursuant to Section 1 of the Terms and Conditions of the Contract, the parties desire to amend the Contract as provided herein effective as of the Amendment Effective Date.

NOW, THEREFORE, for good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged by the parties, and intending to be legally bound, the parties hereby agree as follows:

Agreement:

1. Term. The first sentence of the "TERM" section of the Contract shall be deleted in its entirety and replaced with the following text:

"The term of this Contract will expire on December 31, 2018 (the "Initial Term"). Following the Initial Term, the Contract will automatically renew for a period of three (3) years ("Renewal Term") at a price negotiated in good faith between the parties; provided that during the Renewal Term the price will not exceed […***…], subject to BASF's right to adjust the price during the Renewal Term based on market conditions. Notwithstanding the foregoing, either party may terminate this Agreement either at the end of the Initial Term or any time during the Renewal Term by giving the other party at least […***…] months' written notice of termination, for any reason or no reason . The Initial Term together with the Renewal Term, if any, is referred to herein as the "Term".

2. Price. The "PRICE" section of the Contract shall be deleted in its entirety and replaced with the following text:

"From […***…] through […***…], the price of the Product is $[…***…]/kg. From […***…] through […***…], the price of the Product will be $[…***…]/kg."

3. Miscellaneous. All other terms and conditions of the Agreement will remain unchanged. This Amendment together with the Agreement, and all of the attachments, exhibits and schedules hereto and thereto constitute the entire agreement of the parties with respect to the subject matter hereof and supersede any and all existing or prior agreements and communications, whether written or oral, relating to the subject matter hereof. This Amendment may be executed in counterparts (which may be exchanged by facsimile), each of which shall be deemed an original, but which together shall constitute one and the same instrument. This Amendment shall be governed by and construed in accordance with the internal laws of the State of Delaware, USA, excluding its conflict of laws principles.

[signature page follows]

IN WITNESS WHEREOF, the parties hereto have executed this Amendment to the Agreement as of the date first above written.

HORIZON PHARMA USA, INC.

By: /s/ Jeffrey W. Sherman
Name: Jeffrey W. Sherman, M.D., FACP
Title: Chief Medical Officer

BASF CORPORATION

By: /s/ Danielle Piergentili
Name: Danielle Piergentili
Title: Vice President, Pharma Ingredients & Services – North America

Exhibit 21.1

Subsidiaries of Horizon Pharma Public Limited Company:

NAME:	JURISDICTION OF INCORPORATION:
Andromeda Biotech Limited	Israel
Horizon European Products, LLC	Delaware
Horizon Orphan LLC	Delaware
Horizon Pharma Aon Limited	Ireland
Horizon Pharma Capital Limited	Ireland
Horizon Pharma Dó Limited	Ireland
Horizon Pharma Europe B.V.	Netherlands
Horizon Pharma Finance Limited	Ireland
Horizon Pharma Finance S.à.r.l	Luxembourg
Horizon Pharma France SAS	France
Horizon Pharma Germany GmbH	Germany
Horizon Pharma GmbH	Germany
Horizon Pharma Holdings 2 Limited	Ireland
Horizon Pharma Holdings Limited	Ireland
Horizon Pharma Investment Limited	Bermuda
Horizon Pharma Ireland Limited	Ireland
Horizon Pharma Israel Holding Corp. Ltd	Israel
Horizon Pharma Rheumatology Limited	Ireland
Horizon Pharma Rheumatology LLC	Delaware
Horizon Pharma Services Limited	Ireland
Horizon Pharma Switzerland GmbH	Switzerland
Horizon Pharma Treasury DAC	Ireland
Horizon Pharma Trí Limited	Ireland
Horizon Pharma USA, Inc.	Delaware
Horizon Pharma, Inc.	Delaware
Horizon Pharmaceutical LLC	Delaware
Horizon Therapeutics, LLC	Delaware
Hyperion Holding LLC	Delaware
Hyperion Therapeutics Ireland Holding Limited	Ireland
Hyperion Therapeutics Ireland Operating Limited	Ireland
HZNP Canada Limited	Canada
HZNP European Holdings, C.V.	Netherlands
HZNP Limited	Ireland
HZNP USA LLC	Delaware
Misneach Europe LLC	Delaware

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-3 (No. 333-198852) and Form S-8 (No. 333-198865, 333-203933, 333-211118) of Horizon Pharma plc of our report dated February 27, 2017 relating to the financial statements, financial statement schedule and the effectiveness of internal control over financial reporting, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP
Chicago, Illinois
February 27, 2017

Exhibit 31.1

Certification of Principal Executive Officer

I, Timothy P. Walbert, certify that:

1. I have reviewed this annual report on Form 10-K of Horizon Pharma plc (the "registrant");

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

    a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

    b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

    c. Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

    d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

    a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

    b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 27, 2017

/s/ Timothy P. Walbert
Timothy P. Walbert
Chairman, President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

Certification of Principal Financial Officer

I, Paul W. Hoelscher, certify that:

1. I have reviewed this annual report on Form 10-K of Horizon Pharma plc (the "registrant");

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

    a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

    b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

    c. Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

    d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

    a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

    b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 27, 2017

/s/ Paul W. Hoelscher
Paul W. Hoelscher
Executive Vice President, Chief Financial Officer
(Principal Financial Officer)

Exhibit 32.1

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and 18 U.S.C. Section 1350, I, Timothy P. Walbert, President, Chief Executive Officer and Chairman of the Board of Horizon Pharma plc (the "Company"), certify to the best of my knowledge that:

1. the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2016 (the "Report"), to which this Certification is attached as Exhibit 32.1, fully complies with the requirements of Section 13(a) or 15(d) of the Exchange Act; and
2. the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 27, 2017

/s/ Timothy P. Walbert
Timothy P. Walbert
Chairman, President and Chief Executive Officer
(Principal Executive Officer)

A signed original of this written statement required by Section 906 has been provided to the Company and will be retained by the Company and furnished to the Securities and Exchange Commission or its staff upon request.

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of the Company under the Securities Act of 1933, as amended, or the Exchange Act (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.

Exhibit 32.2

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and 18 U.S.C. Section 1350, I, Paul W. Hoelscher, Executive Vice President and Chief Financial Officer of Horizon Pharma plc (the "Company"), certify to the best of my knowledge that:

1. the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2016 (the "Report"), to which this Certification is attached as Exhibit 32.2, fully complies with the requirements of Section 13(a) or 15(d) of the Exchange Act; and
2. the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 27, 2017

/s/ Paul W. Hoelscher
Paul W. Hoelscher
Executive Vice President, Chief Financial Officer
(Principal Financial Officer)

A signed original of this written statement required by Section 906 has been provided to the Company and will be retained by the Company and furnished to the Securities and Exchange Commission or its staff upon request.

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of the Company under the Securities Act of 1933, as amended, or the Exchange Act (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2017

or

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to

Commission File Number 001-35238

HORIZON PHARMA PUBLIC LIMITED COMPANY

(Exact name of Registrant as specified in its charter)

Ireland	**Not Applicable**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
Connaught House, 1st Floor 1 Burlington Road, Dublin 4, D04 C5Y6, Ireland	**Not Applicable**
(Address of principal executive offices)	**(zip code)**

011 353 1 772 2100

(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	**Name of Each Exchange on Which Registered**
Ordinary shares, nominal value $0.0001 per share	**The NASDAQ Global Select Market**

Securities registered pursuant to Section 12(g) of the Act:

None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐.

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒.

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company.

Large accelerated filer	☒	Accelerated filer	☐
Non-accelerated filer	☐ (Do not check if a smaller reporting company)	Smaller reporting company	☐
Emerging growth company	☐		

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined by Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

The aggregate market value of the registrant's voting ordinary shares held by non-affiliates of the registrant, based upon the $11.87 per share closing sale price of the registrant's ordinary shares on June 30, 2017 (the last business day of the registrant's most recently completed second quarter), was approximately $1.9 billion. Solely for purposes of this calculation, the registrant's directors and executive officers and holders of 10% or more of the registrant's outstanding ordinary shares have been assumed to be affiliates and an aggregate of 1,102,129 ordinary shares held by such persons on June 30, 2017 are not included in this calculation.

As of February 22, 2018, the registrant had outstanding 164,570,004 ordinary shares.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement for the registrant's 2018 Annual General Meeting of Shareholders are incorporated by reference into Part III of this Annual Report on Form 10-K.

HORIZON PHARMA PLC
FORM 10-K — ANNUAL REPORT
For the Fiscal Year Ended December 31, 2017

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PART I

Special Note Regarding Forward-Looking Statements

This Annual Report on Form 10-K contains "forward-looking statements" — that is, statements related to future, not past, events — as defined in Section 21E of the Securities Exchange Act of 1934, as amended, that reflect our current expectations regarding our future growth, results of operations, business strategy and plans, financial condition, cash flows, performance, business prospects, and opportunities, as well as assumptions made by, and information currently available to, our management. Forward-looking statements include any statement that does not directly relate to a current or historical fact. Forward-looking statements generally can be identified by words such as "believe," "may," "could," "will," "estimate," "continue," "anticipate," "intend," "seek," "plan," "expect," "should," "would", or similar expressions. These statements are based on current expectations and assumptions that are subject to risks and uncertainties inherent in our business, which could cause our actual results to differ materially from those indicated in the forward-looking statements. Factors that could cause actual results to differ materially from those indicated in the forward-looking statements include, without limitation: our ability to successfully execute our sales and marketing strategy, including continuing to successfully recruit and retain sales and marketing personnel and to successfully build the market for our medicines; our ability to continue our transition to a rare and rheumatic disease company and build a sustainable pipeline of new medicine candidates; whether we will be able to realize the expected benefits of strategic transactions, including whether and when such transactions will be accretive to our net income; the rate and degree of market acceptance of, and our ability and our distribution and marketing partners' ability to obtain coverage and adequate reimbursement and pricing for, our medicines from government and third-party payers and risks relating to the success of our patient access programs; our ability to maintain regulatory approvals for our medicines; our ability to conduct clinical development and obtain regulatory approvals for our medicine candidates, including potential delays in initiating and completing studies and filing for and obtaining regulatory approvals and whether data from clinical studies will support regulatory approval; our need for and ability to obtain additional financing; the accuracy of our estimates regarding future financial results; our ability to successfully execute our strategy to develop or acquire additional medicines or companies, including disruption from any future acquisition or whether any acquired development programs will be successful; our ability to manage our anticipated future growth; the ability of our medicines to compete with generic medicines, especially those representing the active pharmaceutical ingredients in our medicines as well as new medicines that may be developed by our competitors; our ability and our distribution and marketing partners' ability to comply with regulatory requirements regarding the sales, marketing and manufacturing of our medicines and medicine candidates; the performance of our third-party distribution partners, licensees and manufacturers over which we have limited control; our ability to obtain and maintain intellectual property protection for our medicines; our ability to defend our intellectual property rights with respect to our medicines; our ability to operate our business without infringing the intellectual property rights of others; the loss of key commercial or management personnel; regulatory developments in the United States and other countries, including potential changes in healthcare laws and regulations; and other risks detailed below in Part I — Item 1A. "Risk Factors".

Although we believe that the expectations reflected in our forward-looking statements are reasonable, we cannot guarantee future results, events, levels of activity, performance or achievement. We undertake no obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, unless required by law.

Item 1. Business

Unless otherwise indicated or the context otherwise requires, references to the "Company", "we", "us" and "our" refer to Horizon Pharma plc and its consolidated subsidiaries.

Overview

We are a biopharmaceutical company focused on researching, developing and commercializing innovative medicines that address unmet treatment needs for rare and rheumatic diseases. By fostering a growing pipeline of medicines in development and exploring all potential uses for currently marketed medicines, we strive to make a powerful difference for patients, their caregivers and physicians.

Our Strategy

Our strategy is to continue to build a well-balanced, diversified, high-growth biopharmaceutical company that focuses on addressing unmet treatment needs for rare and rheumatic diseases. We are executing our strategy through the successful commercialization of our existing medicines, a strong commitment to patient access and support and business development efforts focused on acquisitions to accelerate our rare disease leadership with on-market medicines as well as development-stage medicines to fill out our pipeline.

We are building a sustainable biopharmaceutical company by helping ensure that patients have access to their medicines and support services, and by investing in the further development of medicines for patients with rare or underserved diseases. Our growing business is diversified across three business units: orphan, rheumatology and primary care, and is driven by a successful commercial model that focuses on differentiated, long-life medicines, innovative patient access programs and a disciplined business development strategy. Our key areas of focus are:

Business development – We have a disciplined and robust acquisition strategy, and our focus is on rapid value creation and improving the performance of each of the medicines we acquire. We have completed nine acquisitions and one divestiture over the past seven years, including our first acquisition of a development-stage medicine in 2017 and two transformative transactions in 2016 that brought us three rare disease medicines. With our May 2017 acquisition of River Vision Development Corp., or River Vision, we added the late-stage rare disease biologic medicine candidate teprotumumab to our pipeline. Teprotumumab, which successfully completed a Phase 2 clinical trial and is currently enrolling patients in a Phase 3 confirmatory trial, targets the treatment of active moderate-to-severe thyroid eye disease, a debilitating autoimmune condition that presents in patients with Graves' disease. The River Vision acquisition further demonstrates our commitment to rare disease medicines and expands and diversifies our rare disease medicine pipeline to support sustainable longer-term growth.

Clinical development – We strive to diligently unlock the full therapeutic potential of our medicines by working closely with regulatory agencies, premier academic centers with established study consortiums, healthcare professionals and patient groups to facilitate our clinical development programs and generate data for possible new indications that may help more patients in need. We also continue to look at opportunities to augment our rare disease pipeline through development-stage acquisitions and licensing and collaboration agreements.

Revenue diversification – We have successfully diversified our portfolio of commercialized medicines from two in 2013 to eleven today. Our intent is to continue to generate organic growth, broaden our medicine portfolio to ensure net sales are not dominated by any one medicine and increase the proportion of net sales derived from our medicines for rare and rheumatic diseases.

Our strategy has evolved over three phases. When we first launched as a public company in 2011, we rapidly established our infrastructure and commercial footprint, generating earnings and cash flow through the commercialization of our first two medicines. In 2014, we began the next phase of our strategy, focusing on rapid diversification into rare disease medicines through key acquisitions that brought us ACTIMMUNE, RAVICTI, KRYSTEXXA and PROCYSBI. In 2017, we advanced to the third stage of our evolution, building out a pipeline of differentiated and clinically meaningful development-stage medicine candidates to drive sustainable growth over the long term. At the same time, we remain focused on commercial execution and optimizing the growth of our rare disease medicines, as well as considering future commercial asset acquisitions.

As a result of our strategy, we have diversified from a company with two medicines and total net sales of $6.9 million in 2011, to a rare disease medicine focused company with eleven medicines and net sales of $1.1 billion in 2017. Of our eleven medicines, six are for the treatment of rare diseases and represented approximately sixty percent of our 2017 net sales.

Our Company

We are a public limited company formed under the laws of Ireland. We operate through a number of international and U.S. subsidiaries with principal business purposes to perform research and development or manufacturing operations, serve as distributors of our medicines, hold intellectual property assets or provide us with services and financial support.

Our principal executive offices are located at Connaught House, 1st Floor, 1 Burlington Road, Dublin 4, D04 C5Y6, Ireland and our telephone number is 011 353 1 772 2100. Our website address is www.horizonpharma.com. Information found on, or accessible through, our website is not a part of, and is not incorporated into, this Annual Report on Form 10-K.

Acquisitions and Divestitures

During the years ended December 31, 2017, 2016 and 2015, we completed the following acquisitions and divestitures:

- On June 30, 2017, we completed our acquisition of certain rights to interferon gamma-1b from Boehringer Ingelheim International GmbH, or Boehringer Ingelheim International, in all territories outside of the United States, Canada and Japan.
- On June 23, 2017, we sold our European subsidiary that owned the marketing rights to PROCYSBI® (cysteamine bitartrate) delayed-release capsules and QUINSAIR™ (levofloxacin inhalation solution) in Europe, the Middle East and Africa, or EMEA, regions, or the Chiesi divestiture, to Chiesi Farmaceutici S.p.A., or Chiesi.
- On May 8, 2017, we completed our acquisition of River Vision, which added the late development-stage rare disease biologic medicine candidate teprotumumab to our research and development pipeline.
- On October 25, 2016, we completed our acquisition of Raptor Pharmaceutical Corp., or Raptor, which added the rare disease medicines PROCYSBI and QUINSAIR to our medicine portfolio.
- On January 13, 2016, we completed our acquisition of Crealta Holdings LLC, or Crealta, which added the rare disease medicine KRYSTEXXA and the primary care medicine MIGERGOT to our medicine portfolio.
- On May 7, 2015, we completed our acquisition of Hyperion Therapeutics, Inc., or Hyperion, which added the rare disease medicines RAVICTI and BUPHENYL to our medicine portfolio.

The consolidated financial statements presented herein include the results of operations of the acquired Hyperion, Crealta and Raptor businesses from the applicable dates of acquisition. See Note 4 of the Notes to consolidated financial statements, included in Item 15 of this Annual Report on Form 10-K, for further details of our acquisitions and divestitures.

Our Medicines

We believe our medicines address unmet therapeutic needs in orphan diseases, arthritis, pain and inflammation and inflammatory diseases and provide significant advantages over existing therapies.

Our current marketed medicine portfolio consists of the following:

Medicine	Disease	Fiscal Year 2017 Net Sales (in millions)	Marketing Rights
ORPHAN BUSINESS UNIT MEDICINES:			
RAVICTI	Urea cycle disorders	$193.9	Worldwide (1)
PROCYSBI	Nephropathic cystinosis	$137.7	United States and certain other countries (2)
ACTIMMUNE	Chronic granulomatous disease and severe, malignant osteopetrosis	$111.0	Worldwide (3)
BUPHENYL	Urea cycle disorders	$20.8	Worldwide (4)
QUINSAIR	Treatment of chronic pulmonary infections due to *Pseudomonas aeruginosa* in cystic fibrosis patients	$3.4	United States and certain other countries (5)
RHEUMATOLOGY BUSINESS UNIT MEDICINES:			
KRYSTEXXA	Chronic refractory gout (“uncontrolled gout”)	$156.5	Worldwide
RAYOS/LODOTRA	Rheumatoid arthritis, polymyalgia rheumatic, systemic lupus erythematosus and multiple other indications	$57.5	Worldwide (6)
PRIMARY CARE BUSINESS UNIT MEDICINES:			
PENNSAID 2%	Pain of osteoarthritis of the knee(s)	$191.1	United States
DUEXIS	Signs and symptoms of osteoarthritis and rheumatoid arthritis	$121.2	Worldwide (7)
VIMOVO	Signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis	$57.7	United States
MIGERGOT	Vascular headache	$5.5	United States

(1) RAVICTI distribution rights in the Middle East and North Africa have been granted to Swedish Orphan Biovitrum AB, or SOBI. RAVICTI is also available in Europe and Canada through exclusive distribution agreements with SOBI and Innomar Strategies Inc., or Innomar, respectively.

(2) We market PROCYSBI in the United States, Canada and Latin America. Innomar is our exclusive distributor for PROCYSBI in Canada. We also have marketing rights to PROCYSBI in Asia.
(3) ACTIMMUNE is known as IMUKIN outside the United States, Canada and Japan.
(4) BUPHENYL is known as AMMONAPS in certain European countries. The distribution rights for BUPHENYL in Europe, certain Asian, Middle Eastern, North African and other countries have been granted to SOBI. Orphan Pacific, Inc. holds an exclusive distribution agreement for the distribution of AMMONAPS in Japan.
(5) We market QUINSAIR in Canada and Latin America. Innomar is our exclusive distributor for QUINSAIR in Canada. We also have marketing rights for QUINSAIR in the United States and Asia. We have not received regulatory approval to market QUINSAIR in the United States.
(6) Mundipharma International Corporation Limited, or Mundipharma, is our exclusive distributor for LODOTRA in Europe, Asia and Latin America. The majority of LODOTRA sales are in Germany and Italy where reimbursement has been approved.
(7) DUEXIS rights in Latin America have been licensed to Grünenthal S.A., or Grünenthal.

ORPHAN BUSINESS UNIT

Our orphan business unit consists of a stable base of rare disease medicines. The rare disease medicines in our orphan business unit are RAVICTI, PROCYSBI, ACTIMMUNE, BUPHENYL and QUINSAIR.

RAVICTI

RAVICTI is indicated for use as a nitrogen-binding agent for chronic management of adult and pediatric patients two months of age and older with urea cycle disorders, or UCDs, that cannot be managed by dietary protein restriction and/or amino acid supplementation alone. UCDs are rare, life-threatening genetic disorders. RAVICTI must be used with dietary protein restriction and, in some cases, dietary supplements (for example, essential amino acids, arginine, citrulline or protein-free calorie supplements).

UCDs are inherited metabolic diseases caused by a deficiency of one of the enzymes or transporters that constitute the urea cycle. The urea cycle involves a series of biochemical steps in which ammonia, a potent neurotoxin, is converted to urea, which is excreted in the urine. UCD patients may experience episodes during which the ammonia levels in their blood become excessively high, called hyperammonemic crises, which may result in irreversible brain damage, coma or death. We estimate that there are approximately 2,600 patients with UCDs living in the United States, including approximately 1,000 diagnosed patients.

UCD symptoms may first occur at any age depending on the severity of the disorder, with more severe defects presenting earlier in life. However, a prompt diagnosis and careful management of the disease can lead to good clinical outcomes. In February 2018, we submitted a supplemental new drug application to expand the age range for the use of RAVICTI in the chronic management of UCDs in patients from birth to two months.

RAVICTI competes with older-generation nitrogen scavenger medicines. In the United States, RAVICTI competes with generic forms of sodium phenylbutyrate, including BUPHENYL. In Europe and certain other countries, RAVICTI also competes with Pheburane, which is a sugar-coated version of sodium phenylbutyrate. However, the volume of Pheburane and generic forms of sodium phenylbutyrate that must be ingested multiple times per day is significantly greater than RAVICTI, and is a barrier to patient compliance. Additionally, RAVICTI has other advantages over older-generation medicines leading to better patient adherence and compliance rates, such as its better tolerability for patients, it is ingested by mouth and therefore requires little preparation and it has little taste and lower sodium content than its competitors.

Our strategy for RAVICTI is to drive growth through increased awareness and diagnosis of UCDs, and to drive conversion from older-generation nitrogen scavengers, such as generic forms of sodium phenylbutyrate, to RAVICTI, based on the medicine's differentiated benefits.

PROCYSBI

PROCYSBI is indicated for nephropathic cystinosis, a rare and life-threatening metabolic disorder. PROCYSBI capsules contain cysteamine bitartrate in the form of innovative microspheronized beads that are individually coated to create delayed and extended-release properties, allowing patients to maintain consistent therapeutic systemic drug levels over a twelve-hour dosing period. The enteric-coated beads are pH sensitive and bypass the stomach for dissolution and absorption in the more alkaline environment of the proximal small intestine. Randomized controlled clinical trials and extended treatment with PROCYSBI therapy have demonstrated consistent cystine depletion as monitored by levels of the biomarker (and surrogate marker), white blood cell cystine.

PROCYSBI is differentiated by its ability to control cystine concentration continuously over twelve hours. Older therapies require administration of medicine every six hours. By taking PROCYSBI, patients have to dose only twice a day, leaving them greater control over their medication schedule and lifestyle. Additionally, because PROCYSBI can be administered through a feeding tube or mixed with approved food and beverages, the patient can choose a more flexible dosing regimen. PROCYSBI also has fewer known side effects, such as less severe body odor, than older-generation therapies.

We estimate that there are approximately 500 patients diagnosed with cystinosis living in the United States. Nephropathic cystinosis comprises ninety-five percent of known cases of cystinosis. In these patients, elevated cystine leads to cellular dysfunction and death; without treatment, the disease is usually fatal by the end of the first decade of life. Cystinosis is progressive, eventually causing irreversible tissue damage and multi-organ failure, including kidney failure, blindness, muscle wasting and premature death. Nephropathic cystinosis is usually diagnosed in infancy after children display symptoms to physicians, including markedly increased urination, thirst, dehydration, gastrointestinal distress, failure to thrive, rickets, photophobia and kidney symptoms specific to Fanconi syndrome. Management of cystinosis requires lifelong therapy.

In addition to patients who have already been identified, we believe that a number of patients with atypical phenotypic presentation and end-stage renal disease have their condition as a result of undiagnosed late-onset nephropathic cystinosis, and would benefit from treatment with PROCYSBI.

In December 2017, the United States Food and Drug Administration, or FDA, approved an expanded indication for PROCYSBI for the management of nephropathic cystinosis in patients one year and older. Previously, PROCYSBI was approved in the United States for treatment of patients two years and older. Additionally, in June 2017, we received a notice of compliance from Health Canada for PROCYSBI for the treatment of nephropathic cystinosis in adults and children two years of age and older. PROCYSBI is the only cystine-depleting agent approved in Canada for the treatment of nephropathic cystinosis.

Other than PROCYSBI, we are aware of two pharmaceutical products currently approved to treat cystinosis, Cystagon® and Cystaran®. Cystagon, an immediate-release cysteamine bitartrate capsule, is an older-generation systemic cystine-depleting therapy for cystinosis in the United States marketed by Mylan N.V., and by Orphan Europe SARL in markets outside of the United States. Cystagon is PROCYSBI's primary competitor. Cystaran, a cysteamine ophthalmic solution, is approved in the United States for treatment of corneal crystal accumulation in patients with cystinosis and is marketed by Leadiant Biosciences, Inc.

We believe that PROCYSBI will continue to be well received in the market, and continue to expect Cystagon to be the primary competitor for PROCYSBI for the foreseeable future.

Our strategy for PROCYSBI is to drive conversion of patients from Cystagon to PROCYSBI, increase the uptake of diagnosed but untreated patients and identify previously undiagnosed patients who are suitable for treatment.

ACTIMMUNE

ACTIMMUNE is indicated for chronic granulomatous disease, or CGD, and severe, malignant osteopetrosis, or SMO. It is a biologically manufactured protein called interferon gamma-1b that is similar to a protein the human body makes naturally. Interferon gamma helps prevent infection in CGD patients and enhances osteoclast function in SMO patients. ACTIMMUNE is the only medicine approved by the FDA to reduce the frequency and severity of serious infections associated with CGD and for delaying disease progression in patients with SMO. ACTIMMUNE is believed to work by modifying the cellular function of various cells, including those in the immune system and those that help form bones.

CGD is a genetic disorder of the immune system. It is described as a primary immunodeficiency disorder, which means it is not caused by another disease or disorder. In people who have CGD, a type of white blood cell called a phagocyte is defective. These defective phagocytes cannot generate superoxide, leading to an inability to kill harmful microorganisms such as bacteria and fungi. As a result, the immune system is weakened. People with CGD are more likely to have certain problems, such as recurrent severe bacterial and fungal infections and chronic inflammatory conditions. These patients are prone to developing masses called granulomas, which can occur repeatedly in organs throughout the body and cause a variety of problems. CGD is considered a condition that patients can live with and manage. Studies suggest that overall survival has improved over the last decade, with more patients living well into adulthood. Approximately one out of every 100,000 to 200,000 babies in the United States is born with CGD. We estimate that there are approximately 1,600 patients with CGD in the United States.

SMO is a form of osteopetrosis and is sometimes referred to as marble bone disease or malignant infantile osteopetrosis because it occurs in very young children. While exact numbers are not known, it has been estimated that one out of 250,000 children is born with SMO. During normal bone development, existing bone material is constantly being replaced by new bone. Cells called osteoblasts cause new bone formation while other cells called osteoclasts remove old bone through a process called resorption. In people with osteopetrosis, this balance is not maintained and the resorption of old bone material decreases while the formation of new bone continues. This leads to an abnormal increase in bone mass, and osteopetrosis may cause other problems such as blood disorders, decreased ability to fight infection, bone fractures, problems with vision and hearing, and abnormal appearance of the face and head.

ACTIMMUNE currently faces limited competition. There are additional or alternative approaches used to treat patients with CGD and SMO, including the increasing trend towards the use of bone marrow transplants in patients with CGD, however, there are currently no medicines on the market that compete directly with ACTIMMUNE.

Our strategy for ACTIMMUNE includes driving growth by increasing awareness and diagnosis of CGD and increasing the length and persistence of treatment.

BUPHENYL

BUPHENYL tablets for oral administration and BUPHENYL powder for oral, nasogastric, or gastrostomy tube administration are indicated as adjunctive therapy in the chronic management of patients with UCDs involving deficiencies of carbamoyl phosphate synthetase, ornithine transcarbamylase or argininosuccinic acid synthetase.

BUPHENYL is indicated in all patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first twenty-eight days of life). It is also indicated in patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy. It is important that the diagnosis be made early and treatment initiated immediately to improve chances of survival. BUPHENYL must be combined with dietary protein restriction and, in some cases, essential amino acid supplementation.

BUPHENYL is approved for use in the United States and Europe. We distribute BUPHENYL in the United States. The medicine is known as AMMONAPS in certain European countries, where we have granted distribution rights to SOBI through the end of 2021. We provide BUPHENYL in certain other countries through various special access programs and licensed distributors.

QUINSAIR

QUINSAIR is a formulation of the antibiotic drug levofloxacin, suitable for inhalation via a nebulizer, indicated for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adult patients with cystic fibrosis, or CF. QUINSAIR's route of delivery allows higher concentrations of drug in the lung sputum than can be achieved via systemic (for example, oral) administration. QUINSAIR, as approved in Canada and Latin America, is administered twice daily in twenty-eight-day cycles, using a hand-held nebulizer with a disposable handset known as the Zirela® device, manufactured by our partner PARI Pharma GmbH, or PARI, and configured specifically for use with QUINSAIR. QUINSAIR is not approved in the United States.

CF is a rare, life-threatening genetic disease affecting approximately 70,000 people worldwide, and results in buildup of abnormally thick secretions that can cause chronic lung infections and progressive lung damage in many patients that eventually leads to death.

Patients with CF are highly susceptible to colonization with bacterial infections of the lung, largely because their pulmonary mucous secretions are thicker, stickier, and more difficult to expectorate than those of healthy individuals. This creates an environment in the lung that favors bacterial proliferation. As of 2014, a median of approximately thirty-five percent of all patients with CF in the European Union, or EU, were colonized with *Pseudomonas aeruginosa*, a gram-negative bacterial infection. Infection rates climb as patients age.

QUINSAIR was launched in Canada in December of 2016.

Chronic pulmonary infections due to *Pseudomonas aeruginosa* are currently treated primarily with inhaled antibiotics, including tobramycin, an aminoglycoside-class antibiotic sold by Novartis Pharmaceuticals Corporation as TOBI® or in dry-powder-inhalation format as TOBI Podhaler® and sold by others in generic form, aztreonam, a monobacter-class antibiotic which is marketed in an inhaled formulation by Gilead Sciences, Inc. under the tradename Cayston®, and colistimethate sodium, a polymixin-class antibiotic which is approved and marketed in inhaled formulations in Europe. Tobramycin, aztreonam and colistimethane are primarily effective against gram-negative bacteria such as *Pseudomonas aeruginosa*. However, the prevalence of multi-drug-resistant *Pseudomonas aeruginosa* is growing. Thus, we believe there is an unmet need that might be addressed with a new class of inhaled antibiotic such as the fluoruquinolone class that levofloxacin represents.

RHEUMATOLOGY BUSINESS UNIT

The rare disease medicine KRYSTEXXA is the primary marketed medicine in our rheumatology business unit.

KRYSTEXXA

A PEGylated uric acid specific enzyme (uricase), KRYSTEXXA is the first and only FDA-approved medicine for the treatment of chronic gout in adult patients refractory to conventional therapy, or uncontrolled gout. Uncontrolled gout occurs in patients who have failed to normalize serum uric acid, or sUA, and whose signs and symptoms are inadequately controlled with conventional therapies, such as xanthine oxidase inhibitors, or XOIs, at the maximum medically appropriate dose, or for whom these drugs are contraindicated.

KRYSTEXXA has a unique mechanism of action that rapidly reverses disease progression. Unlike conventional XOI therapies, which address the over-production or under-excretion of uric acid, KRYSTEXXA converts uric acid into allantoin, a water-soluble molecule, which the body can easily eliminate through the urine. Renal excretion of allantoin is ten times more efficient than uric acid excretion.

Gout is one of the most common forms of inflammatory arthritis and can be assessed by a simple blood test for the amounts of uric acid in the blood (sUA levels). Typically in gout, when uric acid levels are greater than 6.8 milligrams per deciliter, urate will crystallize and deposit. These hard deposits are known as tophi and may occur anywhere in the body, including joints, as well as organs, such as the kidney and heart. When under-treated medically, tophi often lead to bone erosions and loss of functional ability. Gout flares, a common characteristic of uncontrolled gout, are intensely painful. They may or may not be accompanied by tophi. A systemic disease, uncontrolled gout frequently causes crippling disabilities and significant joint damage. Of the 8.3 million gout sufferers in the United States, we estimate that approximately 100,000 patients have uncontrolled gout.

KRYSTEXXA was approved by the FDA in 2010 following the results of two replicate clinical trials six months in duration involving eighty-five patients. The mean baseline sUA levels for patients in the trial were greater than 10 mg/dL, and patients could have visible or invisible tophi. The primary endpoint for the trials was the ability to maintain a low sUA for eighty percent of the samples taken at months three and six. As a result of the every-other-week dosing of KRYSTEXXA at 8 mg, forty-two percent of KRYSTEXXA patients achieved complete response versus zero percent for the placebo group; and forty-five percent of KRYSTEXXA patients achieved complete resolution of tophi versus eight percent for the placebo group over six months.

We are focused on optimizing and maximizing the peak sales potential of KRYSTEXXA by expanding our commercialization efforts, as well as investing in education, patient and physician outreach, and investigation programs that demonstrate KRYSTEXXA as an effective treatment for uncontrolled gout. We believe that KRYSTEXXA represents a significant opportunity and potential growth driver for our rheumatology business unit.

Since acquiring KRYSTEXXA through the acquisition of Crealta in January 2016, we have increased the growth trajectory of the medicine through the execution of our strong commercial and clinical strategies. This included building out a highly experienced sales, marketing, patient access and medical affairs team to support the physician and patient community. As part of that support, we launched an education campaign designed to build awareness about KRYSTEXXA and the systemic and progressive nature of gout. In addition, we invested in extensive re-analysis of the clinical trial data to elucidate new findings from the trials and expand awareness of KRYSTEXXA as a safe and effective treatment of uncontrolled gout.

In May 2017, we announced increased investment in KRYSTEXXA as part of our strategy to optimize its sales potential, nearly doubling the commercial organization by the end of 2017. In addition to selling and marketing to a larger number of rheumatologists, we are also expanding our outreach to include nephrologists, given that many chronic kidney disease, or CKD, patients have gout, and the disease tends to be more prevalent as CKD advances. While conventional XOI gout therapies can place additional burden on the kidneys and have dosing limitations, KRYSTEXXA has been proven effective and safe for uncontrolled gout patients with CKD without the need to adjust dosing. We therefore believe KRYSTEXXA offers a solution to a clinical need experienced by many nephrologists.

As the only FDA approved medication for the treatment of uncontrolled gout, KRYSTEXXA faces limited direct competition. We believe that the complexity of manufacturing KRYSTEXXA provides a barrier to potential generic competition. However, a number of competitors have medicines in Phase 1 or Phase 2 trials. Though KRYSTEXXA does not have any direct competitors, because there is no other medication approved for uncontrolled gout, other therapies could be used prior to use of KRYSTEXXA, and if effective, could reduce the treatable patient population for KRYSTEXXA.

RAYOS/LODOTRA

RAYOS/LODOTRA is indicated for the treatment of multiple conditions: rheumatoid arthritis, or RA; ankylosing spondylitis, or AS; polymyalgia rheumatica, or PMR; primary systemic amyloidosis; asthma; chronic obstructive pulmonary disease; systemic lupus erythematosus, or SLE; and a number of other conditions. We focus our promotion of RAYOS/LODOTRA on rheumatology indications, including RA and PMR. We sell and market the medicine in the United States as RAYOS. Outside the United States, it is sold and marketed as LODOTRA, and Mundipharma is our exclusive distributor in Europe, Asia and Latin America. The majority of LODOTRA sales are in Germany and Italy, where reimbursement has been approved.

RAYOS/LODOTRA is composed of an active core containing prednisone that is encapsulated by an inactive porous shell, and acts as a barrier between the medicine's active core and the patient's gastrointestinal, or GI, fluids. RAYOS/LODOTRA was developed using Vectura Group plc's, or Vectura, proprietary GeoClock™ and GeoMatrix™ technologies, for which we hold an exclusive worldwide license for the delivery of glucocorticoid, a class of corticosteroid. The delivery system enables a delayed release, synchronizing the prednisone delivery time with the patient's elevated cytokine levels, thereby taking effect at a physiologically optimal point to inhibit cytokine production, and thus significantly reducing the signs and symptoms of RA and PMR.

RA is a chronic disease that causes pain, stiffness and swelling, primarily in the joints; PMR is an inflammatory disorder that causes significant muscle pain and stiffness; SLE is a chronic autoimmune disease that primarily affects women and causes inflammation and pain in the joints and muscles as well as overall fatigue.

RAYOS/LODOTRA competes with a number of medicines in the market to treat RA, including corticosteroids, such as prednisone; traditional disease-modifying anti-rheumatic drugs, or DMARDs, such as methotrexate; and biologic agents, such as Humira and Enbrel. The majority of RA patients are treated with DMARDs, which are typically used as initial therapy in patients with RA. Biologic agents are typically added to DMARDs as combination therapy. It is common for an RA patient to take a combination of a DMARD, an oral corticosteroid, a non-steroidal anti-inflammatory drug, or NSAID, and/or a biologic agent.

PRIMARY CARE BUSINESS UNIT

Our strategy for the primary care business unit, which includes PENNSAID 2%, DUEXIS, VIMOVO and MIGERGOT, is to educate physicians about these clinically differentiated medicines and the benefits they offer. Patients are able to fill prescriptions for these medicines through pharmacies participating in our HorizonCares patient access program, as well as other pharmacies. In addition, we have evolved our commercial strategy to enter into business arrangements with pharmacy benefit managers, or PBMs, and other payers to secure formulary status and reimbursement of our primary care medicines. The business arrangements with the PBMs generally require us to pay administrative fees and rebates to the PBMs and other payers for qualifying prescriptions.

PENNSAID 2%

PENNSAID 2% is indicated for the treatment of pain of osteoarthritis, or OA, of the knee(s). OA is a type of arthritis that is caused by the breakdown and eventual loss of the cartilage of one or more joints.

An analgesic that is easy-to-apply topically directly to the knee, PENNSAID 2% contains diclofenac sodium, a commonly prescribed NSAID to treat OA pain, and dimethyl sulfoxide, or DMSO, a penetrating agent that helps ensure that diclofenac sodium is absorbed through the skin to the site of inflammation and pain. Topical NSAIDs such as PENNSAID 2% are generally viewed as safer alternatives to oral NSAID treatment because they reduce systemic exposure to a fraction of that of an oral NSAID. PENNSAID 2% is the only topical NSAID offered with the convenience of a metered-dose pump, which ensures that the patient receives the correct amount of PENNSAID 2% solution with each use. PENNSAID 2% competes primarily with the generic version of Voltaren Gel, a market leader in the topical NSAID category.

DUEXIS

DUEXIS is indicated for the relief of signs and symptoms of RA and OA and to decrease the risk of developing upper-GI ulcers in patients who are taking ibuprofen for these indications. RA is a chronic disease that causes pain, stiffness and swelling, primarily in the joints. RA is discussed above in the Rheumatology Business Unit section.

DUEXIS provides a fixed-dose combination in tablet form of ibuprofen, the most widely prescribed NSAID, and famotidine, a well-established GI agent used to treat dyspepsia, gastroesophageal reflux disease and active ulcers.

Fixed-dose combination therapy provides significant advantages over multiple-pill regimens: fixed-dose combinations can reduce the number of pills taken; ensure that the correct dosage of each component is taken at the correct time, improving compliance; and is often associated with better treatment outcomes.

In general, DUEXIS faces competition from the separate use of NSAIDs for pain relief and GI medications to address the risk of NSAID-induced ulcers. However, the prescribing information for DUEXIS states that DUEXIS should not be substituted with the single-ingredient products of ibuprofen and famotidine. DUEXIS competes with other NSAIDs, including Celebrex®, manufactured by Pfizer Inc., and celecoxib, a generic form of the medicine supplied by other pharmaceutical companies. DUEXIS also competes with TIVORBEX™ (indomethacin) capsules, VIVLODEX® (meloxicam) capsules and ZORVOLEX ® (diclofenac) capsules marketed by Iroko Pharmaceuticals, LLC.

VIMOVO

VIMOVO is indicated for the relief of signs and symptoms of OA, RA and AS and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers. It is a proprietary, fixed-dose, delayed-release tablet that combines enteric-coated naproxen, an NSAID, surrounded by a layer of immediate-release esomeprazole magnesium. Naproxen has proven anti-inflammatory and analgesic properties, and esomeprazole magnesium reduces the stomach acid secretions that can cause upper-GI ulcers. Both naproxen and esomeprazole magnesium have well-documented and excellent long-term safety profiles, and both medicines have been used by millions of patients worldwide. VIMOVO has been shown to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID associated gastric ulcers. VIMOVO is not interchangeable with the individual components of naproxen and esomeprazole magnesium.

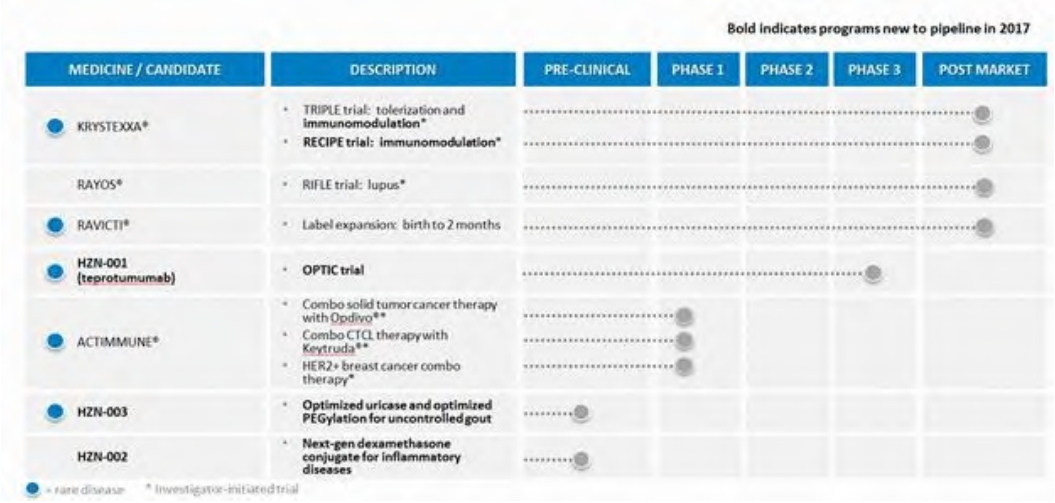
Similar to DUEXIS, VIMOVO faces competition from the separate use of NSAIDs for pain relief and GI medications to address the risk of NSAID-induced ulcers. However, the prescribing information for VIMOVO states that VIMOVO should not be substituted with the single-ingredient products of naproxen and esomeprazole magnesium. VIMOVO also competes with other NSAIDs, including Celebrex, TIVORBEX, VIVLODEX and ZORVOLEX.

MIGERGOT

MIGERGOT is indicated as therapy to abort or prevent vascular headaches, such as migraines, migraine variants or so- called “histaminic cephalalgia”.

Research and Development

Our research and development programs currently include pre-clinical and clinical development of new medicine candidates, activities related to label expansions for existing medicines and the generation of additional clinical data for our existing medicines. We devote significant resources to research and development activities associated with our medicines and medicine candidates, and in 2017 added the first development-stage candidate, teprotumumab, to our pipeline. For the years ended December 31, 2017, 2016 and 2015, we incurred $225.0 million, $60.7 million and $41.9 million, respectively, in research and development, or R&D, expenses. The graphic below summarizes our significant R&D activities in order of the program stage, from post-market to pre-clinical:



Orphan Pipeline Programs

We expanded our orphan pipeline programs in 2017, with the addition of teprotumumab, bringing our orphan development programs to five: HZN-001 (teprotumumab); RAVICTI label expansion; and three ACTIMMUNE oncology-combination programs.

HZN-001: Teprotumumab

Teprotumumab is a human monoclonal antibody inhibitor of insulin-like growth factor type 1 receptor being studied in a confirmatory Phase 3 clinical trial for the treatment of a rare eye disease, thyroid eye disease, or TED. There are no FDA-approved therapies for TED; therefore, there is a significant unmet need for an effective and safe treatment. We added this late-stage rare disease biologic medicine candidate to our pipeline with our acquisition of River Vision in May 2017.

Teprotumumab is in development for the treatment of TED, also referred to as Graves' eye disease, Graves' Orbitopathy or Thyroid-Associated Ophthalmopathy, an eye condition in which the eye muscles and fatty tissue behind the eye become inflamed. This can cause proptosis, where the eyes are pushed forward causing "staring" or "bulging" eyes and the eyes and eyelids become swollen and red. In some cases swelling and stiffness of the muscles occur that move the eyes so that they are no longer in line with each other, or the eyelids are unable to close. It is believed that teprotumumab works by blocking the specific autoimmune pathophysiology that causes active TED, which diminishes local inflammation, prevents orbital fibroblast proliferation and reduces tissue expansion, thus restoring the orbital tissue to a more normal state. We estimate that 15,000 to 20,000 patients are eligible for treatment in the United States. Teprotumumab received orphan drug, fast track and breakthrough therapy designations from the FDA in 2016.

The Phase 2 clinical trial results for teprotumumab demonstrated clinically meaningful and statistically significant results in patients with active moderate-to-severe TED. The primary endpoint of the trial was the responder rate, defined as a reduction of proptosis of ≥ 2mm and a reduction in the Clinical Activity Score, a seven-point scale that measures orbital inflammation and pain, of ≥ 2 points in the study eye at week twenty-four of the trial, without proptosis deterioration (≥ 2mm) in the fellow eye. In the trial, sixty-nine percent of teprotumumab patients achieved the primary endpoint versus twenty percent of the placebo patients ($p < 0.001$). The secondary endpoints were also achieved, and teprotumumab was generally well tolerated with the majority of adverse events being mild. Of note, a treatment-related adverse event was hyperglycemia in diabetic patients, which was controlled by adjusting diabetes medication. The results were published in *The New England Journal of Medicine* in May 2017.

During October 2017, we enrolled the first patient in the confirmatory Phase 3 clinical trial titled "Treatment of Graves' Orbitopathy (Thyroid Eye Disease) to Reduce Proptosis with Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study", or OPTIC. OPTIC will enroll seventy-six patients across eleven centers in the United States, Germany and Italy, and those patients who meet OPTIC Phase 3 eligibility criteria will be randomized to receive eight infusions of teprotumumab or placebo every three weeks for twenty-one weeks. The primary endpoint will measure the proptosis responder rate of ≥ 2 mm reduction of proptosis in the study eye (without deterioration in the fellow eye) at week twenty-four. In addition, the OPTIC trial will measure several secondary endpoints at week twenty-four, including overall responder rate (defined as the percentage of patients with ≥ 2 point reduction in Clinical Activity Score and ≥ 2 mm reduction in proptosis, which was the primary endpoint of the Phase 2 trial), percentage of participants with a Clinical Activity Score value of 0 or 1, mean change in proptosis measurement and mean change in the Graves' Ophthalmopathy Quality of Life questionnaire overall score. Safety will also be evaluated. We anticipate that data from the trial will be available during the second half of 2019.

RAVICTI

We are in the process of seeking FDA approval for a label expansion for RAVICTI for patients from birth to two months. There is a variable age of diagnosis in patients with UCDs (from newborn to adulthood), and the severity of the disease can be associated with the age of onset and enzymatic deficit. However, a prompt diagnosis and careful management of the disease may lead to good clinical outcomes.

ACTIMMUNE

We are supporting a number of investigator-initiated studies to evaluate ACTIMMUNE as a potential immune booster in cancer-combination studies.

A study at the H. Lee Moffitt Cancer Center and Research Institute is evaluating the optimal dosing for a combination therapy of ACTIMMUNE with Taxol® (paclitaxel), Herceptin® (trastuzumab) and Perjeta® (pertuzumab) for the treatment of patients with a certain type of advanced breast cancer. Taxol is marketed by Bristol-Meyers Squibb Company, and Herceptin and Perjeta are marketed by Genentech Inc., or Genentech. Enrollment for the dose escalation portion of the trial is complete and the study has transitioned into the Phase 2 portion. We expect to have data from the trial in 2019.

Two other cancer-combination studies are evaluating ACTIMMUNE in combination with a PD-1 inhibitor in certain cancers. Pre-clinical research has indicated that interferon gamma may enhance the effect of PD-1 inhibitors.

A trial at Fox Chase Cancer Center is evaluating ACTIMMUNE in combination with Opdivo® (nivolumab), a PD-1 inhibitor, in advanced solid tumors. Opdivo is marketed by Bristol-Meyers Squibb Company. Data from the first three cohorts of the Phase 1 dose escalation trial determined the maximum-tolerated dose of ACTIMMUNE in combination with nivolumab. A fourth cohort of patients receiving ACTIMMUNE in combination with nivolumab is still under study.

A trial sponsored by the National Cancer Institute in collaboration with the Cancer Immunotherapy Trials Network is evaluating a combination therapy of ACTIMMUNE with Keytruda® (pembrolizumab), a PD-1 inhibitor, for the treatment of mycosis fungoides and Sézary syndrome, a type of cutaneous T-cell lymphoma. Patients are currently being enrolled in the Phase 2 study. Keytruda is marketed by Merck Sharp & Dohme Corp.

Rheumatology Pipeline Programs

We expanded our rheumatology pipeline programs in 2017 with the addition of two pre-clinical programs to enhance our market leadership position in uncontrolled gout and to augment our rheumatology portfolio. Our rheumatology pipeline is now composed of five programs: HZN-003 (optimized uricase and optimized PEGylation for uncontrolled gout); HZN-002 (next-generation dexamethasone conjugate for inflammatory diseases); TRIPLE trial for KRYSTEXXA; RECIPE trial for KRYSTEXXA; and RIFLE trial for RAYOS (each as defined below). In addition to the pipeline programs, we recently entered into a collaboration agreement with XL-protein GmbH to identify clinical-stage product candidates that could use PASylation technology to construct a next-generation gout biologic.

HZN-003: Potential Next-Generation Biologic for Uncontrolled Gout Using Optimized Uricase and Optimized PEGylation Technology

A biologic for uncontrolled gout, HZN-003 is a pre-clinical, genetically engineered uricase derivative with optimized uricase and optimized PEGylation technology that has the potential to improve the response rate compared to the un-optomized biologic. In addition, it has the potential for subcutaneous dosing. We licensed HZN-003 (formerly MEDI4945) from MedImmune LLC, the global biologics research and development arm of the AstraZeneca Group, late in 2017. HZN-003 is a rheumatology pipeline program with the objective of enhancing our leadership position in the uncontrolled gout market.

HZN-002: Potential Targeted Novel Dexamethasone Conjugate for Inflammatory Diseases

HZN-002 is a pre-clinical, novel dexamethasone conjugate. HZN-002 has the potential to augment our rheumatology portfolio by addressing inflammatory diseases through its targeted delivery technology. We have an option to license HZN-002 under a collaboration and option agreement we entered into with a privately held life-science entity in November 2016.

KRYSTEXXA Life-Cycle Management

KRYSTEXXA is a recombinant protein of uricase, an enzyme not found in humans, and PEGylation. As with many biologic medicines, some people treated with KRYSTEXXA develop antidrug antibodies as part of an immune response to the medicine and lose response to therapy. Our clinical strategy for KRYSTEXXA is to enhance the response rate and improve convenience of dosing.

In January 2016, following our acquisition of Crealta, we assumed responsibility for an investigator-initiated study designed to test the potential reduction of immunogenicity in KRYSTEXXA patients, known as the Tolerization Reduces Intolerance to Pegloticase and Prolongs the Urate Lowering Effect, or TRIPLE, study. The TRIPLE study is a post-market interventional, exploratory open-label, adaptive design study with multiple cohorts. Initial results from the ongoing study data from the TRIPLE trial were presented in November 2017. The data showed a notable reduction in the frequency of infusion reactions when treatment "stopping rules" were used, with infusion reactions occurring in less than one percent of infusions in the study. This compares to infusion reactions reported in twenty-six percent of patients treated with KRYSTEXXA in the Phase 3 trial, which did not incorporate stopping rules. Based on the initial TRIPLE infusion reaction data, and other post-marketing data, we submitted a proposed label update to the prescribing information for KRYSTEXXA to the FDA.

During November 2017, we announced that TRIPLE will include an additional cohort to evaluate the impact of adding the immunomodulator azathioprine for a two-week run-in period, followed by daily azathioprine and KRYSTEXXA every two weeks, for a total of thirteen doses. The immunomodulation arm of the study is expected to begin in the first quarter of 2018.

A second investigator-initiated study evaluating immunomodulation with KRSTEXXA is expected to begin in the first quarter of 2018. The Reducing Immunogenicity to Pegloticase, or RECIPE, trial will evaluate the use of the immunomodulator mycophenolate mofetil, or MMF, along with KRYSTEXXA to improve the response rate to the medicine. RECIPE is a Phase 2, double-blind, multi-site proof-of-concept trial designed to evaluate if a twelve-week course of immunomodulation therapy with daily MMF can safely and meaningfully prevent the incidence of an immune response to KRYSTEXXA. The study will also assess the incidence and types of adverse events and infusion reactions related to the medicine.

RAYOS

We are collaborating with the Lupus Research Alliance and Ampel BioSolutions on a clinical trial for patients with SLE, a chronic autoimmune disease that causes inflammation and pain in the joints and muscles, as well as overall fatigue. The trial, titled RAYOS (delayed release prednisone) Inhibits Fatigue in Lupus Erythematosus, or RIFLE, launched late in 2017 and is studying the effect of RAYOS on the fatigue experienced by SLE patients.

Distribution

We use central third-party logistics, FDA-compliant warehouses for storage and distribution of our medicines into the supply chain. Our third-party logistics providers specialize in integrated operations that include warehousing and transportation services that can be scaled and customized to our needs based on market conditions and the demands and delivery service requirements for our medicines and materials. Their services eliminate the need to build dedicated internal infrastructures that would be difficult to scale without significant capital investment. Our third-party logistics providers warehouse all medicines in controlled FDA-registered facilities. Incoming orders are prepared and shipped through an order entry system to ensure just in time delivery of the medicines.

Sales and Marketing

As of December 31, 2017, our sales force was composed of approximately 430 sales representatives consisting of approximately 25 sales representatives in our Orphan business unit, 140 sales representatives in our Rheumatology business unit and 265 sales representatives in our Primary Care business unit.

Our Orphan and Rheumatology business unit sales representatives focus on marketing our orphan and rheumatology medicines to a limited number of healthcare practitioners who specialize in fields such as pediatric immunology, allergy, infectious diseases, metabolic disorders, rheumatology and nephrology to help them understand the potential benefits of our medicines. We have entered into, and may continue to enter into, agreements with third parties for commercialization of our medicines outside the United States.

Part of our commercial strategy for RAYOS and our primary care medicines is to offer physicians the opportunity to have their patients fill prescriptions through pharmacies participating in our HorizonCares patient access program. For commercial patients who are prescribed our primary care medicines or RAYOS, the HorizonCares program offers co-pay assistance when a third-party commercial payer covers a prescription but requires an eligible patient to pay a co-pay or deductible, and offers full subsidization when a third-party commercial payer rejects coverage for an eligible patient. We have entered into business arrangements with PBMs and other payers to secure formulary status and reimbursement of our medicines, such as our arrangements with Express Scripts, Inc., CVS Caremark and Prime Therapeutics LLC. These arrangements generally require us to pay administrative and rebate payments to the PBMs and/or other payers, and regardless of our agreements with the PBMs, the extent of formulary status and reimbursement ultimately depends to a large extent upon individual healthcare plan formulary decisions.

We have a comprehensive compliance program in place to address adherence with various laws and regulations relating to our sales, marketing, and manufacturing of our medicines, as well as certain third-party relationships, including pharmacies. Specifically with respect to pharmacies, the compliance program utilizes a variety of methods and tools to monitor and audit pharmacies, including those that participate in our patient access programs, to confirm their activities, adjudication and practices are consistent with our compliance policies and guidance.

Manufacturing, Commercial and Supply Agreements

We have agreements with third parties for active pharmaceutical ingredients, or APIs, and manufacturing of our medicines, formulation and development services, fill, finish and packaging services, transportation, and distribution and logistics services for certain medicines. In most cases, we retain certain levels of safety stock or maintain alternate supply relationships that we can utilize without undue disruption of our manufacturing processes if a third party fails to perform its contractual obligations.

RAVICTI

We have clinical and commercial supplies of glycerol phenylbutyrate API manufactured for us by two alternate suppliers, Helsinn Advanced Synthesis SA (Switzerland) and DSM Fine Chemicals Austria (now Patheon Austria GmbH & Co KG) on a purchase-order basis. We have finished RAVICTI drug medicine manufactured by Lyne Laboratories, Inc. under a manufacturing agreement and we have an agreement in place for a fill/finish supplier, Halo Pharmaceuticals, Inc., for European supplies.

Ucyclyd Asset Purchase Agreement

As a result of the Hyperion acquisition, we became subject to an asset purchase agreement with Ucyclyd Pharma, Inc., or Ucyclyd, pursuant to which we are obligated to pay to Ucyclyd tiered mid-to high- single-digit royalties on our global net sales of RAVICTI. The asset purchase agreement cannot be terminated for convenience by either party. However, we have a license to certain Ucyclyd manufacturing technology, and Ucyclyd may have a license to certain of our technology. The party granting a license is permitted to terminate the license if the other party fails to comply with any payment obligations relating to the license and does not cure such failure within a defined time period.

Brusilow License Agreement

As a result of the Hyperion acquisition, we became subject to a license agreement with Saul W. Brusilow, M.D. and Brusilow Enterprises, Inc., or Brusilow, pursuant to which we license patented technology related to RAVICTI from Brusilow. Under such agreement, we are obligated to pay low-single digit royalties to Brusilow on net sales of RAVICTI that are covered by a valid claim of a licensed patent. The license agreement may be terminated for any uncured breach as well as bankruptcy. We may also terminate the agreement at any time by giving Brusilow prior written notice, in which case all rights granted to us would revert to Brusilow.

PROCYSBI

PROCYSBI drug product is comprised of enteric coated beads of cysteamine bitartrate encapsulated in gelatin capsules. PROCYSBI drug product and API, cysteamine bitartrate, are manufactured on a contract basis by third parties.

Patheon Manufacturing Services Agreement

As a result of the Raptor acquisition, we assumed a manufacturing services agreement, as amended, with Patheon Pharmaceuticals Inc., or Patheon. Pursuant to the agreement, we must provide a rolling, non-binding forecast of PROCYSBI, with a portion of the forecast being a firm written order. The agreement has a term that runs until December 31, 2019 and which automatically renews for successive two-year terms if not terminated at least eighteen months in advance.

Cambrex Profarmaco Milano Supply Agreement

As a result of the Raptor acquisition, we assumed an API supply agreement, as amended, with Cambrex Profarmaco Milano, or Cambrex. Pursuant to the agreement, we must provide rolling, non-binding forecasts, with a portion of the forecast being the minimum floor of the firm order that must be placed. The Cambrex supply agreement has an initial term that runs until November 30, 2020, and which automatically renews for successive two-year terms if not terminated at least one year in advance.

UCSD License Agreement

In May 2017, we entered into an amended and restated license agreement with The Regents of the University of California, San Diego, or UCSD. We must pay UCSD a royalty in the mid-single digits on net sales of PROCYSBI in countries where PROCYSBI is covered by a patent right, and a royalty in the low-single digits on net sales of PROCYSBI in countries where PROCYSBI is not covered by a patent right. Each such royalty is subject to reduction for sales of PROCYSBI in countries in the event a generic substitute for PROCYSBI is sold in such countries. We must pay UCSD a minimum annual royalty in an amount less than $0.1 million. Royalties terminate upon the later of (a) the expiration date of the longest-lived patent rights on a country-by-country basis; and (b) twenty years after first commercial sale of PROCYSBI. We must also pay UCSD a percentage in the mid-teens of any fees we receive from our sublicensees under the agreement that are not earned royalties. We may also be obligated to pay UCSD aggregate developmental milestone payments of $0.3 million and aggregate regulatory milestone payments of $1.8 million for each orphan indication and aggregate developmental milestone payments of $0.8 million and aggregate regulatory milestone payments of $3.5 million for each non-orphan indication. We are also subject to certain diligence obligations relating to performing activities for specified indications, including maintaining existing regulatory approvals for PROCYSBI and commercializing PROCYSBI in countries where regulatory approvals have been obtained and using commercially reasonable efforts to develop, obtain regulatory approval, and commercialize certain other licensed medicines in the United States and other countries. Under the terms of our agreement with Chiesi, royalties due to UCSD on sales of PROCYSBI in EMEA will be paid by Chiesi to us, which we will forward to UCSD unless we instruct Chiesi to make such payments directly to UCSD.

ACTIMMUNE

ACTIMMUNE is a recombinant protein that is produced by fermentation of a genetically engineered Escherichia coli bacterium containing the DNA which encodes for the human protein. Purification of the active drug substance is achieved by conventional column chromatography. The resulting active drug substance is then formulated as a highly purified sterile solution and filled in a single-use vial for subcutaneous injection, which is the ACTIMMUNE finished drug medicine. In support of its manufacturing process, we and Boehringer Ingelheim RCV GmbH & Co KG, or Boehringer Ingelheim, store multiple vials of the Escherichia coli bacterium master cell bank and working cell bank in order to ensure adequate backup should any cell bank be lost in a catastrophic event.

Boehringer Ingelheim Supply Agreement

In June 2017, we entered into an exclusive global supply agreement with Boehringer Ingelheim Biopharmaceuticals GmbH, or Boehringer Ingelheim Biopharmaceuticals, pursuant to which Boehringer Ingelheim Biopharmaceuticals is required to manufacture and supply ACTIMMUNE and IMUKIN active drug substance and commercial quantities of the ACTIMMUNE and IMUKIN finished drug medicine. Boehringer Ingelheim Biopharmaceuticals is our sole source supplier for ACTIMMUNE active drug substance and finished drug medicine. Pursuant to the agreement, we are required to purchase minimum quantities of finished drug medicine during the term of the agreement. Boehringer Ingelheim Biopharmaceuticals manufactures our commercial requirements of ACTIMMUNE based on our forecasts and the annual contractual minimum purchase quantity. The supply agreement continues for an indefinite period but can be terminated by either party upon three years notice (but, in such case, cannot be terminated sooner than June 30, 2024), for an uncured material breach by the other party, upon the other party's bankruptcy or insolvency, or upon certain changes of control of the other party. We can terminate the supply agreement in the event we are prevented by regulatory authorities from distributing the product on the market for all indications.

License Agreements

Under a license agreement, as amended, with Genentech who was the original developer of ACTIMMUNE, we are or were obligated to pay royalties to Genentech on our net sales of ACTIMMUNE as follows:

- For the period from November 26, 2014, through May 5, 2018, a royalty in the twenty percent to thirty percent range for the first $3.7 million in net sales achieved in any calendar year and in the one percent to nine percent range for all additional net sales in any year; and
- From May 6, 2018, and for so long as we continue to commercially sell ACTIMMUNE, an annual royalty in the low single digits as a percentage of annual net sales.

Either Genentech or we may terminate the agreement if the other party becomes bankrupt or defaults, however, in the case of a default, the defaulting party has thirty days to cure the default before the license agreement may be terminated.

Under the terms of an assignment and option agreement with Connetics Corporation (which was the predecessor parent company to InterMune Pharmaceuticals Inc. and is now part of GlaxoSmithKline), or Connetics, we are obligated to pay low single-digit royalties to Connetics on our net sales of ACTIMMUNE in the United States.

BUPHENYL

When Hyperion purchased BUPHENYL, Hyperion assumed all of Ucyclyd's rights and obligations under its manufacturing agreements for the medicine. We assumed these agreements when we acquired Hyperion. We purchase API for BUPHENYL from CU Chemie Uetikon GmbH and final manufacturing, testing and packaging of the medicine is provided by Pharmaceutics International Inc.

Under the terms of an amended and restated collaboration agreement with Ucyclyd, we are obligated to pay to Ucyclyd tiered mid to high single-digit royalties on our net sales in the United States of BUPHENYL to UCD patients outside of the FDA approved labeled age range for RAVICTI.

QUINSAIR

QUINSAIR drug product, its API, levofloxacin hemihydrate, and the Zirela nebulizer device are all manufactured on a contract basis by third parties. The API is exclusively supplied by TEVA API Inc. QUINSAIR drug product is manufactured by Catalent Pharma Solutions, LLC. The term of the Catalent supply agreement runs until March 10, 2019. Nebulizers are supplied by PARI in Starnberg, Germany.

KRYSTEXXA

KRYSTEXXA is a PEGylated (synthetic technology used to extend the half-life of uricase), recombinant protein that is produced by fermentation of a genetically engineered Escherichia coli bacterium containing the DNA which encodes for uricase. The complementary DNA coding for the uricase is based on mammalian sequences. Uricase is purified and is then PEGylated with a PEGylation agent to produce the bulk medicine, pegloticase. PEGylation and purification of the active drug substance is achieved by conventional column chromatography. The resulting highly purified sterile solution is filled in a single-use vial for intravenous infusion following dilution. In support of its manufacturing process, we store multiple vials of the Escherichia coli bacterium master cell bank and working cell bank at multiple locations in order to ensure adequate backup should any cell bank be lost in a catastrophic event.

NOF Supply Agreement

In August 2015, Crealta and NOF Corporation, or NOF, in Japan, entered into an exclusive supply agreement for the PEGylation agent used in the manufacture of KRYSTEXXA. Under the terms of this agreement, we are required to issue NOF forecasts of our requirements for the PEGylation agent, a portion of which are binding. The agreement expires in August 2020, however, either we or NOF may terminate the agreement for any reason upon twenty-four months' prior notice. Either we or NOF may also terminate the agreement upon a material breach, if not cured within a specified period of time, or in the event of the other party's insolvency. While there are no minimum purchase obligations under the agreement, we are required to use NOF as our exclusive supplier for the PEGylation agent, subject to certain exceptions if NOF is unable to supply the PEGylation agent.

Bio-Technology General (Israel) Supply Agreement

In March 2007, Savient Pharmaceuticals, Inc. (as predecessor in interest to Crealta), entered into a commercial supply agreement with Bio-Technology General (Israel) Ltd, or BTG Israel, for the production of the bulk KRYSTEXXA medicine, or bulk product. We assumed this agreement as part of the Crealta acquisition and amended the agreement in September 2016. Under this agreement, we have agreed to purchase certain minimum annual order quantities and are obligated to purchase at least eighty percent of our annual world-wide bulk product requirements from BTG Israel. The term of the agreement runs until December 31, 2030, and will automatically renew for successive three year periods unless earlier terminated by either party upon three years' prior written notice. The agreement may be terminated earlier by either party in the event of a force majeure, liquidation, dissolution, bankruptcy or insolvency of the other party, uncured material breach by the other party or after January 1, 2024, upon three years' prior written notice. Under the agreement if the manufacture of the bulk product is moved out of Israel, we may be required to obtain the approval of the Israeli Office of the Chief Scientist, or OCS, because certain KRYSTEXXA intellectual property was initially developed with a grant funded by the OCS and we may be required to pay the OCS additional amounts as a repayment for the OCS grant funding. We issue eighteen-month forecasts of the volume of KRYSTEXXA that we expect to order. The first six months of the forecast are considered binding firm orders.

Exelead PharmaSource Supply Agreement

In October 2008, Savient and Exelead, Inc. (formerly known as Sigma Tau PharmaSource, Inc. (as successor in interest to Enzon Pharmaceuticals, Inc.)), or Exelead, entered into a commercial supply agreement for the packaging and supply of the final drug medicine KRYSTEXXA, which we acquired as part of the Crealta acquisition. This agreement remains in effect until terminated, and either we or Exelead may terminate the agreement with three years notice, given thirty days prior to the agreement anniversary date. Either we or Exelead may also terminate the agreement upon a material default, if not cured within a specified period of time, or in the event of the other party's insolvency or bankruptcy.

Duke University and Mountain View Pharmaceutical License Agreement

In August 1998, Savient entered into an exclusive, worldwide license agreement with Duke University, or Duke, and Mountain View Pharmaceuticals Inc., or MVP, which we acquired as part of the Crealta acquisition. Duke developed the recombinant uricase enzyme used in KRYSTEXXA and MVP developed the PEGylation technology used in the manufacture of KRYSTEXXA. Duke and MVP may terminate the agreement if we commit fraud or for our willful misconduct or illegal conduct; upon our material breach of the agreement, if not cured within a specified period of time; upon written notice if we have committed two or more material breaches under the agreement; or in the event of our bankruptcy or insolvency. Under the terms of the agreement, we are obligated to pay Duke a mid-single digit percentage royalty on our global net sales of KRYSTEXXA and a royalty of between five percent and fifteen percent on any global sublicense revenue. We are also obligated to pay MVP a mid-single digit percentage royalty on our net sales of KRYSTEXXA outside of the United States and royalty of between five percent and fifteen percent on any sublicense revenue outside of the United States. Royalties terminate upon last to expire of licensed patents on a country-by-country basis, and royalties are reduced by a mid-double digit percentage in countries that never had patents.

RAYOS/LODOTRA

We rely on well-established third-party manufacturers for the manufacture of RAYOS/LODOTRA. We purchase the API for RAYOS/LODOTRA from Tianjin Tianyao Pharmaceuticals Co., Ltd. in China and from Sanofi Chimie SA in France. We have contracted with Jagotec AG, or Jagotec, for the production of RAYOS/LODOTRA tablets through its affiliate Vectura, and we entered into an agreement with Patheon for the packaging and assembling of RAYOS/LODOTRA.

We are obligated to pay Jagotec a mid-single digit percentage royalty on our adjusted gross sales of RAYOS/LODOTRA and on any sub-licensing income, which includes any payments not calculated based on the adjusted gross sales of RAYOS/LODOTRA, such as license fees, and lump sum and milestone payments.

PENNSAID 2%

In October 2014, in connection with the acquisition of the U.S. rights to PENNSAID 2% from Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.), or Nuvo, we entered into an exclusive supply agreement with Nuvo, which was amended in February 2016, January 2017 and February 2018, under which Nuvo will manufacture and supply PENNSAID 2% to us. The term of our supply agreement is through December 31, 2029, but the agreement may be terminated earlier by either party for any uncured material breach by the other party of its obligations under the supply agreement or upon the bankruptcy or similar proceeding of the other party.

A key excipient used in PENNSAID 2% as a penetration enhancer is DMSO. We and Nuvo rely on a sole proprietary form of DMSO for which we maintain a substantial safety stock. However, should this supply become inadequate, damaged, destroyed or unusable, we and Nuvo may not be able to qualify a second source.

DUEXIS

We purchase DUEXIS in final, packaged form exclusively from Sanofi-Aventis U.S. LLC, or Sanofi, for our commercial requirements in North America. The first API in DUEXIS is ibuprofen in a direct compression blend called DC85 and is supplied to Sanofi by BASF Corporation, or BASF, in Bishop, Texas. The second API in DUEXIS is famotidine, which is available from a number of international suppliers. Famotidine is currently sourced from two manufacturers, Dr. Reddy's in India and also from Quimica Syntetica (Chemo) in Spain. We currently receive both APIs in powder form and each is blended with a number of U.S. Pharmacopeia inactive ingredients.

BASF Contract

In July 2010, we entered into a contract with BASF for the purchase of DC85, which was subsequently amended effective as of January 2016. Pursuant to the agreement, we are obligated to source a significant majority of our commercial demand for DC85 from BASF. The contract expires in December 2018 and thereafter automatically renews for a period of three years. Either party may terminate the agreement upon twelve months' written notice or in the event of uncured breach by the other party.

Manufacturing and Supply Agreement with Sanofi

In May 2011, we entered into a manufacturing and supply agreement with Sanofi, which was amended in September 2013. Pursuant to the agreement, Sanofi is obligated to manufacture and supply DUEXIS to us in final, packaged form, and we are obligated to purchase DUEXIS exclusively from Sanofi for our commercial requirements in North America and certain countries and territories in Europe, including the EU member states and Scandinavia, and South America. Sanofi must acquire the components necessary to manufacture DUEXIS, including the APIs, and is obligated to acquire all DC85 under the terms of our agreements with suppliers, including the current BASF contract. In order to allow Sanofi to perform its obligations under the agreement, we granted Sanofi a non-exclusive license to our related intellectual property. The agreement term extends until May 2019, and automatically extends for successive two-year terms unless terminated by either party upon two years' prior written notice. Either party may terminate the agreement upon thirty days' prior written notice to the other party in the event of breach by the other party that is not cured within thirty days of notice (which notice period may be longer in certain, limited situations) or in the event we lose regulatory approval to market DUEXIS in all countries worldwide, and either party may terminate the agreement without cause upon two years' prior written notice to the other party at any time after the third anniversary of the first commercial sale of DUEXIS in any country worldwide.

VIMOVO

We purchase VIMOVO in final, packaged form from Patheon for our commercial requirements in North America. The first API in VIMOVO is naproxen which is supplied to Patheon by Divis Laboratories Limited in India. The second API in VIMOVO is esomeprazole magnesium trihydrate, which we source from Minakem Holding SAS in France.

Under a license agreement with Aralez Pharmaceuticals Inc., or Aralez, we are required to pay Aralez a ten percent royalty based on net sales of VIMOVO sold by us, our affiliates or sublicensees during the royalty term, subject to a minimum annual royalty obligation of $7.5 million, which minimum royalty obligations will continue for each year during which one of Aralez's patents covers such medicines in the United States and there are no competing medicines in the United States. The royalty rate may be reduced to a mid-single digit royalty rate as a result of loss of market share to competing medicines.

MIGERGOT

MIGERGOT drug product is ergotamine tartrate and caffeine-containing suppositories. G&W Laboratories Inc., or G&W, performs the sourcing and procurement of the APIs, ergotamine tartrate and caffeine. MIGERGOT drug product is manufactured by G&W in South Plainfield, New Jersey under a supply agreement that expires on December 31, 2023.

Intellectual Property

Our objective is to aggressively patent the technology, inventions and improvements that we consider important to the development of our business. We have a portfolio of patents and applications based on clinical and pharmacokinetic/pharmacodynamic modeling discoveries, and our novel formulations. We intend to continue filing patent applications seeking intellectual property protection as we generate anticipated formulation refinements, new methods of manufacturing and clinical trial results.

We will only be able to protect our technologies and medicines from unauthorized use by third parties to the extent that valid and enforceable patents or trade secrets cover them. As such, our commercial success will depend in part on receiving and maintaining patent protection and trade secret protection of our technologies and medicines as well as successfully defending these patents against third-party challenges.

The patent positions of life sciences companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in such companies' patents has emerged to date in the United States. The patent situation outside the United States is even more uncertain. Changes in either the patent laws or in interpretations of patent laws in the United States or other countries may diminish the value of our intellectual property. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in our patents or in third-party patents. For example:

- we or our licensors might not have been the first to make the inventions covered by each of our pending patent applications and issued patents;
- we or our licensors might not have been the first to file patent applications for these inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies;
- it is possible that none of our pending patent applications or the pending patent applications of our licensors will result in issued patents;
- our issued patents and the issued patents of our licensors may not provide a basis for commercially viable drugs, or may not provide us with any competitive advantages, or may be challenged and invalidated by third parties;
- we may not be successful in any patent litigation to enforce our patent rights, including our pending patent litigation regarding PENNSAID 2%, RAVICTI and/or VIMOVO;
- we may not develop additional proprietary technologies or medicine candidates that are patentable; or
- the patents of others may have an adverse effect on our business.

RAVICTI

We have ownership of U.S. and foreign patents and patent applications covering RAVICTI. If not otherwise invalidated, those patents expire between 2030 and 2032. We also have an exclusive license to U.S. and foreign patents from Brusilow covering RAVICTI which expire in the United States in 2018 and if extended, in certain countries in Europe in 2021. We continue to prosecute and pursue patent protection to obtain additional patent coverage on RAVICTI and its uses.

In the United States, RAVICTI has been granted seven years of orphan drug exclusivity, which will expire in 2020. In the EU, RAVICTI received ten years of marketing exclusivity protection, beginning with its December 2015 marketing authorization.

PROCYSBI

We have U.S. and foreign patents and patent applications covering PROCYSBI, as well as licenses from UCSD to U.S. and foreign patents and patent applications covering PROCYSBI. If not otherwise invalidated, those patents expire between 2027 and 2034. We continue to prosecute and pursue patent protection to obtain additional patent coverage on PROCYSBI and its uses.

PROCYSBI received marketing authorization in September 2013 from the European Communities, or the EC, for marketing in the EU as an orphan medicinal product for the management of proven nephropathic cystinosis.

PROCYSBI received seven years of market exclusivity, through 2020, for patients six years and older as an orphan drug in the United States, and ten years of market exclusivity, through 2023, as an orphan drug in Europe. PROCYSBI received seven years of market exclusivity, through 2022, for patients two years of age to less than six years of age, and seven years of market exclusivity, through 2024, for patients one year of age to less than two years of age, as an orphan drug in the United States. During December 2017, the FDA awarded pediatric exclusivity to PROCYSBI in the United States, which adds an additional six month exclusivity period to the end of each orphan exclusivity period and patent term covering PROCYSBI.

ACTIMMUNE

We have licenses to U.S. patents covering ACTIMMUNE. If not otherwise invalidated, those patents expire in 2022. We continue to prosecute and pursue patent protection to obtain additional patent coverage on ACTIMMUNE and its uses.

QUINSAIR

We have U.S. and foreign patents and patent applications covering QUINSAIR, as well as licenses from PARI to U.S. and foreign patents and patent applications covering QUINSAIR. If not otherwise invalidated, those patents expire between 2020 and 2037. We continue to prosecute and pursue patent protection to obtain additional patent coverage on QUINSAIR and its uses.

QUINSAIR received ten years of market exclusivity in the EU, beginning with its March 2015 marketing authorization.

KRYSTEXXA

We have licenses to U.S. and foreign patents and applications covering KRYSTEXXA. If not otherwise invalidated, those patents expire between 2019 and 2030. We continue to prosecute and pursue patent protection to obtain additional patent coverage on KRYSTEXXA and its uses.

In the United States, KRYSTEXXA has received twelve years of biologic exclusivity, expiring in 2022.

RAYOS/LODOTRA

We have an exclusive license to U.S. and foreign patents and patent applications from Vectura covering RAYOS/LODOTRA. If not otherwise invalidated, those in-licensed patents expire between 2024 and 2028. We continue to prosecute and pursue additional patent coverage on RAYOS/LODOTRA and its uses. However, under our settlement agreement with Teva Pharmaceuticals Industries Limited (formerly known as Actavis Laboratories FL, Inc., which itself was formerly known as Watson Laboratories, Inc. – Florida), or Teva, Teva may enter the market on December 23, 2022, or earlier under certain circumstances.

In the EU, LODOTRA has received ten years of marketing exclusivity protection, beginning with its March 2009 marketing authorization in Germany.

PENNSAID 2%

We have ownership of U.S. patents and patent applications covering PENNSAID 2% from Nuvo. We also co-own other U.S. patent applications with Mallinckrodt LLC. If not otherwise invalidated, those patents expire between 2027 and 2030. However, under our settlement agreements with Perrigo Company plc, or Perrigo, Taro Pharmaceuticals USA, Inc. and Taro Pharmaceutical Industries, Ltd., or collectively Taro, Amneal Pharmaceuticals LLC, or Amneal, and Teligent, Inc., or Teligent, Perrigo, Taro, Amneal, and/or Teligent may enter the market on January 10, 2029, or earlier under certain circumstances. We continue to prosecute and pursue patent protection in the United States to obtain additional patent coverage on PENNSAID 2% and its uses.

DUEXIS

We have multiple patents and patent applications related to DUEXIS. Unless otherwise invalidated, those patents expire in 2026. However, under a settlement agreement with Par Pharmaceutical, Inc. and Par Pharmaceutical Companies, Inc., or collectively Par, Par may enter the market on January 1, 2023, or earlier under certain circumstances.

VIMOVO

We have licenses to U.S. patents and patent applications and trademarks covering VIMOVO from Aralez and AstraZeneca AB. We co-own other U.S. patents and patent applications with Aralez. If not otherwise invalidated, those in-licensed patents expire between 2018 and 2031. We continue to prosecute and pursue patent protection in the United States to obtain additional patent coverage on VIMOVO and its uses.

For a description of our legal proceedings related to intellectual property matters, see Note 19 of the Notes to consolidated financial statements, included in Item 15 of this Annual Report on Form 10-K.

Customers and Information About Geographic Areas

Information regarding our total revenues by product, attributed to U.S and non-U.S. sources and attributed to customers who represented at least 10% of our total revenues in each of the years ended December 31, 2017, 2016 and 2015, as well as the location of our long-lived assets, is included in Note 14 of the Notes to consolidated financial statements, included in Item 15 of this Annual Report on Form 10-K.

Third-Party Coverage and Reimbursement

In both U.S. and foreign markets, our ability to commercialize our medicines successfully depends in significant part on the availability of coverage and adequate reimbursement to healthcare providers from third-party payers, including, in the United States, government payers such as the Medicare and Medicaid programs, managed care organizations and private health insurers. Third-party payers are increasingly challenging the prices charged for medicines and examining their cost effectiveness, in addition to their safety and efficacy. This is especially true in markets where over-the-counter and generic options exist. Even if coverage is made available by a third-party payer, the reimbursement rates paid for covered medicines might not be adequate. For example, third-party payers may use tiered coverage and may adversely affect demand for our medicines by not covering our medicines or by placing them in a more expensive formulary tier relative to competitive medicines (where patients have to pay relatively more out of pocket than for medicines in a lower tier). We cannot be certain that our medicines will be covered by third-party payers or that such coverage, where available, will be adequate, or that our medicines will successfully be placed on the list of drugs covered by particular health plan formularies. Many states have also created preferred drug lists and include drugs on those lists only when the manufacturers agree to pay a supplemental rebate. The industry competition to be included on such formularies and preferred drug lists often leads to downward pricing pressures on pharmaceutical companies. Also, third-party payers may refuse to include a particular branded drug on their formularies or otherwise restrict patient access to a branded drug when a less costly generic equivalent or other therapeutic alternative is available. In addition, because each third-party payer individually approves coverage and reimbursement levels, obtaining coverage and adequate reimbursement is a time-consuming and costly process. We may be required to provide scientific and clinical support for the use of any medicine to each third-party payer separately with no assurance that approval would be obtained, and we may need to conduct pharmacoeconomic studies to demonstrate the cost effectiveness of our medicines for formulary coverage and reimbursement. Even with studies, our medicines may be considered less safe, less effective or less cost-effective than competitive medicines, and third-party payers may not provide coverage and adequate reimbursement for our medicines or our medicine candidates. These pricing and reimbursement pressures may create negative perceptions to any medicine price increases, or limit the amount we may be able to increase our medicine prices, which may adversely affect our medicine sales and results of operations. Where coverage and reimbursement are not adequate, physicians may limit how much or under what circumstances they will prescribe or administer such medicines, and patients may decline to purchase them. This, in turn, could affect our ability to successfully commercialize our medicines and impact our profitability, results of operations, financial condition, and future success.

The U.S. market has seen a trend in which retail pharmacies have become increasingly involved in determining which prescriptions will be filled with the requested medicine or a substitute medicine, based on a number of factors, including potentially perceived medicine costs and benefits, as well as payer medicine substitution policies. Many states have in place requirements for prescribers to indicate “dispense as written” on their prescriptions if they do not want pharmacies to make medicine substitutions; these requirements are varied and not consistent across states. We may need to increasingly spend time and resources to ensure the prescriptions written for our medicines are filled as written, where appropriate.

Coverage policies, third-party reimbursement rates and medicine pricing regulation have been subject to significant change, and may change further at any time, particularly given recent political focus on the pharmaceutical industry. Even if favorable coverage and adequate reimbursement status is attained for one or more medicines, less favorable coverage policies and reimbursement rates may be implemented in the future.

Government Regulation

The FDA and comparable regulatory agencies in state and local jurisdictions and in foreign countries impose extensive requirements upon the clinical development, pre-market approval, manufacture, labeling, marketing, promotion, pricing, import, export, storage and distribution of medicines. These agencies and other regulatory agencies regulate research and development activities and the testing, approval, manufacture, quality control, safety, effectiveness, labeling, storage, recordkeeping, advertising and promotion of drugs and biologics. Failure to comply with applicable FDA or foreign regulatory agency requirements may result in warning letters, fines, civil or criminal penalties, additional reporting obligations and/or agency oversight, suspension or delays in clinical development, recall or seizure of medicines, partial or total suspension of production or withdrawal of a medicine from the market.

In the United States, the FDA regulates drug products under the Federal Food, Drug, and Cosmetic Act and its implementing regulations and biologics additionally under the Public Health Service Act. The process required by the FDA before medicine candidates may be marketed in the United States generally involves the following:

- submission to the FDA of an investigational new drug, or IND, which must become effective before human clinical trials may begin and must be updated annually;
- completion of extensive pre-clinical laboratory tests and pre-clinical animal studies, all performed in accordance with the FDA's Good Laboratory Practice, or GLP, regulations;
- performance of adequate and well-controlled human clinical trials to establish the safety and efficacy of the medicine candidate for each proposed indication;
- submission to the FDA of a new drug application, or NDA, or biologics license application, or BLA, as appropriate, after completion of all pivotal clinical trials to demonstrate the safety, purity and potency of the medicine candidate for the indication for use;
- a determination by the FDA within sixty days of its receipt of an NDA or BLA to file the application for review;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facilities to assess compliance with the FDA's current good manufacturing practices, or cGMPs, regulations for pharmaceuticals; and
- FDA review and approval of an NDA or BLA prior to any commercial marketing or sale of the medicine in the United States.

The development and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our medicine candidates will be granted on a timely basis, if at all.

The results of pre-clinical tests (which include laboratory evaluation as well as GLP studies to evaluate toxicity in animals) for a particular medicine candidate, together with related manufacturing information and analytical data, are submitted as part of an IND to the FDA. The IND automatically becomes effective thirty days after receipt by the FDA, unless the FDA, within the thirty-day time period, raises concerns or questions about the conduct of the proposed clinical trial, including concerns that human research subjects will be exposed to unreasonable health risks. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. IND submissions may not result in FDA authorization to commence a clinical trial. A separate submission to an existing IND must also be made for each successive clinical trial conducted during medicine development. Further, an independent institutional review board, or IRB, for each medical center proposing to conduct the clinical trial must review and approve the plan for any clinical trial before it commences at that center and it must monitor the study until completed. The FDA, the IRB or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk. Clinical testing also must satisfy extensive good clinical practice regulations and regulations for informed consent and privacy of individually identifiable information. Similar requirements to the U.S. IND are required in the European Economic Area, or the EEA, and other jurisdictions in which we may conduct clinical trials.

Clinical Trials. For purposes of NDA or BLA submission and approval, clinical trials are typically conducted in the following sequential phases, which may overlap:

- *Phase 1*. Studies are initially conducted in a limited population to test the medicine candidate for safety, dose tolerance, absorption, distribution, metabolism, and excretion, typically in healthy humans, but in some cases in patients.
- *Phase 2*. Studies are generally conducted in a limited patient population to identify possible adverse effects and safety risks, explore the initial efficacy of the medicine for specific targeted indications and to determine dose range or pharmacodynamics. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more expensive Phase 3 clinical trials.

- *Phase 3*. These are commonly referred to as pivotal studies. When Phase 2 evaluations demonstrate that a dose range of the medicine is effective and has an acceptable safety profile, Phase 3 clinical trials are undertaken in large patient populations to further evaluate dosage, provide substantial evidence of clinical efficacy and further test for safety in an expanded and diverse patient population at multiple, geographically dispersed clinical trial centers.
- *Phase 4*. The FDA may approve an NDA or BLA for a medicine candidate, but require that the sponsor conduct additional clinical trials to further assess the medicine after approval under a post-marketing commitment or post- marketing requirement. In addition, a sponsor may decide to conduct additional clinical trials after the FDA has approved a medicine. Post-approval trials are typically referred to as Phase 4 clinical trials.

The results of drug development, pre-clinical studies and clinical trials are submitted to the FDA as part of an NDA or BLA, as appropriate. Applications also must contain extensive chemistry, manufacturing and control information. Applications must be accompanied by a significant user fee. Once the submission has been accepted for filing, the FDA's goal is to review applications within twelve months of submission or, if the application relates to an unmet medical need in a serious or life-threatening indication, eight months from submission. The review process is often significantly extended by FDA requests for additional information or clarification. The FDA will typically conduct a pre-approval inspection of the manufacturer to ensure that the medicine can be reliably produced in compliance with cGMPs and will typically inspect certain clinical trial sites for compliance with good clinical practice, or GCP. The FDA may refer the application to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it typically follows such recommendations. The FDA may deny approval of an application by issuing a Complete Response Letter if the applicable regulatory criteria are not satisfied. A Complete Response Letter may require additional clinical data and/or trial(s), and/or other significant, expensive and time- consuming requirements related to clinical trials, pre-clinical studies or manufacturing. Data from clinical trials are not always conclusive and the FDA may interpret data differently than we or our collaborators interpret data. Approval may occur with boxed warnings on medicine labeling or Risk Evaluation and Mitigation Strategies, or REMS, which limit the labeling, distribution or promotion of a medicine. Once issued, the FDA may withdraw medicine approval if ongoing regulatory requirements are not met or if safety problems occur after the medicine reaches the market. In addition, the FDA may require testing, including Phase 4 clinical trials, and surveillance programs to monitor the safety effects of approved medicines which have been commercialized and the FDA has the power to prevent or limit further marketing of a medicine based on the results of these post-marketing programs or other information.

Orphan Medicines. Under the Orphan Drug Act, the FDA may designate a medicine as an "orphan drug" if it is intended to treat a rare disease or condition, meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a medicine available in the United States for treatment of the disease or condition will be recovered from sales of the medicine. A company must request orphan drug designation before submitting an NDA for the drug and rare disease or condition. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan drug designation does not shorten the Prescription Drug User Fee Act, or PDUFA, goal dates for the regulatory review and approval process, although it does convey certain advantages such as tax benefits and exemption from the PDUFA application fee.

If a medicine with orphan designation receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the medicine generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor's marketing application for the same drug for the same indication for seven years, except in certain limited circumstances. Orphan exclusivity does not block the approval of a different drug for the same rare disease or condition, nor does it block the approval of the same drug for different indications. If a drug designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity. Orphan exclusivity will not bar approval of another medicine under certain circumstances, including if a subsequent medicine with the same drug for the same indication is shown to be clinically superior to the approved medicine on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand.

In the EU, Regulation (EC) No 141/2000 and Regulation (EC) No. 847/2000 provide that a medicine can be designated as an orphan medicinal product by the EC if its sponsor can establish: that the medicine is intended for the diagnosis, prevention or treatment of (1) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the EU when the application is made, or (2) a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives the medicinal product is unlikely to be developed. For either of these conditions, the applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the EU or, if such method exists, the medicinal product will be of significant benefit to those affected by that condition. Once authorized, orphan medicinal products are entitled to ten years of market exclusivity in all EU Member States (extendable to twelve years for medicines that have complied with an agreed pediatric investigation plan pursuant to Regulation 1901/2006) and in addition a range of other benefits during the development and regulatory review process including scientific assistance for study protocols, authorization through the centralized marketing authorization procedure covering all member countries and a reduction or elimination of registration and marketing authorization fees. However, marketing authorization may be granted to a similar medicinal product with the same orphan indication during the ten year period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if this medicine is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if, at the end of the fifth year, it can be demonstrated on the basis of available evidence that the criteria for its designation as an orphan medicine are no longer satisfied, for example if the original orphan medicinal product has become sufficiently profitable not to justify maintenance of market exclusivity.

Other Regulatory Requirements. Medicines manufactured or distributed pursuant to FDA approvals are subject to continuing regulation by the FDA, including recordkeeping, annual medicine quality review, payment of program fees and reporting requirements. Adverse event experience with the medicine must be reported to the FDA in a timely fashion and pharmacovigilance programs to proactively look for these adverse events are mandated by the FDA. Our medicines may be subject to REMS requirements that affect labeling, distribution or post market reporting. Drug manufacturers and their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMPs, which impose certain procedural and documentation requirements upon us and our third-party manufacturers. Following such inspections, the FDA may issue notices on Form 483 and Untitled Letters or warning letters that could cause us or our third-party manufacturers to modify certain activities. A Form 483 notice, if issued at the conclusion of an FDA inspection, can list conditions the FDA investigators believe may have violated cGMP or other FDA regulations or guidelines. In addition to Form 483 notices and Untitled Letters, failure to comply with the statutory and regulatory requirements can subject a manufacturer to possible legal or regulatory action, such as suspension of manufacturing, seizure of medicine, injunctive action, additional reporting requirements and/or oversight by the agency, import alert or possible civil penalties. The FDA may also require us to recall a drug from distribution or withdraw approval for that medicine.

The FDA closely regulates the post-approval marketing and promotion of pharmaceuticals, including standards and regulations for direct-to-consumer advertising, dissemination of off-label information, industry-sponsored scientific and educational activities and promotional activities involving the Internet, including certain social media activities. Medicines may be marketed only for the approved indications and in accordance with the provisions of the approved label. Further, if there are any modifications to the medicine, including changes in indications, labeling, or manufacturing processes or facilities, we may be required to submit and obtain FDA approval of a new or supplemental application, which may require us to develop additional data or conduct additional pre-clinical studies and clinical trials. Failure to comply with these requirements can result in adverse publicity, Untitled letters, corrective advertising and potential administrative, civil and criminal penalties, as well as damages, fines, withdrawal of regulatory approval, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs, additional reporting requirements and/or oversight by the agency, and imprisonment, any of which could adversely affect our ability to sell our medicines or operate our business and also adversely affect our financial results.

Physicians may, in their independent medical judgment, prescribe legally available pharmaceuticals for uses that are not described in the medicine's labeling and that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, impose stringent restrictions on manufacturers' communications regarding off-label use. Additionally, a significant number of pharmaceutical companies have been the target of inquiries and investigations by various U.S. federal and state regulatory, investigative, prosecutorial and administrative entities in connection with the promotion of medicines for off-label uses and other sales practices. These investigations have alleged violations of various U.S. federal and state laws and regulations, including claims asserting antitrust violations, violations of the Food, Drug and Cosmetic Act, false claims laws, the Prescription Drug Marketing Act, or PDMA, anti-kickback laws, and other alleged violations in connection with the promotion of medicines for unapproved uses, pricing and Medicare and/or Medicaid reimbursement. If our promotional activities, including any promotional activities that a contracted sales force may perform on our behalf, fail to comply with these regulations or guidelines, we may be subject to warnings from, or enforcement action by, these authorities. In addition, our failure to follow FDA rules and guidelines relating to promotion and advertising may cause the FDA to issue warning letters or untitled letters, suspend or withdraw an approved medicine from the market, require corrective advertising or a recall or institute fines or civil fines, additional reporting requirements and/or oversight or could result in disgorgement of money, operating restrictions, injunctions or criminal prosecution, any of which could harm our business. In addition, the distribution of prescription medicines is subject to the PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription medicine samples and impose requirements to ensure accountability in distribution, including a drug pedigree which tracks the distribution of prescription drugs. Further, under the Drug Quality and Security Act, drug manufacturers are subject to a number of requirements, including, medicine identification, tracing and verification, among others, that are designed to detect and remove counterfeit, stolen, contaminated or otherwise potentially harmful drugs from the U.S. drug supply chain. These requirements will be phased in over several years and compliance will likely increase the costs of the manufacture and distribution of drug medicines.

Outside the United States, the ability of our partners and us to market a medicine is contingent upon obtaining marketing authorization from the appropriate regulatory authorities. The requirements governing marketing authorization, pricing and reimbursement vary widely from country to country and region to region.

The EU and the EEA consist of the twenty-eight Member States of the EU, plus Norway, Iceland and Liechtenstein which are Member States of the EEA. These Member States have all acceded to the single market rules governing the supervision of medicinal products. Under the prevailing rules, medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. There are three procedures for an MA to be obtained:

- the Centralized MA, which is issued by the EC through the Centralized Procedure, based on the scientific opinion of the Committee for Medicinal Products for Human Use of the EMA, and which is valid throughout the entire territory of the EU/EEA. When decisions on granting of a Centralized MA are taken by the EU, the EEA Member States will take corresponding decisions on the basis the relevant acts to permit marketing of medicinal products. The Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products, and medicinal products containing a new active substance indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune and viral diseases. The Centralized Procedure is optional for products containing a new active substance not yet authorized in the EU/EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU.
- Decentralized Procedure MAs are available for products not falling within the mandatory scope of the Centralized Procedure. An identical dossier is submitted to the competent authorities of each of the Member States in which the MA is sought, one of which is selected by the applicant as the Reference Member State, or RMS, to lead the evaluation of the regulatory submission. The competent authority of the RMS prepares a draft assessment report, a draft summary of the product characteristics, or SmPC, and a draft of the labeling and package leaflet as distilled from the preliminary evaluation, which are sent to the other Member States (referred to as the Concerned Member States, or CMS) for their approval. If the CMS raise no objections, based on a potential serious risk to public health, to the assessment, SmPC, labeling, or packaging proposed by the RMS, the RMS records the agreement, closes the procedure and informs the applicant accordingly. Each Member State concerned by the procedure is required to adopt a national decision to grant a national MA in conformity with the approved assessment report, SmPC and the labeling and package leaflet as approved. Where a product has already been authorized for marketing in a Member State of the EEA, the granted national MA can be used for mutual recognition in other Member States through the Mutual Recognition Procedure, or MRP, resulting in progressive national approval of the product in the EU/EEA.

- National MAs, which are issued by a single competent authority of the Member States of the EEA and only covers their respective territory, are also available for products not falling within the mandatory scope of the Centralized Procedure. Once a product has been authorized for marketing in a Member State of the EEA through the National Procedure, this National MA can also be recognized in other Member States through the MRP.

Under the procedures described above, before granting the MA, the EMA or the competent authority(ies) of the Member State(s) of the EEA prepare an assessment of the risk-benefit balance of the product against the scientific criteria concerning its quality, safety and efficacy.

Under Regulation (EC) No 726/2004/EC and Directive 2001/83/EC (each as amended), the EU has adopted a harmonized approach to data and market protection or exclusivity (known as the 8 + 2 + 1 formula). The data exclusivity period begins to run on the date when the first MA is granted in the EU. It confers on the MA holder of the reference medicinal product eight years of data protection and ten years of market protection. A reference medicinal product is defined to mean a medicinal product authorized based on a full dossier consisting of pharmaceutical and pre-clinical testing results and clinical trial data, such as a medicinal product containing a new active substance. The ten-year market protection can be extended cumulatively to a maximum period of eleven years if during the first eight years of those ten years of protection period, the MA holder obtains an authorization for one or more new therapeutic indications that are deemed to bring a significant clinical benefit compared to existing therapies.

The protection period means that an applicant for a generic medicinal product is not permitted to rely on pre-clinical pharmacological, toxicological, and clinical data contained in the file of the reference medicinal product of the originator until the first eight years of data protection have expired. Thereafter, a generic product application may be submitted and generic companies may rely on the pre-clinical and clinical data relating to the reference medicinal product to support approval of the generic product. However, a generic cannot market until ten years have elapsed from the initial authorization of the reference medicinal product or eleven years if the protection period is extended, based on the formula of 8+2+1.

In addition to the above, where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication. Finally, where a change of classification of a medicinal product has been authorized on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorization for a change of classification of the same substance for one year after the initial change was authorized.

The 8 + 2 + 1 exclusivity scheme applies to products that have been authorized in the EU by either the EMA through the Centralized Procedure or the competent authorities of the Member States of the EEA nationally, including through the Decentralized and Mutual Recognition procedures.

For a medicinal product which is designated as orphan under Regulation 141/2000, it will benefit from a period of ten years of orphan market exclusivity which essentially constitutes a period of market monopoly. During this period of orphan market exclusivity, no EU regulatory authority is permitted to accept or approve an application for marketing authorization for a similar medicinal product or an extension application for the same therapeutic indication. This period can be extended cumulatively to a total of twelve years if the marketing authorization holder or applicant complies with the requirements for an agreed pediatric investigation plan pursuant to Regulation 1901/2006.

The holder of a Centralized MA or National MA is subject to various obligations under the applicable EU laws, such as pharmacovigilance obligations, requiring it to, among other things, report and maintain detailed records of adverse reactions, and to submit periodic safety update reports to the competent authorities. The holder must also ensure that the manufacturing and batch release of its product is in compliance with the applicable requirements. The MA holder is further obligated to ensure that the advertising and promotion of its products complies with applicable EU laws and industry code of practice as implemented in the domestic laws of the Member States of the EU/EEA. The advertising and promotional rules are enforced nationally by the EU/EEA Member States.

Healthcare Fraud and Abuse Laws. As a pharmaceutical company, certain federal and state healthcare laws and regulations pertaining to fraud and abuse and patients' rights are and will be applicable to our business. We may be subject to various federal and state laws targeting fraud and abuse in the healthcare industry. For example, in the United States, there are federal and state anti-kickback laws that prohibit the payment or receipt of kickbacks, bribes or other remuneration intended to induce the purchase or recommendation of healthcare products and services or reward past purchases or recommendations. Violations of these laws can lead to civil and criminal penalties, including fines, imprisonment, additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement, and exclusion from participation in federal healthcare programs. These laws are applicable to manufacturers of products regulated by the FDA, such as us, and pharmacies, hospitals, physicians and other potential purchasers of such products.

The federal Anti-Kickback Statute prohibits persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, to induce either the referral of an individual, or the furnishing, recommending, or arranging for a good or service, for which payment may be made under a federal healthcare program, such as the Medicare and Medicaid programs. The term "remuneration" is defined as any remuneration, direct or indirect, overt or covert, in cash or in kind, and has been broadly interpreted to include anything of value, including for example, gifts, discounts, the furnishing of supplies or equipment, credit arrangements, payments of cash, waivers of payment, ownership interests and providing anything at less than its fair market value. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute may have been violated, and enforcement will depend on the relevant facts and circumstances. The Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the ACA, among other things, amended the intent requirement of the federal Anti-Kickback Statute to state that a person or entity need not have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the ACA provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act (discussed below) or the civil monetary penalties statute, which imposes penalties against any person who is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent, or to have offered improper inducements to federal health care program beneficiaries to select a particular provider or supplier. The federal Anti-Kickback Statute is broad, and despite a series of narrow safe harbors, prohibits many arrangements and practices that are lawful in businesses outside of the healthcare industry. Many states have also adopted laws similar to the federal Anti-Kickback Statute, some of which apply to the referral of patients for healthcare items or services reimbursed by any source, not only the Medicare and Medicaid programs, and do not contain identical safe harbors. In addition, where such activities involve foreign government officials, they may also potentially be subject to the Foreign Corrupt Practices Act. Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities, including our activities with physician customers, pharmacies, and patients, as well as our activities pursuant to partnerships with other companies and pursuant to contracts with contract research organizations, could be subject to challenge under one or more of such laws.

The federal False Claims Act prohibits any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. A claim includes "any request or demand" for money or property presented to the U.S. government. In addition, the ACA specified that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act. The federal False Claims Act has been the basis for numerous enforcement actions and settlements by pharmaceutical and other healthcare companies in connection with various alleged financial relationships with customers. In addition, a number of pharmaceutical manufacturers have reached substantial financial settlements in connection with allegedly causing false claims to be submitted because of the companies' marketing of products for unapproved, and thus non-reimbursable, uses. Certain marketing practices, including off-label promotion, may also violate false claims laws, as might violations of the federal physician self-referral laws, such as the Stark laws, which prohibit a physician from making a referral to certain designated health services with which the physician or the physician's family member has a financial interest and prohibit submission of a claim for reimbursement pursuant to the prohibited referral. The "qui tam" provisions of the False Claims Act allow a private individual to bring civil actions on behalf of the federal government alleging that the defendant has submitted a false claim to the federal government, and to share in any monetary recovery. In addition, various states have enacted similar fraud and abuse statutes or regulations, including, without limitation, false claims laws analogous to the False Claims Act, and laws analogous to the federal Anti-Kickback Statute, that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payer, and there are also federal criminal false claims laws.

Separately, there are a number of other fraud and abuse laws that pharmaceutical manufacturers must be mindful of, particularly after a medicine candidate has been approved for marketing in the United States. For example, a federal criminal law enacted as part of, the Health Insurance Portability and Accountability Act of 1996, or HIPAA, prohibits knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payers. The false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. There are also federal civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payers that are false or fraudulent, as well as federal and state consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

Healthcare Privacy and Security Laws. We may be subject to, or our marketing activities may be limited by, HIPAA, as amended by the Health Information Technology and Clinical Health Act and their respective implementing regulations, which established uniform standards for certain "covered entities" (healthcare providers, health plans and healthcare clearinghouses) governing the conduct of certain electronic healthcare transactions and protecting the security and privacy of protected health information. Among other things, HIPAA's privacy and security standards are directly applicable to "business associates" — independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. In addition to possible civil and criminal penalties for violations, state attorneys general are authorized to file civil actions for damages or injunctions in federal courts to enforce HIPAA and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. In the EU/EEA, Directive 95/46/EC (as amended) applies to identified or identifiable personal data processed by automated means (for example, a computer database of customers) and data contained in, or intended to be part of, non-automated filing systems (traditional paper files) as well as transfer of such data to a country outside of the EU/EEA. Effective as of May 25, 2018, Directive 95/46/EC will be replaced by the EU General Data Protection Regulation (2016/679), or GDPR. Under the GDPR, fines of up to €20.0 million or up to 4% of the annual global turnover of the infringer, whichever is greater, could be imposed for significant non-compliance.

"Sunshine" and Marketing Disclosure Laws. There are an increasing number of federal and state "sunshine" laws that require pharmaceutical manufacturers to make reports to states on pricing and marketing information. Several states have enacted legislation requiring pharmaceutical companies to, among other things, establish marketing compliance programs, file periodic reports with the state, and make periodic public disclosures on sales and marketing activities, and prohibiting certain other sales and marketing practices. In addition, a similar federal requirement requires manufacturers, including pharmaceutical manufacturers, to track and report to the federal government certain payments and other transfers of value made to physicians and other healthcare professionals and teaching hospitals and ownership or investment interests held by physicians and their immediate family members. The federal government began disclosing the reported information on a publicly available website in 2014. Certain states, such as Massachusetts, also make the reported information publicly available. In addition, there are state and local laws that require pharmaceutical representatives to be licensed and comply with codes of conduct, transparency reporting, and other obligations. These laws may adversely affect our sales, marketing, and other activities with respect to our medicines in the United States by imposing administrative and compliance burdens on us. If we fail to track and report as required by these laws or otherwise comply with these laws, we could be subject to the penalty provisions of the pertinent state and federal authorities. In the EU/EEA, declaration of transfers of value to healthcare professionals is subject to the requirements under the voluntary industry code of practice. France however has a statutory regime similar to the U.S. Sunshine Act.

Government Price Reporting. For those marketed medicines which are covered in the United States by the Medicaid programs, we have various obligations, including government price reporting and rebate requirements, which generally require medicines be offered at substantial rebates/discounts to Medicaid and certain purchasers (including "covered entities" purchasing under the 340B Drug Discount Program). We are also required to discount such medicines to authorized users of the Federal Supply Schedule of the General Services Administration, under which additional laws and requirements apply. These programs require submission of pricing data and calculation of discounts and rebates pursuant to complex statutory formulas, as well as the entry into government procurement contracts governed by the Federal Acquisition Regulations, and the guidance governing such calculations is not always clear. Compliance with such requirements can require significant investment in personnel, systems and resources, but failure to properly calculate our prices, or offer required discounts or rebates could subject us to substantial penalties. One component of the rebate and discount calculations under the Medicaid and 340B programs, respectively, is the "additional rebate", a complex calculation which is based, in part, on the rate at which a branded drug price increases over time more than the rate of inflation (based on the Consumer Price Index for All Urban Consumers). This comparison is based on the baseline pricing data for the first full quarter of sales associated with a branded drug's NDA, and baseline data cannot generally be reset, even on transfer of the NDA to another manufacturer. This "additional rebate" calculation can, in some cases where price increase have been relatively high versus the first quarter of sales of the NDA, result in Medicaid rebates up to 100 percent of a drug's "average manufacturer price" and 340B prices of one penny. Subject to the control of Directive 89/105/EEC, pricing and reimbursement in the EU/EEA is governed by national rules and policy and may vary from Member State to Member State.

In General. Because of the breadth of these laws and the narrowness of available statutory and regulatory exemptions, it is possible that some of our business activities in the United States could be subject to challenge under one or more of such laws. Moreover, state governmental agencies may propose or enact laws and regulations that extend or contradict federal requirements. If we or our operations are found to be in violation of any of the state or federal laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including significant civil and criminal penalties, damages, fines, imprisonment, exclusion from participation in U.S. federal or state healthcare programs, additional reporting requirements and/or oversight and the curtailment or restructuring of our operations. To the extent that any medicine we make is sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals. Any penalties, damages, fines, curtailment or restructuring of our operations could materially adversely affect our ability to operate our business and our financial results. Although compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. Moreover, achieving and sustaining compliance with applicable federal, state and foreign privacy, security, sunshine, government price reporting, and fraud laws may prove costly.

Impact of Healthcare Reform and Recent Public Scrutiny of Specialty Drug Pricing on Coverage, Reimbursement, and Pricing. In the United States and other potentially significant markets for our medicines, federal and state authorities as well as third-party payers are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative medicines and therapies, which has resulted in lower average net selling prices. Further, there is increased scrutiny of prescription drug pricing practices by federal and state lawmakers and enforcement authorities. In addition, there is an emphasis on managed healthcare in the United States and on country-specific and regional pricing and reimbursement controls in the EU, both of which will put additional pressure on medicine pricing, reimbursement and usage, which may adversely affect our future medicine sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical reimbursement policies and pricing in general.

The U.S. and some foreign jurisdictions are considering or have enacted a number of additional legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our medicines profitably. Among policy makers and payers in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs (including a number of proposals pertaining to prescription drugs, specifically), improving quality and/or expanding access. At the federal level, the Trump administration's budget proposal for fiscal year 2019 contains further drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid and to eliminate cost sharing for generic drugs for low-income patients. While any proposed measures will require Congress to pass legislation to become effective, these provisions reinforce the administration's focus on controlling drug prices. At the state level, in Massachusetts, the MassHealth program has requested permission from the federal government to use commercial tools, such as a closed formulary, to negotiate more favorable rebate agreements from drug manufacturers. There also has been particular and increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices over the course of 2016 and 2017, particularly with respect to drugs that have been subject to relatively large price increases over relatively short time periods. There have been several recent state and federal lawmaker inquiries and proposed legislation as was the case in California designed to, among other things, bring more transparency to drug pricing, by requiring drug companies to notify insurers and government regulators of price increases and provide an explanation of the reasons for the increase. There have also been actions to review the relationship between pricing and manufacturer patient assistance programs, and reform government program reimbursement methodologies for drugs. In the United States, the pharmaceutical industry has already been significantly affected by major legislative initiatives, including, for example, the ACA. The ACA, among other things, imposes a significant annual fee on companies that manufacture or import branded prescription drug medicines. It also contains substantial provisions intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, and impose additional health policy reforms, any or all of which may affect our business. Since its enactment, there have been judicial and Congressional challenges to numerous provisions of the ACA. In January 2017, the United States House of Representatives and Senate passed legislation, the concurrent budget resolution for fiscal year 2017, which initiates actions that would repeal certain aspects of the ACA. Further, on January 20, 2017, U.S. President Donald Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA, to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. In May 2017, following the passage of the budget resolution for fiscal year 2017, the U.S. House of Representatives passed legislation known as the American Health Care Act, which, if enacted, would have amended and repealed significant portions of the ACA. The U.S. Senate considered but did not adopt other legislation to amend and/or replace elements of the ACA and authority to act under the fiscal year 2017 budget resolution expired on September 30, 2017. However, on October 12, 2017, U.S. President Donald Trump signed another Executive Order directing certain federal agencies to propose regulations or guidelines to permit small businesses to form association health plans, expand the availability of short-term, limited duration insurance, and expand the use of health reimbursement arrangements, which may circumvent some of the requirements for health insurance mandated by the ACA. In addition, citing legal guidance from the U.S. Department of Justice and the U.S. Department of Health and Human Services, or HHS, the Trump administration has concluded that cost-sharing reduction, or CSR, payments to insurance companies required under the ACA have not received necessary appropriations from Congress and announced that it will discontinue these payments immediately until such appropriations are made. The loss of the CSR payments is expected to increase premiums on certain policies issued by qualified health plans under the ACA. Finally, while Congress has not passed comprehensive ACA repeal or replace legislation, the federal income tax legislation signed into law on December 22, 2017 includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate". We continue to evaluate the effect that the ACA and additional actions by Congress to possibly repeal and replace it has on our business.

Other legislative changes have also been proposed and adopted since the ACA was enacted. For example, the Budget Control Act of 2011 resulted in aggregate reductions in Medicare payments to providers of up to two percent per fiscal year, starting in 2013, and the American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Such laws, and others that may affect our business that have been recently enacted or may in the future be enacted, may result in additional reductions in Medicare and other healthcare funding. In the future, there will likely continue to be additional proposals relating to the reform of the U.S. healthcare system, some of which could further limit coverage and reimbursement of medicines, including our medicine candidates. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payers. Further, the Bipartisan Budget Act of 2018, or the BBA, among other things, amends the ACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans (also known as the Medicare "Donut Hole"), and also increases in 2019 the percentage that a drug manufacturer must discount the cost of prescription drugs from 50 percent under current law to 70 percent. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our medicines.

Irish Law Matters

As we are an Irish-incorporated company, the following matters of Irish law are relevant to the holders of our ordinary shares.

Irish Restrictions on Import and Export of Capital. Except as indicated below, there are no restrictions imposed specifically on non-residents of Ireland dealing in Irish domestic securities, which includes ordinary shares of Irish companies. Dividends and redemption proceeds also continue to be freely transferable to non-resident holders of such securities. The Financial Transfers Act 1992 gives power to the Minister for Finance of Ireland to restrict financial transfers between Ireland and other countries and persons. Financial transfers are broadly defined and include all transfers that would be movements of capital or payments within the meaning of the treaties governing the member states of the EU. The acquisition or disposal of interests in shares issued by an Irish incorporated company and associated payments falls within this definition. In addition, dividends or payments on redemption or purchase of shares and payments on a liquidation of an Irish incorporated company would fall within this definition. The Criminal Justice (Terrorist Offences) Act 2005 also gives the Minister of Finance of Ireland the power to take various measures, including the freezing or seizure of assets, in order to combat terrorism. At present the Financial Transfers Act 1992, certain EU regulations (as implemented into Irish law) and the Criminal Justice (Terrorist Offences) Act 2005 prohibit financial transfers involving certain persons and entities associated with the ISIL (Da'esh) and Al-Qaida organizations, the late Slobodan Milosevic and associated persons, Republic of Guinea-Bissau, Myanmar/Burma, Belarus, certain persons indicted by the International Criminal Tribunal for the former Yugoslavia, the late Osama bin Laden, Al-Qaida, the Taliban of Afghanistan, Democratic Republic of Congo, Democratic People's Republic of Korea (North Korea), Iran, Iraq, Côte d'Ivoire, Lebanon, Liberia, Zimbabwe, South Sudan, Sudan, Somalia, Republic of Guinea, Afghanistan, Egypt, Eritrea, Libya, Syria, Tunisia, Burundi, the Central African Republic, Ukraine, Yemen, Bosnia and Herzegovina, certain known terrorists and terrorist groups, and countries that harbor certain terrorist groups, without the prior permission of the Central Bank of Ireland or the Minister of Finance (as applicable).

Any transfer of, or payment in respect of, a share or interest in a share involving the government of any country that is currently the subject of United Nations or EU sanctions, any person or body controlled by any of the foregoing, or by any person acting on behalf of the foregoing, may be subject to restrictions pursuant to such sanctions as implemented into Irish law.

Irish Taxes Applicable to U.S. Holders

Withholding Tax on Dividends. While we have no current plans to pay dividends, dividends on our ordinary shares would generally be subject to Irish Dividend Withholding Tax, or DWT, at the standard rate of income tax (currently twenty percent), unless an exemption applies.

Dividends on our ordinary shares that are owned by residents of the United States and held beneficially through the Depositary Trust Company, or DTC, will not be subject to DWT provided that the address of the beneficial owner of the ordinary shares in the records of the broker is in the United States.

Dividends on our ordinary shares that are owned by residents of the United States and held directly (outside of DTC) will not be subject to DWT provided that the shareholder has completed the appropriate Irish DWT form and this form remains valid. Such shareholders must provide the appropriate Irish DWT form to our transfer agent at least seven business days before the record date for the first dividend payment to which they are entitled.

If any shareholder who is resident in the United States receives a dividend subject to DWT, he or she should generally be able to make an application for a refund from the Irish Revenue Commissioners on the prescribed form (DWT Claim Form 1).

While the U.S./Ireland Double Tax Treaty contains provisions regarding withholding tax, due to the wide scope of the exemptions from DWT available under Irish domestic law, it would generally be unnecessary for a U.S. resident shareholder to rely on the treaty provisions.

Income Tax on Dividends. A shareholder who is neither resident nor ordinarily resident in Ireland and who is entitled to an exemption from DWT generally has no additional liability to Irish income tax or to the universal social charge on a dividend from us unless that shareholder holds our ordinary shares through a branch or agency in Ireland through which a trade is carried on.

A shareholder who is neither resident nor ordinarily resident in Ireland and who is not entitled to an exemption from DWT generally has no additional liability to Irish income tax or to the universal social charge on a dividend from us. The DWT deducted by us discharges the liability to Irish income tax and to the universal social charge. This however is not the case where the shareholder holds the ordinary shares through a branch or agency in Ireland through which a trade is carried on.

Irish Tax on Capital Gains. A shareholder who is neither resident nor ordinarily resident in Ireland and does not hold our ordinary shares in connection with a trade or business carried on by such shareholder in Ireland through a branch or agency should not be within the charge to Irish tax on capital gains on a disposal of our ordinary shares.

Capital Acquisitions Tax. Irish capital acquisitions tax, or CAT, is composed principally of gift tax and inheritance tax. CAT could apply to a gift or inheritance of our ordinary shares irrespective of the place of residence, ordinary residence or domicile of the parties. This is because our ordinary shares are regarded as property situated in Ireland as our share register must be held in Ireland. The person who receives the gift or inheritance has primary liability for CAT.

CAT is levied at a rate of 33 percent above certain tax-free thresholds. The appropriate tax-free threshold is dependent upon (i) the relationship between the donor and the donee and (ii) the aggregation of the values of previous gifts and inheritances received by the donee from persons within the same category of relationship for CAT purposes. Gifts and inheritances passing between spouses are exempt from CAT. Our shareholders should consult their own tax advisers as to whether CAT is creditable or deductible in computing any domestic tax liabilities.

Stamp Duty. Irish stamp duty (if any) may become payable in respect of ordinary share transfers. However, a transfer of our ordinary shares from a seller who holds shares through DTC to a buyer who holds the acquired shares through DTC will not be subject to Irish stamp duty. A transfer of our ordinary shares (i) by a seller who holds ordinary shares outside of DTC to any buyer, or (ii) by a seller who holds the ordinary shares through DTC to a buyer who holds the acquired ordinary shares outside of DTC, may be subject to Irish stamp duty (currently at the rate of one percent of the price paid or the market value of the ordinary shares acquired, if greater). The person accountable for payment of stamp duty is the buyer or, in the case of a transfer by way of a gift or for less than market value, all parties to the transfer.

A shareholder who holds ordinary shares outside of DTC may transfer those ordinary shares into DTC without giving rise to Irish stamp duty provided that the shareholder would be the beneficial owner of the related book-entry interest in those ordinary shares recorded in the systems of DTC (and in exactly the same proportions) as a result of the transfer and at the time of the transfer into DTC there is no sale of those book-entry interests to a third party being contemplated by the shareholder. Similarly, a shareholder who holds ordinary shares through DTC may transfer those ordinary shares out of DTC without giving rise to Irish stamp duty provided that the shareholder would be the beneficial owner of the ordinary shares (and in exactly the same proportions) as a result of the transfer, and at the time of the transfer out of DTC there is no sale of those ordinary shares to a third party being contemplated by the shareholder. In order for the share registrar to be satisfied as to the application of this Irish stamp duty treatment where relevant, the shareholder must confirm to us that the shareholder would be the beneficial owner of the related book-entry interest in those ordinary shares recorded in the systems of DTC (and in exactly the same proportions) (or vice-versa) as a result of the transfer and there is no agreement for the sale of the related book-entry interest or the ordinary shares or an interest in the ordinary shares, as the case may be, by the shareholder to a third party being contemplated.

Employees

As of December 31, 2017, we had approximately 1,010 full-time employees. Of our employees as of December 31, 2017, approximately 185 were engaged in development, regulatory and manufacturing activities, approximately 610 were engaged in sales and marketing and approximately 215 were engaged in administration, including business development, finance, legal, information systems, facilities and human resources. None of our employees is subject to a collective bargaining agreement. We consider our employee relations to be satisfactory.

Available Information

We make available free of charge on or through our internet website our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and all amendments to those reports as soon as reasonably practicable after such material is electronically filed with or furnished to the Securities and Exchange Commission. We also regularly post copies of our press releases as well as copies of presentations and other updates about our business on our website. Our website address is www.horizonpharma.com. The information contained in or that can be accessed through our website is not part of this Annual Report on Form 10-K. Information is also available through the Securities and Exchange Commission's website at www.sec.gov or is available at the Securities and Exchange Commission's Public Reference Room located at 100 F Street, NE, Washington DC, 20549. Information on the operation of the Public Reference Room is available by calling the Securities and Exchange Commission at 800-SEC-0330.

Item 1A. Risk Factors

Certain factors may have a material adverse effect on our business, financial condition and results of operations, and you should carefully consider them. Accordingly, in evaluating our business, we encourage you to consider the following discussion of risk factors in its entirety, in addition to other information contained in this report as well as our other public filings with the Securities and Exchange Commission, or SEC.

Risks Related to Our Business and Industry

Our ability to generate revenues from our medicines is subject to attaining significant market acceptance among physicians, patients and healthcare payers.

Our current medicines, and other medicines or medicine candidates that we may develop or acquire, may not attain market acceptance among physicians, patients, healthcare payers or the medical community. We have a limited history of commercializing medicines and most of our medicines have not been on the market for an extensive period of time, which subjects us to numerous risks as we attempt to increase our market share. We believe that the degree of market acceptance and our ability to generate revenues from our medicines will depend on a number of factors, including:

- timing of market introduction of our medicines as well as competitive medicines;
- efficacy and safety of our medicines;
- continued projected growth of the markets in which our medicines compete;
- prevalence and severity of any side effects;

- if and when we are able to obtain regulatory approvals for additional indications for our medicines;
- acceptance by patients, primary care physicians and key specialists;
- availability of coverage and adequate reimbursement and pricing from government and other third-party payers;
- potential or perceived advantages or disadvantages of our medicines over alternative treatments, including cost of treatment and relative convenience and ease of administration;
- strength of sales, marketing and distribution support;
- the price of our medicines, both in absolute terms and relative to alternative treatments;
- impact of past and limitation of future medicine price increases;
- our ability to maintain a continuous supply of medicine for commercial sale;
- the effect of current and future healthcare laws;
- the performance of third-party distribution partners, over which we have limited control; and
- medicine labeling or medicine insert requirements of the U.S. Food and Drug Administration, or FDA, or other regulatory authorities.

With respect to RAVICTI, which is approved to treat a very limited patient population, our ability to grow sales will depend in large part on our ability to transition urea cycle disorder, or UCD, patients from BUPHENYL or generic equivalents, which are comparatively much less expensive, to RAVICTI and to encourage patients and physicians to continue RAVICTI therapy once initiated. With respect to PROCYSBI, which is also approved to treat a very limited patient population, our ability to grow sales will depend in large part on our ability to transition patients from the first-generation immediate-release cysteamine therapy to PROCYSBI, to identify additional patients with nephropathic cystinosis and to encourage patients and physicians to continue therapy once initiated. With respect to ACTIMMUNE, while it is the only FDA-approved treatment for chronic granulomatous disease, or CGD, and severe, malignant osteopetrosis, or SMO, they are very rare conditions and, as a result, our ability to grow ACTIMMUNE sales will depend on our ability to access a wider patient population, obtain marketing approval for additional indications and encourage patients and physicians to continue treatment once initiated. Unless QUINSAIR is approved for marketing in additional countries, our ability to drive growth of this medicine will largely depend on expanding its use in Canada. With respect to KRYSTEXXA, our ability to grow sales will be affected by the success of our sales and marketing strategies, including our marketing efforts in nephrology, and life cycle management, including studies designed to improve the response rate to KRYSTEXXA, our proposed label update submission to the FDA relating to additional data based on post-marketing studies and investigator-initiated trials evaluating new approaches to the clinical use of KRYSTEXXA that are expected to begin enrolling patients in the first quarter of 2018, which could expand the patient population and usage of KRYSTEXXA. With respect to each of BUPHENYL, RAYOS/LODOTRA, PENNSAID 2% w/w, or PENNSAID 2%, DUEXIS and VIMOVO their higher cost compared to the generic or branded forms of their active ingredients alone may limit adoption by physicians, patients and healthcare payers. With respect to DUEXIS and VIMOVO, studies indicate that physicians do not commonly co-prescribe gastrointestinal, or GI, protective agents to high-risk patients taking nonsteroidal anti-inflammatory drugs, or NSAIDs. We believe this is due in part to a lack of awareness among physicians prescribing NSAIDs regarding the risk of NSAID-induced upper GI ulcers, in addition to the inconvenience of prescribing two separate medications and patient compliance issues associated with multiple prescriptions. If physicians remain unaware of, or do not otherwise believe in, the benefits of combining GI protective agents with NSAIDs, our market opportunity for DUEXIS and VIMOVO will be limited. Some physicians may also be reluctant to prescribe DUEXIS or VIMOVO due to the inability to vary the dose of ibuprofen and naproxen, respectively, or if they believe treatment with NSAIDs or GI protective agents other than those contained in DUEXIS and VIMOVO, including those of its competitors, would be more effective for their patients. If our current medicines or any other medicine that we may seek approval for, or acquire, fail to attain market acceptance, we may not be able to generate significant revenue to achieve or sustain profitability, which would have a material adverse effect on our business, results of operations, financial condition and prospects (including, possibly, the value of our ordinary shares).

Our future prospects are highly dependent on our ability to successfully formulate and execute commercialization strategies for each of our medicines. Failure to do so would adversely impact our financial condition and prospects.

A substantial majority of our resources are focused on the commercialization of our current medicines. Our ability to generate significant medicine revenues and to achieve commercial success in the near-term will initially depend almost entirely on our ability to successfully commercialize these medicines in the United States.

With respect to our rare disease medicines, RAVICTI, PROCYSBI, ACTIMMUNE, BUPHENYL, QUINSAIR and KRYSTEXXA, our commercialization strategy includes efforts to increase awareness of the rare conditions that each medicine is designed to treat, enhancing efforts to identify target patients and in certain cases pursue opportunities for label expansion and more effective use through clinical trials. With respect to RAVICTI and PROCYSBI, our strategy includes accelerating the transition of patients from first-generation therapies, and increasing the diagnosis of the associated rare conditions through patient and physician outreach. In addition, our strategy with respect to ACTIMMUNE includes pursuing label expansion for additional indications, such as for advanced urothelial carcinoma and renal cell carcinoma, and price increases, but we cannot be certain that our pricing strategy will not result in downward pressure on sales or that we or others will be able to successfully complete clinical trials and obtain regulatory approvals in additional indications. Our strategy with respect to KRYSTEXXA includes the continued enhancement of the marketing campaign with improved immunogenicity data, continued volume growth and pricing optimization.

With respect to our primary care medicines PENNSAID 2%, DUEXIS, and VIMOVO, our strategy has more recently included entering into rebate agreements with pharmacy benefit managers, or PBMs, for certain of our primary care medicines where we believe the rebates and costs justify expanded formulary access for patients. However, we cannot guarantee that we will be able to secure additional rebate agreements on commercially reasonable terms, that expected volume growth will sufficiently offset the rebates and fees paid to PBMs or that our existing agreements with PBMs will have the intended impact on formulary access. Net pricing for PENNSAID 2%, DUEXIS and VIMOVO was significantly below expectations during the year ended December 31, 2017 as a result of higher patient assistance costs, which were due to lower-than-anticipated adoption rates of our primary care medicines onto certain healthcare plan formularies, and higher commercial rebate levels compared to our expectations. In addition, the mix of PBM healthcare plans that adopted our primary care medicines onto their formulary was more heavily weighted towards those plans for which we pay a higher commercial rebate, which resulted in higher commercial rebate costs to us than we anticipated. If we are unable to realize the expected benefits of our contractual arrangements with the PBMs we may continue to experience reductions in net sales from our primary care business unit. Also, we experienced a higher rate of managed care control in our non-contracted business during the year ended December 31, 2017, which resulted in significantly lower net pricing. For each of our primary care medicines, we expect that our commercial success will depend on our sales and marketing efforts in the United States and the impact of numerous efforts at federal, state and local levels to further reduce reimbursement and net pricing of primary care medicines.

Our strategy for RAYOS in the United States is to focus on the rheumatology indications approved for RAYOS, including our collaboration with the Alliance for Lupus Research, or ALR, to study the effect of RAYOS on the fatigue experienced by systemic lupus erythematosus, or SLE, patients.

Our overall commercialization strategy also includes plans to expand sales in Europe and other countries outside the United States directly or through distributors for certain of our orphan and rheumatology medicines. In November 2015, we received approval of the Committee for Medicinal Products for Human Use of the European Medicines Agency, or EMA, for RAVICTI for use as an adjunctive therapy for chronic management of adult and pediatric UCD patients greater than two months of age. RAVICTI became available in Europe in the fourth quarter of 2017 through an exclusive distribution agreement with Swedish Orphan Biovitrum AB, or SOBI, however we cannot guarantee we will be able to successfully implement our commercial plans for RAVICTI in Europe. Although LODOTRA is approved for marketing in countries outside the United States, to date it has only been marketed in a limited number of countries.

If any of our commercial strategies are unsuccessful or we fail to successfully modify our strategies over time due to changing market conditions, our ability to increase market share for our medicines, grow revenues and to achieve and sustain profitability will be harmed.

In order to increase adoption and sales of our medicines, we will need to continue developing our commercial organization as well as recruit and retain qualified sales representatives.

Part of our strategy is to continue to build a biopharmaceutical company to successfully execute the commercialization of our medicines in the U.S. market, and in selected markets outside the United States where we have commercial rights. We may not be able to successfully commercialize our medicines in the United States or in any other territories where we have commercial rights. In order to commercialize any approved medicines, we must continue to build our sales, marketing, distribution, managerial and other non-technical capabilities. During the second quarter of 2017, we effected a workforce reduction in the primary care business unit. As of December 31, 2017, we had approximately 430 sales representatives in the field, consisting of approximately 25 orphan disease sales representatives, 140 rheumatology sales specialists and 265 primary care sales representatives. We cannot be certain that we will be able to adequately market our primary care medicines following the reduction in our sales force or that we will be able to continue retaining the current members of our primary care sales force. We currently have limited resources compared to some of our competitors, and the continued development of our own commercial organization to market our medicines and any additional medicines we may acquire will be expensive and time-consuming. We also cannot be certain that we will be able to continue to successfully develop this capability.

As a result of the evolving role of various constituents in the prescription decision making process, we focus on hiring sales representatives for our primary care business unit and RAYOS with successful business to business experience. For example, we have faced challenges due to pharmacists increasingly switching a patient's intended prescription from DUEXIS and VIMOVO to a generic or over-the-counter brand of their active ingredients, despite such substitution being off-label in the case of DUEXIS and VIMOVO. We have faced similar challenges for BUPHENYL, RAYOS and PENNSAID 2% with respect to generic brands. While we believe the profile of our representatives is better suited for this evolving environment, we cannot be certain that our representatives will be able to successfully protect our market for BUPHENYL, RAYOS, PENNSAID 2%, DUEXIS and VIMOVO or that we will be able to continue attracting and retaining sales representatives with our desired profile and skills. We will also have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train and retain commercial personnel. To the extent we rely on additional third parties to commercialize any approved medicines, we may receive less revenue than if we commercialized these medicines ourselves. In addition, we may have little or no control over the sales efforts of any third parties involved in our commercialization efforts. In the event we are unable to successfully develop and maintain our own commercial organization or collaborate with a third-party sales and marketing organization, we may not be able to commercialize our medicines and medicine candidates and execute on our business plan.

If we are unable to effectively train and equip our sales force, our ability to successfully commercialize our medicines will be harmed.

As we continue to acquire additional medicines through acquisition transactions, the members of our sales force may have limited experience promoting certain of our medicines. To the extent we employ an acquired entity's original sales forces to promote acquired medicines, we may not be successful in continuing to retain these employees and we otherwise will have limited experience marketing these medicines under our commercial organization. As a result, we are required to expend significant time and resources to train our sales force to be credible and persuasive in convincing physicians to prescribe and pharmacists to dispense our medicines. In addition, we must train our sales force to ensure that a consistent and appropriate message about our medicines is being delivered to our potential customers. Our sales representatives may also experience challenges promoting multiple medicines when we call on physicians and their office staff. We have experienced, and may continue to experience, turnover of the sales representatives that we hired or will hire, requiring us to train new sales representatives. If we are unable to effectively train our sales force and equip them with effective materials, including medical and sales literature to help them inform and educate physicians about the benefits of our medicines and their proper administration and label indication, as well as our patient access programs, our efforts to successfully commercialize our medicines could be put in jeopardy, which could have a material adverse effect on our financial condition, share price and operations.

If we cannot successfully implement our patient access programs or increase formulary access and reimbursement for our medicines in the face of increasing pressure to reduce the price of medications, the adoption of our medicines by physicians, patients and payers may decline.

There continues to be immense pressure from healthcare payers, PBMs and others to use less expensive generics or over-the-counter brands instead of branded medicines. For example, some of the largest PBMs previously placed DUEXIS and VIMOVO on their formulary exclusion lists. Additional healthcare plans, including those that contract with these PBMs but use different formularies, may also choose to exclude our medicines from their formularies or restrict coverage to situations where a generic or over-the-counter medicine has been tried first. Many payers and PBMs also require patients to make co-payments for branded medicines, including many of our medicines, in order to incentivize the use of generic or other lower-priced alternatives instead. Legislation enacted in most states in the United States allows, or in some instances mandates, that a pharmacist dispenses an available generic equivalent when filling a prescription for a branded medicine, in the absence of specific instructions from the prescribing physician. Because our medicines (other than BUPHENYL) do not currently have FDA-approved generic equivalents in the United States, we do not believe our medicines should be subject to mandatory generic substitution laws. However, we understand that some pharmacies may attempt to obtain physician authorization to switch prescriptions for DUEXIS or VIMOVO to prescriptions for multiple generic medicines with similar active pharmaceutical ingredients, or APIs, to ensure payment for the medicine if the physician's prescription for the branded medicine is not immediately covered by the payer, despite such substitution being off-label in the case of DUEXIS and VIMOVO. If these limitations in coverage and other incentives result in patients refusing to fill prescriptions or being dissatisfied with the out-of-pocket costs of their medications, or if pharmacies otherwise seek and receive physician authorization to switch prescriptions, not only would we lose sales on prescriptions that are ultimately not filled, but physicians may be dissuaded from writing prescriptions for our medicines in the first place in order to avoid potential patient non-compliance or dissatisfaction over medication costs, or to avoid spending the time and effort of responding to pharmacy requests to switch prescriptions.

Part of our commercial strategy to increase adoption and access to our medicines in the face of these incentives to use generic alternatives is to offer physicians the opportunity to have patients fill prescriptions through independent pharmacies participating in our HorizonCares patient access program. Through HorizonCares, financial assistance may be available to reduce eligible patients' out-of-pocket costs for prescriptions filled. Because of this assistance, eligible patients' out-of-pocket cost for our medicines when dispensed through HorizonCares may be significantly lower than such costs when our medicines are dispensed outside of the HorizonCares program. However, to the extent physicians do not direct prescriptions currently filled through traditional pharmacies, including those associated with or controlled by PBMs, to pharmacies participating in our HorizonCares program, we may experience a significant decline in PENNSAID 2%, DUEXIS and VIMOVO prescriptions. Our ability to increase utilization of our patient access programs will depend on physician and patient awareness and comfort with the programs, and we have limited ability to influence whether physicians use our patient access programs to prescribe our medicines or whether patients will agree to receive our medicines through our HorizonCares program. In addition, the HorizonCares program is not available to federal health care program (such as Medicare and Medicaid) beneficiaries. We have also contracted with certain PBMs and other payers to secure formulary status and reimbursement for certain of our primary care medicines, which generally require us to pay administrative fees and rebates to the PBMs and other payers for qualifying prescriptions. While we have business relationships with two of the largest PBMs, Express Scripts and CVS Caremark, that have resulted in DUEXIS and VIMOVO being removed from the Express Scripts and CVS Caremark exclusion lists starting in 2017, as well as a rebate agreement with another PBM, Prime Therapeutics LLC, and we believe these agreements will secure formulary status for certain of our medicines, we cannot guarantee that we will be able to agree to terms with other PBMs and other payers, or that such terms will be commercially reasonable to us. Despite our agreements with PBMs, the extent of formulary status and reimbursement will ultimately depend to a large extent upon individual healthcare plan formulary decisions. If healthcare plans that contract with PBMs with which we have agreements do not adopt formulary changes recommended by the PBMs with respect to our medicines, we may not realize the expected access and reimbursement benefits from these agreements. In addition, we generally pay higher rebates for prescriptions covered under plans that adopt a PBM-chosen formulary than for plans that adopt custom formularies. Consequently, the success of our PBM contracting strategy will depend not only on our ability to expand formulary adoption among healthcare plans, but also upon the relative mix of healthcare plans that have PBM-chosen formularies versus custom formularies. During the year ended December 31, 2017, the adoption rates of our primary care medicines onto certain healthcare plan formularies were lower than we had anticipated and as a result, we incurred higher patient assistance costs than we expected, and the mix of healthcare plans adopting our primary care medicines onto their formularies was more heavily weighted towards plans that use PBM-chosen formularies, which resulted in higher rebate costs than we expected. If we are unable to realize the expected benefits of our contractual arrangements with the PBMs we may continue to experience reductions in net sales from our primary care business unit. If we are unable to increase adoption of HorizonCares for filling prescriptions of our medicines or to secure formulary status and reimbursement through arrangements with PBMs and other payers, particularly with healthcare plans that use custom formularies, our ability to achieve net sales growth for our primary care business unit would be impaired.

There has been negative publicity and inquiries from Congress and enforcement authorities regarding the use of specialty pharmacies and drug pricing. Our patient access programs are not involved in the prescribing of medicines and are solely to assist in ensuring that when a physician determines one of our medicines offers a potential clinical benefit to their patients and they prescribe one for an eligible patient, financial assistance may be available to reduce the patient's out-of-pocket costs. In addition, all pharmacies that fill prescriptions for our medicines are fully independent, including those that participate in HorizonCares. We do not own or possess any option to purchase an ownership stake in any pharmacy that distributes our medicines, and our relationship with each pharmacy is non-exclusive and arm's length. All of our sales are processed through pharmacies independent of us. Despite this, the negative publicity and interest from Congress and enforcement authorities regarding specialty pharmacies may result in physicians being less willing to participate in our patient access programs and thereby limit our ability to increase patient access and adoption of our medicines.

We may also encounter difficulty in forming and maintaining relationships with pharmacies that participate in our patient access programs. We currently depend on a limited number of pharmacies participating in HorizonCares to fulfill patient prescriptions under the HorizonCares program. If these HorizonCares participating pharmacies are unable to process and fulfill the volume of patient prescriptions directed to them under the HorizonCares program, our ability to maintain or increase prescriptions for our medicines will be impaired. The commercialization of our medicines and our operating results could be affected should any of the HorizonCares participating pharmacies choose not to continue participation in our HorizonCares program or by any adverse events at any of those HorizonCares participating pharmacies. For example, pharmacies that dispense our medicines could lose contracts that they currently maintain with managed care organizations, or MCOs, including PBMs. Pharmacies often enter into agreements with MCOs. They may be required to abide by certain terms and conditions to maintain access to MCO networks, including terms and conditions that could limit their ability to participate in patient access programs like ours. Failure to comply with the terms of their agreements with MCOs could result in a variety of penalties, including termination of their agreement, which could negatively impact the ability of those pharmacies to dispense our medicines and collect reimbursement from MCOs for such medicines.

The HorizonCares program may implicate certain federal and state laws related to, among other things, unlawful schemes to defraud, excessive fees for services, tortious interference with patient contracts and statutory or common law fraud. We have a comprehensive compliance program in place to address adherence with various laws and regulations relating to the selling, marketing and manufacturing of our medicines, as well as certain third-party relationships, including pharmacies. Specifically with respect to pharmacies, the compliance program utilizes a variety of methods and tools to monitor and audit pharmacies, including those that participate in the HorizonCares program, to confirm their activities, adjudication and practices are consistent with our compliance policies and guidance. Despite our compliance efforts, to the extent the HorizonCares program is found to be inconsistent with applicable laws or the pharmacies that participate in our patient access programs do not comply with applicable laws, we may be required to restructure or discontinue such programs, terminate our relationship with certain pharmacies, or be subject to other significant penalties. In November 2015, we received a subpoena from the U.S. Attorney's Office for the Southern District of New York requesting documents and information related to our patient access programs and other aspects of our marketing and commercialization activities. We are unable to predict how long this investigation will continue or its outcome, but we have incurred and anticipate that we may continue to incur significant costs in connection with the investigation, regardless of the outcome. We may also become subject to similar investigations by other governmental agencies or Congress. The investigation by the U.S. Attorney's Office and any additional investigations of our patient access programs and sales and marketing activities may result in damages, fines, penalties, exclusion, additional reporting requirements and/or oversight or other administrative sanctions against us.

If the cost of maintaining our patient access programs increases relative to our sales revenues, we could be forced to reduce the amount of patient financial assistance that we offer or otherwise scale back or eliminate such programs, which could in turn have a negative impact on physicians' willingness to prescribe and patients' willingness to fill prescriptions of our medicines. While we believe that our arrangements with PBMs will result in broader inclusion of certain of our primary care medicines on healthcare plan formularies, and therefore increase payer reimbursement and lower our cost of providing patient access programs, these arrangements generally require us to pay administrative and rebate payments to the PBMs and/or other payers and their effectiveness will ultimately depend to a large extent upon individual healthcare plan formulary decisions that are beyond the control of the PBMs. If our arrangements with PBMs and other payers do not result in increased prescriptions and reductions in our costs to provide our patient access programs that are sufficient to offset the administrative fees and rebate payments to the PBMs and/or other payers, our financial results may continue to be harmed.

If we are unable to successfully implement our commercial plans and facilitate adoption by patients and physicians of any approved medicines through our sales, marketing and commercialization efforts, then we will not be able to generate sustainable revenues from medicine sales which will have a material adverse effect on our business and prospects.

Coverage and reimbursement may not be available, or reimbursement may be available at only limited levels, for our medicines, which could make it difficult for us to sell our medicines profitably or to successfully execute planned medicine price increases.

Market acceptance and sales of our medicines will depend in large part on global coverage and reimbursement policies and may be affected by future healthcare reform measures, both in the United States and other key international markets. Successful commercialization of our medicines will depend in part on the availability of governmental and third-party payer reimbursement for the cost of our medicines. Government health administration authorities, private health insurers and other organizations generally provide reimbursement for healthcare. In particular, in the United States, private health insurers and other third-party payers often provide reimbursement for medicines and services based on the level at which the government (through the Medicare or Medicaid programs) provides reimbursement for such treatments. In the United States, the EU and other significant or potentially significant markets for our medicines and medicine candidates, government authorities and third-party payers are increasingly attempting to limit or regulate the price of medicines and services, particularly for new and innovative medicines and therapies, which has resulted in lower average selling prices. Further, the increased scrutiny of prescription drug pricing practices and emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the EU will put additional pressure on medicine pricing, reimbursement and usage, which may adversely affect our medicine sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical reimbursement policies and pricing in general. These pressures may create negative reactions to any medicine price increases, or limit the amount by which we may be able to increase our medicine prices, which may adversely affect our medicine sales and results of operations.

Patients are unlikely to use our medicines unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our medicines. Third-party payers may limit coverage to specific medicines on an approved list, also known as a formulary, which might not include all of the FDA-approved medicines for a particular indication. Moreover, a third-party payer's decision to provide coverage for a medicine does not imply that an adequate reimbursement rate will be approved. Additionally, one third-party payer's decision to cover a particular medicine does not ensure that other payers will also provide coverage for the medicine, or will provide coverage at an adequate reimbursement rate. Even though we have contracts with some PBMs in the United States, that does not guarantee that they will perform in accordance with the contracts, nor does that preclude them from taking adverse actions against us, which could materially adversely affect our operating results. In addition, the existence of such PBM contracts does not guarantee coverage by such PBM's contracted health plans or adequate reimbursement to their respective providers for our medicines. For example, two significant PBMs placed DUEXIS and VIMOVO on their exclusion lists beginning in 2015, which has resulted in a loss of coverage for patients whose healthcare plans have adopted these PBM lists. While DUEXIS and VIMOVO were removed from the Express Scripts and CVS Caremark exclusion lists starting in 2017, we cannot guarantee that Express Scripts or CVS Caremark will not later add these medicines back to their exclusion lists or that we will be able to otherwise expand formulary access for DUEXIS and VIMOVO under health plans that contract with Express Scripts and/or CVS Caremark. Additional healthcare plan formularies may also exclude our medicines from coverage due to the actions of certain PBMs, future price increases we may implement, our use of the HorizonCares program or any other co-pay programs, or other reasons. If our strategies to mitigate formulary exclusions are not effective, these events may reduce the likelihood that physicians prescribe our medicines and increase the likelihood that prescriptions for our medicines are not filled.

Outside of the United States, the success of our medicines, including RAVICTI, PROCYSBI, QUINSAIR, LODOTRA and IMUKIN, will depend largely on obtaining and maintaining government coverage, because in many countries patients are unlikely to use prescription drugs that are not covered by their government healthcare programs. We launched RAVICTI in Canada in November 2016 and RAVICTI became available in Europe in the fourth quarter of 2017 through our partnership with SOBI. PROCYSBI was launched in Canada in October 2017 and QUINSAIR was launched in Canada in December 2016. We cannot be certain that existing reimbursement in such countries will be maintained or that we will be able to secure reimbursement in additional countries. The majority of LODOTRA sales are in Germany and Italy where reimbursement has been approved. Negotiating coverage and reimbursement with governmental authorities can delay commercialization by 12 months or more. Coverage and reimbursement policies may adversely affect our ability to sell our medicines on a profitable basis. In many international markets, governments control the prices of prescription pharmaceuticals, including through the implementation of reference pricing, price cuts, rebates, revenue-related taxes and profit control, and we expect prices of prescription pharmaceuticals to decline over the life of the medicine or as volumes increase. Many countries in the EU have increased the amount of discounts required on medicines, and we expect these discounts to continue as countries attempt to manage healthcare expenditures, especially in light of current economic conditions. As a result of these pricing practices, it may become difficult to achieve or sustain profitability or expected rates of growth in revenue or results of operations. Any shortfalls in revenue could adversely affect our business, financial condition and results of operations.

In light of such policies and the uncertainty surrounding proposed regulations and changes in the coverage and reimbursement policies of governments and third-party payers, we cannot be sure that coverage and reimbursement will be available for any of our medicines in any additional markets or for any other medicine candidates that we may develop. Also, we cannot be sure that reimbursement amounts will not reduce the demand for, or the price of, our medicines. If coverage and reimbursement are not available or are available only at limited levels, we may not be able to successfully commercialize our medicines.

We expect to experience pricing pressures in connection with the sale of our medicines due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative proposals relating to outcomes and quality. For example, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the ACA, increased the mandated Medicaid rebate from 15.1% to 23.1%, expanded the rebate to Medicaid managed care utilization and increased the types of entities eligible for the federal 340B drug discount program. On January 30, 2017, the White House Office of Management and Budget withdrew the draft August 2015 Omnibus Guidance document that was issued by the Department of Health and Human Services, or HHS, Health Resources and Services Administration, or HRSA, that addressed a broad range of topics including, among other items, the definition of a patient's eligibility for 340B drug pricing. However, as concerns continue to grow over the need for tighter oversight, there remains the possibility that HRSA or another agency under the HHS will propose a similar regulation or that Congress will explore changes to the 340B program through legislation. For example, the Centers for Medicare & Medicaid Services has issued a final rule that would revise the Medicare hospital outpatient prospective payment system for calendar year 2018, including a new reimbursement methodology for drugs purchased under the 340B program for Medicare patients. In addition, HHS has currently set July 1, 2018, for implementation of the final rule setting forth the calculation of the ceiling price and application of civil monetary penalties under the 340B program. A material portion of KRYSEXXA prescriptions are written by healthcare providers that are eligible for 340B drug pricing and therefore any reduction in 340B pricing, whether in the form of the final rule or otherwise, or an expansion of healthcare providers eligible for 340B drug pricing, would likely have a negative impact on our net sales from KRYSTEXXA.

There may be additional pressure by payers, healthcare providers, state governments, federal regulators and Congress, to use generic drugs that contain the active ingredients found in our medicines or any other medicine candidates that we may develop or acquire. If we fail to successfully secure and maintain coverage and adequate reimbursement for our medicines or are significantly delayed in doing so, we will have difficulty achieving market acceptance of our medicines and expected revenue and profitability which would have a material adverse effect on our business, results of operations, financial condition and prospects.

We may also experience pressure from payers as well as state and federal government authorities concerning certain promotional approaches that we may implement such as our HorizonCares program or any other co-pay or free medicine programs whereby we assist qualified patients with certain out-of-pocket expenditures for our medicine. Certain enforcement authorities and members of Congress have initiated inquiries about co-pay assistance programs. Some state legislatures have been considering proposals that would restrict or ban co-pay coupons. For example, legislation was recently signed into law in California that would limit the use of co-pay coupons in cases where a lower cost generic drug is available and if individual ingredients in combination therapies are available over the counter at a lower cost. It is possible that similar legislation could be proposed and enacted in additional states. If we are unsuccessful with our HorizonCares program or any other co-pay initiatives or free medicine programs, or we alternatively are unable to secure expanded formulary access through additional arrangements with PBMs or other payers, we would be at a competitive disadvantage in terms of pricing versus preferred branded and generic competitors. We may also experience financial pressure in the future which would make it difficult to support investment levels in areas such as managed care contract rebates, HorizonCares and other access tools.

We are solely dependent on third parties to commercialize certain of our medicines outside the United States. Failure of these third parties or any other third parties to successfully commercialize our medicines and medicine candidates in the applicable jurisdictions could have a material adverse effect on our business.

SOBI is our exclusive distributor for RAVICTI in Europe. Innomar Strategies Inc., or Innomar, is our exclusive distributor for RAVICTI, PROCYSBI and QUINSAIR in Canada. We rely on other third-party distributors for commercialization of BUPHENYL (known as AMMONAPS in certain European countries) in certain territories outside the United States for which we currently have rights. Mundipharma International Corporation Limited, or Mundipharma, is our exclusive distributor for LODOTRA in Europe, Asia and Latin America. We have limited contractual rights to force these third parties to invest significantly in commercialization of these medicines in our markets. In the event that SOBI, Innomar, our current ex-U.S. distributors for BUPHENYL, Mundipharma, or any other third party with any future commercialization

rights to any of our medicines or medicine candidates fail to adequately commercialize those medicines or medicine candidates because they lack adequate financial or other resources, decide to focus on other initiatives or otherwise, our ability to successfully commercialize our medicines or medicine candidates in the applicable jurisdictions would be limited, which would adversely affect our business, financial condition, results of operations and prospects. We have had disagreements with Mundipharma under our European agreements and may continue to have disagreements, which could harm commercialization of LODOTRA in Europe or result in the termination of our agreements with Mundipharma. In addition, our agreements with SOBI, Innomar, our current ex-U.S. distributors for BUPHENYL and Mundipharma, may be terminated by either party in the event of a bankruptcy of the other party or upon an uncured material breach by the other party. If these third parties terminated their agreements, we may not be able to secure an alternative distributor in the applicable territory on a timely basis or at all, in which case our ability to generate revenues from the sale of RAVICTI, PROCYSBI, BUPHENYL, QUINSAIR or LODOTRA, outside the United States would be materially harmed.

Our medicines are subject to extensive regulation, and we may not obtain additional regulatory approvals for our medicines.

The clinical development, manufacturing, labeling, packaging, storage, recordkeeping, advertising, promotion, export, marketing and distribution and other possible activities relating to our medicines and our medicine candidates are, and will be, subject to extensive regulation by the FDA and other regulatory agencies. Failure to comply with FDA and other applicable regulatory requirements may, either before or after medicine approval, subject us to administrative or judicially imposed sanctions.

To market any drugs or biologics outside of the United States, we and current or future collaborators must comply with numerous and varying regulatory and compliance related requirements of other countries. Approval procedures vary among countries and can involve additional medicine testing and additional administrative review periods, including obtaining reimbursement and pricing approval in select markets. The time required to obtain approval in other countries might differ from that required to obtain FDA approval. The regulatory approval process in other countries may include all of the risks associated with FDA approval as well as additional, presently unanticipated, risks. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others.

Applications for regulatory approval, including a marketing authorization application, or MAA, for marketing new drugs in Europe, must be supported by extensive clinical and pre-clinical data, as well as extensive information regarding chemistry, manufacturing and controls, or CMC, to demonstrate the safety and effectiveness of the applicable medicine candidate. The number and types of pre-clinical studies and clinical trials that will be required for regulatory approval varies depending on the medicine candidate, the disease or the condition that the medicine candidate is designed to target and the regulations applicable to any particular medicine candidate. Despite the time and expense associated with pre-clinical and clinical studies, failure can occur at any stage, and we could encounter problems that cause us to repeat or perform additional pre-clinical studies, CMC studies or clinical trials. Regulatory authorities could delay, limit or deny approval of a medicine candidate for many reasons, including because they:

- may not deem a medicine candidate to be adequately safe and effective;
- may not find the data from pre-clinical studies, CMC studies and clinical trials to be sufficient to support a claim of safety and efficacy;
- may interpret data from pre-clinical studies, CMC studies and clinical trials significantly differently than we do;
- may not approve the manufacturing processes or facilities associated with our medicine candidates;
- may conclude that we have not sufficiently demonstrated long-term stability of the formulation for which we are seeking marketing approval;
- may change approval policies (including with respect to our medicine candidates' class of drugs) or adopt new regulations; or
- may not accept a submission due to, among other reasons, the content or formatting of the submission.

Even if we believe that data collected from our pre-clinical studies, CMC studies and clinical trials of our medicine candidates are promising and that our information and procedures regarding CMC are sufficient, our data may not be sufficient to support marketing approval by regulatory authorities, or regulatory interpretation of these data and procedures may be unfavorable. Even if approved, medicine candidates may not be approved for all indications requested and such approval may be subject to limitations on the indicated uses for which the medicine may be marketed, restricted distribution methods or other limitations. Our business and reputation may be harmed by any failure or significant delay in obtaining regulatory approval for the sale of any of our medicine candidates. We cannot predict when or whether regulatory approval will be obtained for any medicine candidate we develop.

With respect to QUINSAIR, the FDA indicated in previous written and verbal communications with Raptor Pharmaceutical Corp., or Raptor, and with the drug's previous sponsor, that it believed the data submitted in connection with EMA's subsequent approval of QUINSAIR for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adults with cystic fibrosis, or CF, did not provide substantial evidence of efficacy and safety to support FDA approval of QUINSAIR for treatment of patients with CF. In October 2016, the FDA expressed its recommendation that an additional clinical trial should be conducted, and noted that if Raptor submitted a new drug application, or NDA, without conducting an additional clinical trial, the FDA would review the submission to determine whether it is acceptable for filing.

Prior to our acquisition of Raptor, Raptor planned to pursue the development of QUINSAIR for use in the indication of bronchiectasis, or BE, not associated with CF. Raptor submitted a protocol to the FDA in August 2016 for a Phase 2, placebo-controlled study of QUINSAIR in adults with BE. Feedback from the FDA was received in October 2016 requesting additional information and changes to the proposed study protocol. Raptor was also exploring further clinical development of QUINSAIR for the treatment of pulmonary nontuberculous mycobacteria, or NTM infection, based on third-party data generated pertaining to the susceptibility of certain pathogens to treatment with levofloxacin and other fluoroquinolone molecules. No clinical data has been generated with QUINSAIR in patients with BE or with NTM infections, either by Raptor, subsequently by Horizon or by other parties. This creates uncertainty regarding the potential efficacy of QUINSAIR in these indications.

We will evaluate all development opportunities, including all obligations to use commercial reasonable efforts to further develop QUINSAIR. However, we may determine not to pursue such further development.

The ultimate approval and commercial marketing of any of our medicines in additional indications or geographies is subject to substantial uncertainty. Failure to gain additional regulatory approvals would limit the potential revenues and value of our medicines and could cause our share price to decline.

The amount of our medicine sales in the Member States of the European Economic Area, or EEA, is dependent in part upon the pricing and reimbursement decisions adopted in each of the EEA countries, which may not be at acceptable levels to us.

One or more EEA countries may not support pricing within our target pricing and reimbursement range for our medicines due to budgetary decisions made by regional, national and local health authorities and third-party payers in the EEA, which would negatively affect our revenues. The pricing and reimbursement process in EEA countries can be lengthy, involved and difficult to predict. Failure to timely complete the pricing and reimbursement process in the EEA countries will delay our ability to market our medicines in the EEA and to derive revenues from those countries.

We may be subject to penalties and litigation and large incremental expenses if we fail to comply with regulatory requirements or experience problems with our medicines.

Even after we achieve regulatory approvals, we are subject to ongoing obligations and continued regulatory review with respect to many operational aspects including our manufacturing processes, labeling, packaging, distribution, storage, adverse event monitoring and reporting, dispensation, advertising, promotion and recordkeeping. These requirements include submissions of safety and other post-marketing information and reports, ongoing maintenance of medicine registration and continued compliance with current good manufacturing practices, or cGMPs, good clinical practices, or GCPs, good pharmacovigilance practice, good distribution practices and good laboratory practices, or GLPs. If we, our medicines or medicine candidates, or the third-party manufacturing facilities for our medicines or medicine candidates fail to comply with applicable regulatory requirements, a regulatory agency may:

- impose injunctions or restrictions on the marketing, manufacturing or distribution of a medicine, suspend or withdraw medicine approvals, revoke necessary licenses or suspend medicine reimbursement;
- issue warning letters, show cause notices or untitled letters describing alleged violations, which may be publicly available;

- suspend any ongoing clinical trials or delay or prevent the initiation of clinical trials;
- delay or refuse to approve pending applications or supplements to approved applications we have filed;
- refuse to permit drugs or precursor or intermediary chemicals to be imported or exported to or from the United States;
- suspend or impose restrictions or additional requirements on operations, including costly new manufacturing quality or pharmacovigilance requirements;
- seize or detain medicines or require us to initiate a medicine recall; and/or
- commence criminal investigations and prosecutions.

Moreover, existing regulatory approvals and any future regulatory approvals that we obtain will be subject to limitations on the approved indicated uses and patient populations for which our medicines may be marketed, the conditions of approval, requirements for potentially costly, post-market testing and requirements for surveillance to monitor the safety and efficacy of the medicines. In the EEA, the advertising and promotion of pharmaceuticals is strictly regulated. The direct-to-consumer promotion of prescription pharmaceuticals is not permitted, and some countries in the EEA require the notification and/or prior authorization of promotional or advertising materials directed at healthcare professionals. The FDA, EMA and other authorities in the EEA countries strictly regulate the promotional claims that may be made about prescription medicines, and our medicine labeling, advertising and promotion are subject to continuing regulatory review. Physicians nevertheless may prescribe our medicines to their patients in a manner that is inconsistent with the approved label or that is off-label. Positive clinical trial results in any of our medicine development programs increase the risk that approved pharmaceutical forms of the same APIs may be used off-label in those indications. If we are found to have improperly promoted off-label uses of approved medicines, we may be subject to significant sanctions, civil and criminal fines and injunctions prohibiting us from engaging in specified promotional conduct.

In addition, engaging in improper promotion of our medicines for off-label uses in the United States can subject us to false claims litigation under federal and state statutes. These false claims statutes in the United States include the federal False Claims Act, which allows any individual to bring a lawsuit against a pharmaceutical company on behalf of the federal government alleging submission of false or fraudulent claims or causing to present such false or fraudulent claims for payment by a federal program such as Medicare or Medicaid. Growth in false claims litigation has increased the risk that a pharmaceutical company will have to defend a false claim action, pay civil money penalties, settlement fines or restitution, agree to comply with burdensome reporting and compliance obligations and be excluded from Medicare, Medicaid and other federal and state healthcare programs.

The regulations, policies or guidance of regulatory agencies may change and new or additional statutes or government regulations may be enacted that could prevent or delay regulatory approval of our medicine candidates or further restrict or regulate post-approval activities. For example, the Food and Drug Administration Safety and Innovation Act requires the FDA to issue new guidance describing its policy regarding internet and social media promotion of regulated medical products, and the FDA may soon specify new restrictions on this type of promotion. In January 2014, the FDA released draft guidance on how drug companies can fulfill their regulatory requirements for post-marketing submission of interactive promotional media, and though the guidance provided insight into how the FDA views a company's responsibility for certain types of social media promotion, there remains a substantial amount of uncertainty. We cannot predict the likelihood, nature or extent of adverse government regulation that may arise from pending or future legislation or administrative action, either in the United States or abroad. If we are unable to achieve and maintain regulatory compliance, we will not be permitted to market our drugs, which would materially adversely affect our business, results of operations and financial condition.

Our limited history of commercial operations makes evaluating our business and future prospects difficult and may increase the risk of any investment in our ordinary shares.

We face considerable risks and difficulties as a company with limited commercial operating history, particularly as a global consolidated entity with operating subsidiaries that also have limited operating histories. If we do not successfully address these risks, our business, prospects, operating results and financial condition will be materially and adversely harmed. Our limited commercial operating history, including our limited history commercializing our current medicines, makes it particularly difficult for us to predict our future operating results and appropriately budget for our expenses. In the event that actual results differ from our estimates or we adjust our estimates in future periods, our operating results and financial position could be materially affected. For example, we may underestimate the resources we will require to successfully integrate recent or future medicine or company acquisitions, or to commercialize our medicines, or not realize the benefits we expect to derive from our recent or future acquisitions. In addition, we have a limited history implementing our commercialization strategy focused on patient access, and we cannot guarantee that we will be able to successfully implement this strategy or that it will represent a viable strategy over the long term.

We have rights to medicines in certain jurisdictions but have no control over third parties that have rights to commercialize those medicines in other jurisdictions, which could adversely affect our commercialization of these medicines.

Following our sale of the rights to PROCYSBI and QUINSAIR in the Europe, Middle East and Africa, or EMEA, regions to Chiesi Farmaceutici S.p.A, or Chiesi, in June 2017, or the Chiesi divestiture, Chiesi has marketing and distribution rights to PROCYSBI and QUINSAIR in EMEA. Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.), or Nuvo, has retained its rights to PENNSAID 2% in territories outside of the United States and in March 2017, Nuvo announced that it had entered into an exclusive license agreement with Sayre Therapeutics PVT Ltd. to distribute, market and sell PENNSAID 2% in India, Sri Lanka, Bangladesh and Nepal. Nuvo also announced that it expects to complete PENNSAID 2% out-licensing agreements for other territories throughout 2018. Similarly, AstraZeneca AB, or AstraZeneca, has retained its existing rights to VIMOVO, in territories outside of the United States, including the right to use the VIMOVO name and related trademark. We have little or no control over Chiesi's activities with respect to PROCYSBI and QUINSAIR in EMEA, over Nuvo's or its existing and future commercial partners' activities with respect to PENNSAID 2% outside of the United States, or over AstraZeneca's activities with respect to VIMOVO outside the United States or even though those activities could impact our ability to successfully commercialize these medicines. For example, Chiesi or its assignees, Nuvo or its assignees or AstraZeneca or its assignees can make statements or use promotional materials with respect to PROCYSBI, QUINSAIR, PENNSAID 2% or VIMOVO, respectively, outside of the United States that are inconsistent with our positioning of the medicines in the United States, and could sell PROCYSBI, QUINSAIR, PENNSAID 2% or VIMOVO, respectively, in foreign countries at prices that are dramatically lower than the prices we charge in the United States. These activities and decisions, while occurring outside of the United States, could harm our commercialization strategy in the United States, in particular because AstraZeneca is continuing to market VIMOVO outside the United States under the same VIMOVO brand name that we are using in the United States. In addition, medicine recalls or safety issues with these medicines outside the United States, even if not related to the commercial medicine we sell in the United States, could result in serious damage to the brand in the United States and impair our ability to successfully market them. We also rely on Chiesi, Nuvo and AstraZeneca or their assignees to provide us with timely and accurate safety information regarding the use of these medicines outside of the United States, as we have or will have limited access to this information ourselves.

We rely on third parties to manufacture commercial supplies of all of our medicines, and we currently intend to rely on third parties to manufacture commercial supplies of any other approved medicines. The commercialization of any of our medicines could be stopped, delayed or made less profitable if those third parties fail to provide us with sufficient quantities of medicine or fail to do so at acceptable quality levels or prices or fail to maintain or achieve satisfactory regulatory compliance.

The facilities used by our third-party manufacturers to manufacture our medicines and medicine candidates must be approved by the applicable regulatory authorities. We do not control the manufacturing processes of third-party manufacturers and are currently completely dependent on our third-party manufacturing partners. In addition, we are required to obtain AstraZeneca's consent prior to engaging any third-party manufacturers for esomeprazole, one of the APIs in VIMOVO, other than the third-party manufacturer(s) used by AstraZeneca or its affiliates or licensees. To the extent such manufacturers are unwilling or unable to manufacture esomeprazole for us on commercially acceptable terms, we cannot guarantee that AstraZeneca would consent to our use of alternate sources of supply.

We rely on an exclusive supply agreement with Boehringer Ingelheim Biopharmaceuticals GmbH, or Boehringer Ingelheim Biopharmaceuticals, for manufacturing and supply of ACTIMMUNE. ACTIMMUNE is manufactured by starting with cells from working cell bank samples which are derived from a master cell bank. We and Boehringer Ingelheim Biopharmaceuticals separately store multiple vials of the master cell bank. In the event of catastrophic loss at our or Boehringer Ingelheim Biopharmaceuticals' storage facility, it is possible that we could lose multiple cell banks and have the manufacturing capacity of ACTIMMUNE severely impacted by the need to substitute or replace the cell banks. We rely on NOF Corporation, or NOF, as our exclusive supplier of the PEGylation agent that is a critical raw material in the manufacture of KRYSTEXXA. If NOF failed to supply such PEGylation agent, it may lead to KRYSTEXXA supply constraints. In addition, a key excipient used in PENNSAID 2% as a penetration enhancer is dimethyl sulfoxide, or DMSO. We and Nuvo, our exclusive supplier of PENNSAID 2%, rely on a sole proprietary form of DMSO for which we maintain a substantial safety stock. However, should this supply become inadequate, damaged, destroyed or unusable, we and Nuvo may not be able to qualify a second source.

If any of our third-party manufacturers cannot successfully manufacture material that conforms to our specifications and the applicable regulatory authorities' strict regulatory requirements, or pass regulatory inspection, they will not be able to secure or maintain regulatory approval for the manufacturing facilities. For example, Pharmaceutics International, Inc., or PII, our manufacturer of BUPHENYL, was found to be non-compliant for cGMPs by the Medicines and Healthcare Products Regulatory Agency, or the MHRA, which could restrict PII from supplying BUPHENYL in the EU. However, BUPHENYL was considered to be critical to public health and as a result, the MHRA issued a certificate of cGMP compliance for PII, which is valid until June 30, 2018. Additionally, we provided PII with a notice of termination of our supply agreement for BUPHENYL, and are in the process of negotiating a new supply agreement with them. We consider our BUPHENYL inventory on hand to be sufficient to meet current and future commercial requirements during the negotiation process. In addition, we have no control over the ability of third-party manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or any other applicable regulatory authorities do not approve these facilities for the manufacture of our medicines or if they withdraw any such approval in the future, or if our suppliers or third-party manufacturers decide they no longer want to supply our primary active ingredients or manufacture our medicines, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our medicines. To the extent any third-party manufacturers that we engage with respect to our medicines are different from those currently being used for commercial supply in the United States, the FDA will need to approve the facilities of those third-party manufacturers used in the manufacture of our medicines prior to our sale of any medicine using these facilities.

Although we have entered into supply agreements for the manufacture and packaging of our medicines, our manufacturers may not perform as agreed or may terminate their agreements with us. We currently rely on single source suppliers for certain of our medicines. If our manufacturers terminate their agreements with us, we may have to qualify new back-up manufacturers. We rely on safety stock to mitigate the risk of our current suppliers electing to cease producing bulk drug medicine or ceasing to do so at acceptable prices and quality. However, we can provide no assurance that such safety stocks would be sufficient to avoid supply shortfalls in the event we have to identify and qualify new contract manufacturers.

The manufacture of medicines requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of medicines often encounter difficulties in production, particularly in scaling up and validating initial production. These problems include difficulties with production costs and yields, quality control, including stability of the medicine, quality assurance testing, shortages of qualified personnel, as well as compliance with strictly enforced federal, state and foreign regulations. Furthermore, if microbial, viral or other contaminations are discovered in the medicines or in the manufacturing facilities in which our medicines are made, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the contamination. We cannot assure that issues relating to the manufacture of any of our medicines will not occur in the future. Additionally, our manufacturers may experience manufacturing difficulties due to resource constraints or as a result of labor disputes or unstable political environments. If our manufacturers were to encounter any of these difficulties, or otherwise fail to comply with their contractual obligations, our ability to commercialize our medicines or provide any medicine candidates to patients in clinical trials would be jeopardized.

Any delay or interruption in our ability to meet commercial demand for our medicines will result in the loss of potential revenues and could adversely affect our ability to gain market acceptance for these medicines. In addition, any delay or interruption in the supply of clinical trial supplies could delay the completion of clinical trials, increase the costs associated with maintaining clinical trial programs and, depending upon the period of delay, require us to commence new clinical trials at additional expense or terminate clinical trials completely.

Failures or difficulties faced at any level of our supply chain could materially adversely affect our business and delay or impede the development and commercialization of any of our medicines or medicine candidates and could have a material adverse effect on our business, results of operations, financial condition and prospects.

We have experienced growth and expanded the size of our organization substantially in connection with our acquisition transactions, and we may experience difficulties in managing this growth as well as potential additional growth in connection with future medicine, development program or company acquisitions.

As of December 31, 2013, we employed approximately 300 full-time employees as a consolidated entity. As of December 31, 2017, we employed approximately 1,010 full-time employees, including approximately 430 sales representatives, representing a substantial change to the size of our organization. We have also experienced, and may continue to experience, turnover of the sales representatives that we hired or will hire in connection with the commercialization of our medicines, requiring us to hire and train new sales representatives. Our management, personnel, systems and facilities currently in place may not be adequate to support this recent and anticipated growth, and we may not be able to retain or recruit qualified personnel in the future due to competition for personnel among pharmaceutical businesses.

As our commercialization plans and strategies continue to develop, we will need to continue to recruit and train sales and marketing personnel. Our ability to manage any future growth effectively may require us to, among other things:

- continue to manage and expand the sales and marketing efforts for our existing medicines;
- enhance our operational, financial and management controls, reporting systems and procedures;
- expand our international resources;
- successfully identify, recruit, hire, train, maintain, motivate and integrate additional employees;
- establish and increase our access to commercial supplies of our medicines and medicine candidates;
- expand our facilities and equipment; and
- manage our internal development efforts effectively while complying with our contractual obligations to licensors, licensees, contractors, collaborators, distributors and other third parties.

Our acquisitions have resulted in many changes, including significant changes in the corporate business and legal entity structure, the integration of other companies and their personnel with us, and changes in systems. We are currently undertaking numerous complex transition activities associated with our acquisitions, and we may encounter unexpected difficulties or incur unexpected costs, including:

- difficulties in achieving growth prospects from combining third-party businesses with our business;
- difficulties in the integration of operations and systems;
- difficulties in the assimilation of employees and corporate cultures;
- challenges in preparing financial statements and reporting timely results at both a statutory level for multiple entities and jurisdictions and at a consolidated level for public reporting;
- challenges in keeping existing physician prescribers and patients and increasing adoption of acquired medicines;
- difficulties in achieving anticipated cost savings, synergies, business opportunities and growth prospects from the combination;
- potential unknown liabilities, adverse consequences and unforeseen increased expenses associated with the transaction; and
- challenges in attracting and retaining key personnel.

If any of these factors impair our ability to continue to integrate our operations with those of any companies or businesses we acquire, we may not be able to realize the business opportunities, growth prospects and anticipated tax synergies from combining the businesses. In addition, we may be required to spend additional time or money on integration that otherwise would be spent on the development and expansion of our business.

We may not be successful in growing our commercial operations outside the United States, and could encounter other challenges in growing our commercial presence in Europe, including due to risks associated with political and economic instability, operating under different legal requirements and tax complexities. If we are unable to manage our commercial growth outside of the United States, our opportunities to expand sales in other countries will be limited or we may experience greater costs with respect to our ex-U.S. commercial operations.

We are also broadening our acquisition strategy to potentially include development-stage assets or programs, which entails additional risk to us. For example, if we are unable to identify programs that ultimately result in approved medicines, we may spend material amounts of our capital and other resources evaluating, acquiring and developing medicines that ultimately do not provide a return on our investment. We have less experience evaluating development-stage assets and may be at a disadvantage compared to other entities pursuing similar opportunities. Regardless, development-stage programs generally have a high rate of failure and we cannot guarantee that any such programs will ultimately be successful. We will also need to enhance our clinical development and regulatory functions to properly evaluate and develop earlier-stage opportunities, which may include recruiting personnel that are knowledgeable in therapeutic areas we have not yet pursued. If we are unable to acquire promising development-stage assets or eventually obtain marketing approval for them, we may not be able to create a meaningful pipeline of new medicines and eventually realize a return on our investments.

Our management may also have to divert a disproportionate amount of its attention away from day-to-day activities and toward managing these growth and integration activities. Our future financial performance and our ability to execute on our business plan will depend, in part, on our ability to effectively manage any future growth and our failure to effectively manage growth could have a material adverse effect on our business, results of operations, financial condition and prospects.

We face significant competition from other biotechnology and pharmaceutical companies, including those marketing generic medicines and our operating results will suffer if we fail to compete effectively.

The biotechnology and pharmaceutical industries are intensely competitive. We have competitors both in the United States and international markets, including major multinational pharmaceutical companies, biotechnology companies and universities and other research institutions. Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff, experienced marketing and manufacturing organizations and well-established sales forces. Additional consolidations in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors and we will have to find new ways to compete and may have to potentially merge with or acquire other businesses to stay competitive. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or in-licensing on an exclusive basis, medicines that are more effective and/or less costly than our medicines.

RAVICTI and BUPHENYL face competition from generic NaPBA tablets and powder in treating UCD. Lucane Pharma, or Lucane, is seeking approval via an Abbreviated New Drug Application, or ANDA, in the United States for taste-masked NaPBA. If this ANDA is approved, this formulation may also compete with RAVICTI and BUPHENYL in treating UCD in the United States. PROCYSBI faces competition from Cystagon (immediate-release cysteamine bitartrate capsules) for the treatment of cystinosis and Cystaran (cysteamine ophthalmic solution) for treatment of corneal crystal accumulation in patients with cystinosis. QUINSAIR faces competition from Tobramycin solution, which is available as a generic medicine for treatment of chronic *Pseudomonas aeruginosa* lung infections in patients with CF, TOBI Podhaler, Cayston and colistimethate. While KRYSTEXXA faces limited direct competition, a number of competitors have drugs in Phase 1 or Phase 2 trials. On December 22, 2015, AstraZeneca secured approval from the FDA for ZURAMPIC (lesinurad) 200mg tablets in combination with a xanthine oxidase inhibitor, or XOI, for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with an XOI alone. In April 2016, the U.S. rights to ZURAMPIC were licensed to Ironwood Pharmaceuticals Inc. Although ZURAMPIC is not a direct competitor because it has not been approved for refractory gout, this therapy could be used prior to use of KRYSTEXXA and if effective, could reduce the target patient population for KRYSTEXXA. PENNSAID 2% faces competition from generic versions of diclofenac sodium topical solutions that are priced significantly less than the price we charge for PENNSAID 2%. The generic version of Voltaren Gel is the market leader in the topical NSAID category. Legislation enacted in most states in the United States allows, or in some instances mandates, that a pharmacist dispense an available generic equivalent when filling a prescription for a branded medicine, in the absence of specific instructions from the prescribing physician. DUEXIS and VIMOVO face competition from other NSAIDs, including Celebrex®, marketed by Pfizer Inc., and celecoxib, a generic form of the medicine marketed by other pharmaceutical companies. DUEXIS and VIMOVO also face significant competition from the separate use of NSAIDs for pain relief and GI protective medications to reduce the risk of NSAID-induced upper GI ulcers. Both NSAIDs and GI protective medications are available in generic form and may be less expensive to use separately than DUEXIS or VIMOVO, despite such substitution being off-label in the case of DUEXIS and VIMOVO. Because pharmacists often have economic and other incentives to prescribe lower-cost generics, if physicians prescribe PENNSAID 2%, DUEXIS,

or VIMOVO, those prescriptions may not result in sales. If physicians do not complete prescriptions through our HorizonCares program or otherwise provide prescribing instructions prohibiting generic diclofenac sodium topical solutions as a substitute for PENNSAID 2%, the substitution of generic ibuprofen and famotidine separately as a substitution for DUEXIS or generic naproxen and branded Nexium® (esomeprazole) as a substitute for VIMOVO, sales of PENNSAID 2%, DUEXIS and VIMOVO may suffer despite any success we may have in promoting PENNSAID 2%, DUEXIS or VIMOVO to physicians. In addition, other medicine candidates that contain ibuprofen and famotidine in combination or naproxen and esomeprazole in combination, while not currently known or FDA approved, may be developed and compete with DUEXIS or VIMOVO, respectively, in the future.

We have also entered into settlement and license agreements that may allow certain of our competitors to sell generic versions of certain of our medicines in the United States, subject to the terms of such agreements. We granted (i) a non-exclusive license (that is only royalty-bearing in some circumstances) to manufacture and commercialize a generic version of DUEXIS in the United States after January 1, 2023, (ii) non-exclusive licenses to manufacture and commercialize generic versions of PENNSAID 2% in the United States after January 10, 2029, and (iii) a non-exclusive license to manufacture and commercialize a generic version of RAYOS tablets in the United States after December 23, 2022, or each earlier under certain circumstances.

Patent litigation is currently pending in the United States District Court for the Eastern District of Texas against Par Pharmaceutical, Inc., or Par Pharmaceutical, and in the United States District Court for the District of New Jersey against Par Pharmaceutical and against Lupin Limited and Lupin Pharmaceuticals, Inc., or collectively Lupin, who are each intending to market generic versions of RAVICTI prior to the expiration of certain of our patents listed in the Orange Book. These cases are collectively known as the RAVICTI cases and arise from Paragraph IV Patent Certification notice letters from each of Par Pharmaceutical and Lupin advising each had filed an ANDA with the FDA seeking approval to market a generic version of RAVICTI before the expiration of the patents-in-suit.

Patent litigation is currently pending in the United States District Court for the District of New Jersey against several companies intending to market a generic version of PENNSAID 2% prior to the expiration of certain of our patents listed in the FDA's Orange Book, or the Orange Book. These cases are collectively known as the PENNSAID 2% cases, and involve the following sets of defendants: (i) Actavis Laboratories UT, Inc., formerly known as Watson Laboratories, Inc., Actavis, Inc. and Actavis plc, or collectively Actavis; and (ii) Lupin. These cases arise from Paragraph IV Patent Certification notice letters from each of Actavis and Lupin advising each had filed an ANDA with the FDA seeking approval to market a generic version of PENNSAID 2% before the expiration of the patents-in-suit.

Patent litigation is currently pending in the United States District Court for the District of New Jersey and the Court of Appeals for the Federal Circuit against several companies intending to market a generic version of VIMOVO before the expiration of certain of our patents listed in the Orange Book. These cases are collectively known as the VIMOVO cases, and involve the following sets of defendants: (i) Dr. Reddy's Laboratories Inc. and Dr. Reddy's Laboratories Ltd., or collectively Dr. Reddy's; (ii) Lupin; and (iii) Mylan Pharmaceuticals Inc., Mylan Laboratories Limited, and Mylan Inc., or collectively Mylan. Patent litigation is currently pending before the Court of Appeals for the Federal Circuit against a fourth generic company, Teva Pharmaceuticals Industries Limited (formerly known as Actavis Laboratories FL, Inc., which itself was formerly known as Watson Laboratories, Inc. – Florida) and Actavis Pharma, Inc., or collectively Actavis Pharma. The cases arise from Paragraph IV Patent Certification notice letters from each of Dr. Reddy's, Lupin, Mylan and Actavis Pharma advising each had filed an ANDA with the FDA seeking approval to market generic versions of VIMOVO before the expiration of the patents-in-suit.

If we are unsuccessful in any of the VIMOVO cases or PENNSAID 2% cases, we will likely face generic competition with respect to VIMOVO and/or PENNSAID 2% and sales of VIMOVO and/or PENNSAID 2% will be substantially harmed. If we are unsuccessful in any of the RAVICTI cases, RAVICTI would likely face generic competition in the United States when its orphan exclusivity expires (currently scheduled to occur in February 2020), and its sales would likely materially decline.

ACTIMMUNE is the only medicine currently approved by the FDA specifically for the treatment of CGD and SMO. While there are additional or alternative approaches used to treat patients with CGD and SMO, there are currently no medicines on the market that compete directly with ACTIMMUNE. A widely accepted protocol to treat CGD in the United States is the use of concomitant "triple prophylactic therapy" comprising ACTIMMUNE, an oral antibiotic agent and an oral antifungal agent. However, the FDA-approved labeling for ACTIMMUNE does not discuss this "triple prophylactic therapy," and physicians may choose to prescribe one or both of the other modalities in the absence of ACTIMMUNE. Because of the immediate and life-threatening nature of SMO, the preferred treatment option for SMO is often to have the

patient undergo a bone marrow transplant which, if successful, will likely obviate the need for further use of ACTIMMUNE in that patient. Likewise, the use of bone marrow transplants in the treatment of patients with CGD is becoming more prevalent, which could have a material adverse effect on sales of ACTIMMUNE and its profitability. We are aware of a number of research programs investigating the potential of gene therapy as a possible cure for CGD. Additionally, other companies may be pursuing the development of medicines and treatments that target the same diseases and conditions which ACTIMMUNE is currently approved to treat. As a result, it is possible that our competitors may develop new medicines that manage CGD or SMO more effectively, cost less or possibly even cure CGD or SMO. In addition, U.S. healthcare legislation passed in March 2010 authorized the FDA to approve biological products, known as biosimilars, that are similar to or interchangeable with previously approved biological products, like ACTIMMUNE, based upon potentially abbreviated data packages. Biosimilars are likely to be sold at substantially lower prices than branded medicines because the biosimilar manufacturer would not have to recoup the research and development and marketing costs associated with the branded medicine. Though we are not currently aware of any biosimilar under development, the development and commercialization of any competing medicines or the discovery of any new alternative treatment for CGD or SMO could have a material adverse effect on sales of ACTIMMUNE and its profitability.

BUPHENYL's composition of matter patent protection and orphan drug exclusivity have expired. Because BUPHENYL has no regulatory exclusivity or listed patents, there is nothing to prevent a competitor from submitting an ANDA for a generic version of BUPHENYL and receiving FDA approval. Generic versions of BUPHENYL to date have been priced at a discount relative to BUPHENYL or RAVICTI, and physicians, patients, or payers may decide that this less expensive alternative is preferable to BUPHENYL and RAVICTI. If this occurs, sales of BUPHENYL and/or RAVICTI could be materially reduced, but we would nevertheless be required to make royalty payments to Ucyclyd Pharma, Inc., or Ucyclyd, and another external party, at the same royalty rates. While Ucyclyd and its affiliates are generally contractually prohibited from developing or commercializing new medicines, anywhere in the world, for the treatment of UCD or hepatic encephalopathy, or HE, which are chemically similar to RAVICTI, they may still develop and commercialize medicines that compete with RAVICTI. For example, medicines approved for indications other than UCD and HE may still compete with RAVICTI if physicians prescribe such medicines off-label for UCD or HE. We are also aware that Orphan Europe SARL, or Orphan Europe, is conducting a clinical trial of carglumic acid to treat some of the UCD enzyme deficiencies for which RAVICTI was approved. Promethera Biosciences SA has successfully completed Phase I/II trials of its cell-based therapy for the treatment of UCD and plans to conduct a Phase IIb/III clinical trial. Carglumic acid is approved for maintenance therapy for chronic hyperammonemia and to treat hyperammonenic crises in Nacetylglutamate synthase deficiency, a rare UCD subtype, and is sold under the name Carbaglu. If the results of this trial are successful and Orphan Europe is able to complete development and obtain approval of Carbaglu to treat additional UCD enzyme deficiencies, RAVICTI would face additional competition from this compound.

The availability and price of our competitors' medicines could limit the demand, and the price we are able to charge, for our medicines. We will not successfully execute on our business objectives if the market acceptance of our medicines is inhibited by price competition, if physicians are reluctant to switch from existing medicines to our medicines, or if physicians switch to other new medicines or choose to reserve our medicines for use in limited patient populations.

In addition, established pharmaceutical companies may invest heavily to accelerate discovery and development of novel compounds or to acquire novel compounds that could make our medicines obsolete. Our ability to compete successfully with these companies and other potential competitors will depend largely on our ability to leverage our experience in clinical, regulatory and commercial development to:

- develop and acquire medicines that are superior to other medicines in the market;
- attract qualified clinical, regulatory, and sales and marketing personnel;
- obtain patent and/or other proprietary protection for our medicines and technologies;
- obtain required regulatory approvals; and
- successfully collaborate with pharmaceutical companies in the discovery, development and commercialization of new medicine candidates.

If we are unable to maintain or realize the benefits of orphan drug exclusivity, we may face increased competition with respect to certain of our medicines.

Under the Orphan Drug Act of 1983, the FDA may designate a medicine as an orphan drug if it is a drug intended to treat a rare disease or condition affecting fewer than 200,000 people in the United States. A company that first obtains FDA approval for a designated orphan drug for the specified rare disease or condition receives orphan drug marketing exclusivity for that drug for a period of seven years from the date of its approval. RAVICTI and PROCYSBI have been granted orphan drug exclusivity by the FDA, which we expect will provide orphan drug marketing exclusivity in the United States until February 2020 and December 2020, respectively, with exclusivity for PROCYSBI extending to 2022 for patients ages one to six years. In addition, teprotumumab has been granted orphan drug designation and, if approved by the FDA, would be eligible for seven years of marketing exclusivity in the United States following such approval. However, despite orphan drug exclusivity, the FDA can still approve another drug containing the same active ingredient and used for the same orphan indication if it determines that a subsequent drug is safer, more effective or makes a major contribution to patient care, and orphan exclusivity can be lost if the orphan drug manufacturer is unable to ensure that a sufficient quantity of the orphan drug is available to meet the needs of patients with the rare disease or condition. Orphan drug exclusivity may also be lost if the FDA later determines that the initial request for designation was materially defective. In addition, orphan drug exclusivity does not prevent the FDA from approving competing drugs for the same or similar indication containing a different active ingredient. If orphan drug exclusivity is lost and we were unable to successfully enforce any remaining patents covering RAVICTI or PROCYSBI, we could be subject to generic competition and revenues from RAVICTI or PROCYSBI could decrease materially. In addition, if a subsequent drug is approved for marketing for the same or a similar indication as RAVICTI or PROCYSBI despite orphan drug exclusivity, we may face increased competition and lose market share with respect to these medicines. RAVICTI will benefit from a period of 10 years of orphan market exclusivity in the EU, concurrently applied to each of the approved six sub-types of the UCDs. This will run concurrently with its marketing exclusivity status.

Our business operations may subject us to numerous commercial disputes, claims and/or lawsuits and such litigation may be costly and time-consuming and could materially and adversely impact our financial position and results of operations.

Operating in the pharmaceutical industry, particularly the commercialization of medicines, involves numerous commercial relationships, complex contractual arrangements, uncertain intellectual property rights, potential product liability and other aspects that create heightened risks of disputes, claims and lawsuits. In particular, we may face claims related to the safety of our medicines, intellectual property matters, employment matters, tax matters, commercial disputes, competition, sales and marketing practices, environmental matters, personal injury, insurance coverage and acquisition or divestiture-related matters. For example, the active ingredient in QUINSAIR, levofloxacin, is currently subject to product liability claims. Any commercial dispute, claim or lawsuit may divert management's attention away from our business, we may incur significant expenses in addressing or defending any commercial dispute, claim or lawsuit, and we may be required to pay damage awards or settlements or become subject to equitable remedies that could adversely affect our operations and financial results.

We are currently in litigation with multiple generic drug manufacturers regarding intellectual property infringement. For example, we are currently involved in Hatch Waxman litigation with generic drug manufacturers related to, RAVICTI, PENNSAID 2% and VIMOVO.

Similarly, from time to time we are involved in disputes with distributors, PBMs and licensing partners regarding our rights and performance of obligations under contractual arrangements. For example, we were previously in litigation with Express Scripts related to alleged breach of contract claims.

Litigation related to these disputes may be costly and time-consuming and could materially and adversely impact our financial position and results of operations if resolved against us.

A variety of risks associated with operating our business and marketing our medicines internationally could materially adversely affect our business.

In addition to our U.S. operations, we have operations in Ireland, Bermuda, the Grand Duchy of Luxembourg, or Luxembourg, Switzerland, Germany, Canada, the Grand Cayman Islands and in Israel (through Andromeda Biotech Ltd). RAVICTI received marketing authorization from Health Canada, or HC, in March 2016 and marketing approval in the EU in November 2015. We launched RAVICTI in Canada in November 2016 and RAVICTI became available in Europe in the fourth quarter of 2017 through our partnership with SOBI. PROCYSBI received marketing authorization from HC in June 2017 and we launched PROCYSBI in Canada in October 2017. BUPHENYL is currently marketed in various territories outside the United States by third-party distributors. QUINSAIR received marketing authorization from HC in June 2015 and we launched QUINSAIR in Canada in December 2016. We face risks associated with our international operations, including possible unfavorable regulatory, pricing and reimbursement, political, tax and labor conditions, which could harm our business. We are subject to numerous risks associated with international business activities, including:

- compliance with differing or unexpected regulatory requirements for our medicines;
- compliance with Irish laws and the maintenance of our Irish tax residency with respect to our overall corporate structure and administrative operations, including the need to generally hold meetings of our board of directors and make decisions in Ireland, which may make certain corporate actions more cumbersome, costly and time-consuming;
- difficulties in staffing and managing foreign operations;
- in certain circumstances, including with respect to the commercialization of RAVICTI in select countries throughout Europe, commercialization of BUPHENYL in select countries throughout Europe, the Middle East, and the Asia-Pacific region, commercialization of LODOTRA in Europe and certain Asian, Latin American, Middle Eastern and African countries, and commercialization of DUEXIS in Latin America, increased dependence on the commercialization efforts and regulatory compliance of third-party distributors or strategic partners;
- compliance with German laws with respect to our Horizon Pharma GmbH subsidiary through which Horizon Pharma Switzerland GmbH conducts most of its European operations;
- foreign government taxes, regulations and permit requirements;
- U.S. and foreign government tariffs, trade restrictions, price and exchange controls and other regulatory requirements;
- anti-corruption laws, including the Foreign Corrupt Practices Act, or the FCPA;
- economic weakness, including inflation, natural disasters, war, events of terrorism or political instability in particular foreign countries;
- fluctuations in currency exchange rates, which could result in increased operating expenses and reduced revenues, and other obligations related to doing business in another country;
- compliance with tax, employment, immigration and labor laws, regulations and restrictions for employees living or traveling abroad;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad;
- changes in diplomatic and trade relationships; and
- challenges in enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States.

Our business activities outside of the United States are subject to the FCPA and similar anti-bribery or anti-corruption laws, regulations or rules of other countries in which we operate, including the United Kingdom's Bribery Act 2010, or the U.K. Bribery Act. The FCPA and similar anti-corruption laws generally prohibit offering, promising, giving, or authorizing others to give anything of value, either directly or indirectly, to non-U.S. government officials in order to improperly influence any act or decision, secure any other improper advantage, or obtain or retain business. The FCPA also requires public companies to make and keep books and records that accurately and fairly reflect the transactions of the company and to devise and maintain an adequate system of internal accounting controls. The U.K. Bribery Act prohibits giving, offering, or promising bribes to any person, including non-United Kingdom, or U.K., government officials and private persons, as well as requesting, agreeing to receive, or accepting bribes from any person. In addition, under the U.K. Bribery Act, companies which carry on a business or part of a business in the U.K. may be held liable for bribes given, offered or promised to any person, including non-U.K. government officials and private persons, by employees and persons associated with the company in order to obtain or retain business or a business advantage for the company. Liability is strict, with no element of a corrupt state of mind, but a defense of having in place adequate procedures designed to prevent bribery is available. Furthermore, under the U.K. Bribery Act there is no exception for facilitation payments. As described above, our business is heavily regulated and therefore involves significant interaction with public officials, including officials of non-U.S. governments. Additionally, in many other countries, the health care providers who prescribe pharmaceuticals are employed by their government, and the purchasers of pharmaceuticals are government entities; therefore, any dealings with these prescribers and purchasers may be subject to regulation under the FCPA. Recently the SEC and the U.S. Department of Justice have increased their FCPA enforcement activities with respect to pharmaceutical companies. In addition, under the Dodd–Frank Wall Street Reform and Consumer Protection Act, private individuals who report to the SEC original information that leads to successful enforcement actions may be eligible for a monetary award. We are engaged in ongoing efforts that are designed to ensure our compliance with these laws, including due diligence, training, policies, procedures and internal controls. However, there is no certainty that all employees and third-party business partners (including our distributors, wholesalers, agents, contractors, and other partners) will comply with anti-bribery laws. In particular, we do not control the actions of manufacturers and other third-party agents, although we may be liable for their actions. Violation of these laws may result in civil or criminal sanctions, which could include monetary fines, criminal penalties, and disgorgement of past profits, which could have a material adverse impact on our business and financial condition.

These and other risks associated with our international operations may materially adversely affect our business, financial condition and results of operations.

If we fail to develop or acquire other medicine candidates or medicines, our business and prospects would be limited.

A key element of our strategy is to develop or acquire and commercialize a portfolio of other medicines or medicine candidates in addition to our current medicines, through business or medicine acquisitions. Because we do not engage in proprietary drug discovery, the success of this strategy depends in large part upon the combination of our regulatory, development and commercial capabilities and expertise and our ability to identify, select and acquire approved or clinically enabled medicine candidates for therapeutic indications that complement or augment our current medicines, or that otherwise fit into our development or strategic plans on terms that are acceptable to us. Identifying, selecting and acquiring promising medicines or medicine candidates requires substantial technical, financial and human resources expertise. Efforts to do so may not result in the actual acquisition or license of a particular medicine or medicine candidate, potentially resulting in a diversion of our management's time and the expenditure of our resources with no resulting benefit. If we are unable to identify, select and acquire suitable medicines or medicine candidates from third parties or acquire businesses at valuations and on other terms acceptable to us, or if we are unable to raise capital required to acquire businesses or new medicines, our business and prospects will be limited.

Moreover, any medicine candidate we acquire may require additional, time-consuming development or regulatory efforts prior to commercial sale or prior to expansion into other indications, including pre-clinical studies if applicable, and extensive clinical testing and approval by the FDA and applicable foreign regulatory authorities. All medicine candidates are prone to the risk of failure that is inherent in pharmaceutical medicine development, including the possibility that the medicine candidate will not be shown to be sufficiently safe and/or effective for approval by regulatory authorities. In addition, we cannot assure that any such medicines that are approved will be manufactured or produced economically, successfully commercialized or widely accepted in the marketplace or be more effective or desired than other commercially available alternatives.

In addition, if we fail to successfully commercialize and further develop our medicines, there is a greater likelihood that we will fail to successfully develop a pipeline of other medicine candidates to follow our existing medicines or be able to acquire other medicines to expand our existing portfolio, and our business and prospects would be harmed.

Our prior medicine and company acquisitions and any other strategic transactions that we may pursue in the future could have a variety of negative consequences, and we may not realize the benefits of such transactions or attempts to engage in such transactions.

We have completed multiple medicine and company acquisitions and our strategy is to engage in additional strategic transactions with third parties, such as acquisitions of companies or divisions of companies and asset purchases of medicines, medicine candidates or technologies that we believe will complement or augment our existing business. We may also consider a variety of other business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and other investments. Any such transaction may require us to incur non-recurring and other charges, increase our near and long-term expenditures, pose significant integration challenges, create additional tax, legal, accounting and operational complexities in our business, require additional expertise, result in dilution to our existing shareholders and disrupt our management and business, which could harm our operations and financial results. For example, we assumed responsibility for the existing patent infringement litigation with respect to RAVICTI upon the closing of our acquisition of Hyperion Therapeutics, Inc., or Hyperion, and have assumed responsibility for completing post-marketing clinical trials of RAVICTI that are required by the FDA and are ongoing. We expect that the RAVICTI litigation will result in substantial on-going expenses and potential distractions to our management team.

In connection with our acquisition of Raptor, we assumed contractual obligations under agreements with Tripex Pharmaceuticals, LLC, or Tripex, and PARI Pharma GmbH, or PARI, related to QUINSAIR. Under the agreement with Tripex, we are required to pursue commercially reasonable efforts to initiate, and subsequently to complete, an additional clinical trial of QUINSAIR in a non-CF patient population within a specified period of time and an obligation to progress toward submitting an NDA for approval of QUINSAIR in the United States for use in all or part of the CF patient population. These obligations are subject to certain exceptions due to, for example, manufacturing delays not under our control, or delays caused by the FDA. If we fail to properly exercise such efforts to initiate and complete an appropriate clinical trial, or fail to submit an NDA for U.S. approval in the CF patient population, during the time periods specified in the agreement, we may be subject to various claims by Tripex and parties affiliated with Tripex. In addition, if we do not spend a minimum amount on QUINSAIR development in each of the three years following our acquisition of Raptor, we may also be obligated to pre-pay a milestone payment related to initiating a clinical trial for QUINSAIR in a non-CF indication. During October 2017, we triggered a milestone payment under this agreement, and we paid Tripex $20.0 million in November 2017. Under the license agreement with PARI, we are required to comply with diligence milestones related to development and commercialization of QUINSAIR in the United States and to spend a specified minimum amount per year on development activities in the United States until submission of the NDA for QUINSAIR in the United States. If we do not comply with these obligations, our licenses to certain intellectual property related to QUINSAIR may become non-exclusive in the United States or could be terminated. We are also subject to contractual obligations under an amended and restated license agreement with the Regents of the University of California, San Diego, or UCSD, with respect to PROCYSBI, including obligations to consider engaging in the development of PROCYSBI for the treatment of non-alcoholic steatohepatitis, or NASH, and related diligence obligations if we undertake such development. Under the amended and restated license agreement with USCD, we also are subject to diligence obligations to identify a third party to undertake development of PROCYSBI for the treatment of Huntington's disease. To the extent that we fail to perform the diligence obligations under the agreement, UCSD may, with respect to such indication, terminate the license or otherwise cause the license to become non-exclusive. If one or more of these licenses was terminated, we would have no further right to use or exploit the related intellectual property, which would limit our ability to develop PROCYSBI or QUINSAIR in other indications, and could impact our ability to continue commercializing PROCYSBI or QUINSAIR in their approved indications. In connection with our acquisition of the U.S. rights to VIMOVO, we assumed primary responsibility for the existing patent infringement litigation with respect to VIMOVO, and have also agreed to reimburse certain legal expenses of Aralez Pharmaceuticals Inc. with respect to its continued involvement in such litigation.

We face significant competition in seeking appropriate strategic transaction opportunities and the negotiation process for any strategic transaction can be time-consuming and complex. In addition, we may not be successful in our efforts to engage in certain strategic transactions because our financial resources may be insufficient and/or third parties may not view our commercial and development capabilities as being adequate. We may not be able to expand our business or realize our strategic goals if we do not have sufficient funding or cannot borrow or raise additional capital. There is no assurance that following any of our recent acquisition transactions or any other strategic transaction, we will achieve the anticipated revenues, net income or other benefits that we believe justify such transactions. In addition, any failures or delays in entering into strategic transactions anticipated by analysts or the investment community could seriously harm our consolidated business, financial condition, results of operations or cash flow.

We may not be able to successfully maintain our current advantageous tax status and resulting tax rates, which could adversely affect our business and financial condition, results of operations and growth prospects.

Our parent company is incorporated in Ireland and has subsidiaries maintained in multiple jurisdictions, including Ireland, the United States, Switzerland, Luxembourg, Germany, Canada, the Grand Cayman Islands and Bermuda. Prior to our merger transaction in September 2014 with Vidara Therapeutics International Public Limited Company, or Vidara, and such transaction, the Vidara Merger, Vidara was able to achieve a favorable tax rate through the performance of certain functions and ownership of certain assets in tax-efficient jurisdictions, including Ireland and Bermuda, together with intra-group service and transfer pricing agreements, each on an arm's length basis. We are continuing a substantially similar structure and arrangements. Nevertheless, our effective tax rate may be different than experienced in the past due to numerous factors, including passage of the Tax Act (as defined below), changes to the tax laws of jurisdictions that we operate in other than the United States made in response to the Tax Act, changes in the mix of our profitability from jurisdiction to jurisdiction, future changes to U.S. tax law (including for example, the enactment of new U.S. tax treaties or changes to existing tax treaties), and our inability to secure or sustain acceptable agreements with tax authorities (if applicable). Any of these factors could cause us to experience an effective tax rate significantly different from previous periods or our current expectations. Taxing authorities, such as the U.S. Internal Revenue Service, or IRS, actively audit and otherwise challenge these types of arrangements, and have done so in the pharmaceutical industry. We expect that these challenges will continue as a result of the recent increase in scrutiny and political attention on corporate tax structures. The IRS may challenge our structure and transfer pricing arrangements through an audit or lawsuit. Responding to or defending such a challenge could be expensive and consume time and other resources, and divert management's time and focus from operating our business. We cannot predict whether taxing authorities will conduct an audit or file a lawsuit challenging this structure, the cost involved in responding to any such audit or lawsuit, or the outcome. If we are unsuccessful in defending such a challenge, we may be required to pay taxes for prior periods, interest, fines or penalties, and may be obligated to pay increased taxes in the future, any of which could require us to reduce our operating expenses, decrease efforts in support of our medicines or seek to raise additional funds, all of which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

The IRS may not agree with our conclusion that our parent company should be treated as a foreign corporation for U.S. federal income tax purposes following the combination of the businesses of Horizon Pharma, Inc., or HPI, and Vidara.

Although our parent company is incorporated in Ireland, the IRS may assert that it should be treated as a U.S. corporation (and, therefore, a U.S. tax resident) for U.S. federal income tax purposes pursuant to Section 7874 of the Internal Revenue Code of 1986, as amended, or the Code. A corporation is generally considered a tax resident in the jurisdiction of its organization or incorporation for U.S. federal income tax purposes. Because our parent company is an Irish incorporated entity, it would generally be classified as a foreign corporation (and, therefore, a non-U.S. tax resident) under these general rules. Section 7874 of the Code provides an exception pursuant to which a foreign incorporated entity may, in certain circumstances, be treated as a U.S. corporation for U.S. federal income tax purposes.

Under Section 7874 of the Code, a foreign corporation will be treated as a U.S. corporation for U.S. federal tax purposes if, due to an acquisition of a U.S. corporation, at least 80 percent of its stock (by vote or value) is held by former stockholders of the acquired U.S. corporation. We believe that we should be treated as a foreign corporation because the former stockholders of HPI owned (within the meaning of Section 7874 of the Code) less than 80 percent (by both vote and value) of the combined entity's stock immediately after the Vidara Merger. However, there can be no assurance that there will not exist in the future a subsequent change in the facts or in law which might cause our parent company to be treated as a domestic corporation for U.S. federal income tax purposes, including with retroactive effect.

Further, there can be no assurance that the IRS will agree with the position that the ownership test was satisfied. If our parent company were unable to be treated as a foreign corporation for U.S. federal income tax purposes, one of our significant strategic reasons for completing the Vidara Merger would be nullified and we may not be able to recoup the significant investment in completing the transaction.

Future changes to U.S. and non-U.S. tax laws could materially adversely affect our company.

Under current law, we expect our parent company to be treated as a foreign corporation for U.S. federal income tax purposes. However, changes to the rules in Section 7874 of the Code or regulations promulgated thereunder or other guidance issued by the U.S. Department of the Treasury, or the U.S. Treasury, or the IRS could adversely affect our parent company's status as a foreign corporation for U.S. federal income tax purposes or the taxation of transactions between members of our group, and any such changes could have prospective or retroactive application. If our parent company is treated as a domestic corporation, more of our income will be taxed by the United States which may substantially increase our effective tax rate.

On April 4, 2016, the U.S. Treasury and the IRS issued temporary regulations and in January 2017 issued final regulations that expand the scope of transactions subject to the rules designed to eliminate the U.S. tax benefits of so-called inversion transactions. Under the temporary regulations, the former stockholders of U.S. corporations acquired by a foreign corporation within thirty-six months of the signing date of the last such acquisition are aggregated for the purpose of determining whether the foreign corporation will be treated as a domestic corporation for U.S. federal tax purposes because at least 80 percent of the stock of the foreign corporation is held by former stockholders of a U.S. corporation. The requirement to aggregate the stockholders in such acquisitions for the purpose of determining whether the 80 percent threshold is met may limit our ability to use our stock to acquire U.S. corporations or their assets in the future. In April 2017, the President of the United States issued an executive order (Executive Order 13789) requesting that the Secretary of the United States Treasury review every significant regulation issued over the year and a half period beginning on January 1, 2016, including certain inversion regulations. While the Secretary of the United States Treasury completed that review in 2017 and made certain recommendations with respect to certain regulations that were deemed to impose an undue financial burden, add undue complexity, or exceed statutory authority, at present, it is unclear what actions may be taken as a result of the U.S. Treasury's recommendations or what impact any such actions may have on us.

The U.S. Treasury and the IRS also issued proposed regulations on April 4, 2016 as well as final and temporary regulations in October 2016 that address whether an interest in a related corporation is debt or equity for United States federal income tax purposes. These regulations could result in recharacterization of inter-company debt to equity for certain of our inter-company debt and such a recharacterization could result in more of our future income being taxed by the United States and thereby increase our effective tax rate. We are continuing to evaluate the impact that these regulations may have and will reflect such impact on our financial statements as required.

In addition, the Organization for Economic Co-operation and Development released its Base Erosion and Profit Shifting project final report on October 5, 2015. This report provides the basis for international standards for corporate taxation that are designed to prevent, among other things, the artificial shifting of income to tax havens and low-tax jurisdictions, the erosion of the tax base through interest deductions on inter-company debt and the artificial avoidance of permanent establishments (i.e., tax nexus with a jurisdiction). Legislation to adopt these standards has been enacted or is currently under consideration in a number of jurisdictions. On June 7, 2017, several countries, including many countries that we operate and have subsidiaries in, participated in the signing ceremony adopting the Organization for Economic Co-operation and Development's Multilateral Convention to Implement Tax Treaty Related Measures to Prevent Base Erosion and Profit Shifting, commonly referred to as the MLI. The MLI is intended to provide countries with a tool through which they can amend their income tax treaties. Although not yet effective, the MLI may modify thousands of tax treaties making it more difficult for us to obtain advantageous tax-treaty benefits. As a result, our income may be taxed in jurisdictions where it is not currently taxed and at higher rates of tax than it is currently taxed, which may substantially increase our effective tax rate.

On July 12, 2016, the Anti-Tax Avoidance Directive, or ATAD, was formally adopted by the Economic and Financial Affairs Council of the European Union, or EU. The stated objective of the ATAD is to provide for the effective and swift coordinated implementation of anti-base erosion and profit shifting measures at EU level. Like all Directives, the ATAD is binding as to the results it aims to achieve though EU Member States are free to choose the form and method of achieving those results. In addition, the ATAD contains a number of optional provisions that present an element of choice as to how it will be implemented into law. Elements of the ATAD must be transposed into Irish law by January 1, 2019, and although it is difficult at this stage to determine with precision the impact that the ATAD will have in light of its optional provisions, its implementation could materially increase our effective tax rate.

On December 22, 2017, new legislation was signed into law (H.R. 1, "An Act to provide for reconciliation pursuant to titles II and V of the concurrent resolution on the budget for fiscal year 2018", informally titled the Tax Cuts and Jobs Act, or the Tax Act) that significantly revises the Code. The Tax Act, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the tax deduction for interest expense to 30% of adjusted earnings (except for certain small businesses), implementation of a "base erosion anti-abuse tax" which requires U.S. corporations to make an alternative determination of taxable income without regard to tax deductions for certain payments to affiliates, taxation of certain non-U.S. corporations' earnings considered to be "global intangible low taxed income", or GILTI, repeal of the alternative minimum tax, or AMT, for corporations and changes to a taxpayer's ability to either utilize or refund the AMT credits previously generated, changes to the limitation on deductions for certain executive compensation particularly with respect to the removal of the previously allowed performance based compensation exception, changes in the attribution rules relating to shareholders of certain "controlled foreign corporations", limitation of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss carrybacks, one-time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing

many business deductions and credits. Notwithstanding the reduction in the U.S. corporate income tax rate, the overall impact of the Tax Act is uncertain and our business and financial condition could be adversely affected. The impact of the Tax Act on holders of our ordinary shares is also uncertain and could be adverse. For example, recent changes in federal income tax law resulting in additional taxes owed by U.S. shareholders under the new GILTI tax rules or related to "controlled foreign corporations" may discourage U.S. investors from owning or acquiring 10% or greater of our outstanding ordinary shares, which other shareholders may have viewed as beneficial or may otherwise negatively impact the trading price of our ordinary shares. We are unable to predict what federal tax law may be proposed or enacted in the future or what effect such changes would have on our business, but such changes, to the extent they are brought into tax legislation, regulations, policies or practices, could affect our effective tax rates in the future in countries where we have operations and have an adverse effect on our overall tax rate in the future, along with increasing the complexity, burden and cost of tax compliance. We urge our shareholders to consult with their legal and tax advisors with respect to this legislation and the potential tax consequences of investing in or holding our ordinary shares.

If we are not successful in attracting and retaining highly qualified personnel, we may not be able to successfully implement our business strategy.

Our ability to compete in the highly competitive biotechnology and pharmaceuticals industries depends upon our ability to attract and retain highly qualified managerial, scientific and medical personnel. We are highly dependent on our management, sales and marketing and scientific and medical personnel, including our executive officers composed of our Chairman, President and Chief Executive Officer, Timothy P. Walbert; our Executive Vice President, Chief Business Officer, Robert F. Carey; our Executive Vice President, Chief Financial Officer, Paul W. Hoelscher; our Executive Vice President, Chief Administrative Officer, Barry J. Moze; our Executive Vice President, Chief Medical Officer, Jeffrey W. Sherman, M.D., FACP; our Executive Vice President, Head of Research and Development and Chief Scientific Officer, Shao-Lee Lin, M.D., Ph.D; our Executive Vice President, Chief Human Resources Officer, Irina P. Konstantinovsky; our Executive Vice President, General Counsel, Brian K. Beeler; our Executive Vice President, Primary Care Business Unit, George P. Hampton; our Executive Vice President, Technical Operations, Michael A. DesJardin; our Senior Vice President, Orphan Business Unit, Eric B. Mosbrooker and our Senior Vice President, Rheumatology Business Unit, Vikram Karnani. In order to retain valuable employees at our company, in addition to salary and cash incentives, we provide a mix of performance stock units, or PSUs, stock options and restricted stock units, or RSUs, that vest over time. The value to employees of PSUs, stock options and RSUs will be significantly affected by movements in our share price that are beyond our control, and may at any time be insufficient to counteract more lucrative offers from other companies.

Despite our efforts to retain valuable employees, members of our management, sales and marketing, regulatory affairs, clinical development, medical affairs and development teams may terminate their employment with us on short notice. Although we have written employment arrangements with all of our employees, these employment arrangements generally provide for at-will employment, which means that our employees can leave our employment at any time, with or without notice. The loss of the services of any of our executive officers or other key employees and our inability to find suitable replacements could potentially harm our business, financial condition and prospects. We do not maintain "key man" insurance policies on the lives of these individuals or the lives of any of our other employees. Our success also depends on our ability to continue to attract, retain and motivate highly skilled junior, mid-level, and senior managers as well as junior, mid-level, and senior sales and marketing and scientific and medical personnel.

Many of the other biotechnology and pharmaceutical companies with whom we compete for qualified personnel have greater financial and other resources, different risk profiles and longer histories in the industry than we do. They also may provide more diverse opportunities and better chances for career advancement. Some of these characteristics may be more appealing to high quality candidates than that which we have to offer. If we are unable to continue to attract and retain high quality personnel, the rate and success at which we can develop and commercialize medicines and medicine candidates will be limited.

We are, with respect to our current medicines, and will be, with respect to any other medicine or medicine candidate for which we obtain FDA or EMA approval or which we acquire, subject to ongoing FDA or EMA obligations and continued regulatory review, which may result in significant additional expense. Additionally, any other medicine candidate, if approved by the FDA or the EMA, could be subject to labeling and other restrictions and market withdrawal, and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our medicines.

Any regulatory approvals that we obtain for our medicine candidates may also be subject to limitations on the approved indicated uses for which the medicine may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials and surveillance to monitor the safety and efficacy of the medicine candidate. In addition, with respect to our current FDA-approved medicines (and with respect to our medicine candidates, if approved), the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for the medicine are subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMPs, GCPs, international council for harmonization, or ICH, guidelines and GLPs, which are regulations and guidelines enforced by the FDA for all of our medicines in clinical development, for any clinical trials that we conduct post-approval. With respect to RAVICTI, the FDA imposed several post-marketing requirements and a post-marketing commitment, which include remaining obligations to conduct studies in UCD patients during the first two months of life and from two months to two years of age, including a study of the pharmacokinetics in both age groups, and a randomized study to determine the safety and efficacy in UCD patients who are treatment naïve to phenylbutyrate treatment. Although we are committed to carrying out these commitments, there are challenges in conducting studies in pediatric patients including availability of study sites, patients, and obtaining parental informed consent. In May 2017, the FDA approved our supplemental new drug application, or sNDA, for RAVICTI to expand the age range for chronic management of UCDs from two years of age and older to two months of age and older. We are in the process of seeking approval for a label expansion for RAVICTI, with assessments in progress studying the use of RAVICTI in patients from birth to two months.

In addition, the FDA closely regulates the marketing and promotion of drugs and biologics. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, restrict manufacturers' promotional communications. A significant number of pharmaceutical companies have been the target of inquiries and investigations by various U.S. federal and state regulatory, investigative, prosecutorial and administrative entities in connection with the promotion of medicines for off-label uses and other sales practices. These investigations have alleged violations of various U.S. federal and state laws and regulations, including claims asserting antitrust violations, violations of the Food, Drug and Cosmetic Act, false claims laws, the Prescription Drug Marketing Act, anti-kickback laws, and other alleged violations in connection with the promotion of medicines for unapproved uses, pricing and Medicare and/or Medicaid reimbursement. While Congress has recently considered legislation that would modify or eliminate restrictions for off-label promotion, we do not have sufficient information to anticipate if the current regulatory environment will change.

Later discovery of previously unknown problems with a medicine, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on the marketing or manufacturing of the medicine, withdrawal of the medicine from the market, or voluntary or mandatory medicine recalls;
- refusal by the FDA to approve pending applications or supplements to approved applications filed by us or our strategic partners, or suspension or revocation of medicine license approvals;
- medicine seizure or detention, or refusal to permit the import or export of medicines; and
- injunctions, the imposition of civil or criminal penalties, or exclusion, debarment or suspension from government healthcare programs.

If we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would have a material adverse effect on our business, results of operations, financial condition and prospects.

We are subject to federal, state and foreign healthcare laws and regulations and implementation or changes to such healthcare laws and regulations could adversely affect our business and results of operations.

The United States and some foreign jurisdictions are considering or have enacted a number of legislative and regulatory proposals to regulate and to change the healthcare system in ways that could affect our ability to sell our medicines profitably. In the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs (including a number of proposals pertaining to prescription drugs, specifically), improving quality and/or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives.

If we are found to be in violation of any of these laws or any other federal or state regulations, we may be subject to civil and/or criminal penalties, damages, fines, exclusion, additional reporting requirements and/or oversight from federal health care programs and the restructuring of our operations. Any of these could have a material adverse effect on our business and financial results. Since many of these laws have not been fully interpreted by the courts, there is an increased risk that we may be found in violation of one or more of their provisions. Any action against us for violation of these laws, even if we ultimately are successful in our defense, will cause us to incur significant legal expenses and divert our management's attention away from the operation of our business.

In January 2017, the United States House of Representatives and Senate passed legislation, the concurrent budget resolution for fiscal year 2017, which initiates actions that would repeal certain aspects of the ACA. Further, on January 20, 2017, U.S. President Donald Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA, to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. In May 2017, following the passage of the budget resolution for fiscal year 2017, the U.S. House of Representatives passed legislation known as the American Health Care Act, which, if enacted, would have amended and repealed significant portions of the ACA. The U.S. Senate considered but did not adopt other legislation to amend and/or replace elements of the ACA and authority to act under the fiscal year 2017 budget resolution expired on September 30, 2017. However, on October 12, 2017, U.S. President Donald Trump signed another Executive Order directing certain federal agencies to propose regulations or guidelines to permit small businesses to form association health plans, expand the availability of short-term, limited duration insurance, and expand the use of health reimbursement arrangements, which may circumvent some of the requirements for health insurance mandated by the ACA. In addition, citing legal guidance from the U.S. Department of Justice and the HHS, the Trump administration has concluded that cost-sharing reduction, or CSR, payments to insurance companies required under the ACA have not received necessary appropriations from Congress and announced that it will discontinue these payments immediately until such appropriations are made. The loss of the CSR payments is expected to increase premiums on certain policies issued by qualified health plans under the ACA. Finally, while Congress has not passed comprehensive ACA repeal or replace legislation, the federal income tax legislation signed into law on December 22, 2017 includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate". We continue to evaluate the effect that the ACA and additional actions by Congress to possibly repeal and replace it has on our business.

In addition, drug pricing by pharmaceutical companies has come under increased scrutiny. Specifically, there have been several recent state and U.S. Congressional inquiries and proposed federal and state legislation designed to, among other things, bring more transparency to drug pricing by requiring drug companies to notify insurers and government regulators of price increases and provide an explanation of the reasons for the increase, reduce the out-of-pocket cost of prescription drugs, review the relationship between pricing and manufacturer patient programs, reduce the cost of drugs under Medicare, and reform government program reimbursement methodologies. Legislation was recently signed into law in California that requires drug manufactures to provide advance notice and explanation to state regulators, health plans and insurers and PBMs for price increases of more than 16% over two years. Moreover, U.S. President Donald Trump has discussed the need for federal legislation, regulation or Executive Order to regulate the prices of medicines. For example, the Trump administration's budget proposal for the U.S. government's fiscal year 2019 contains further drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid and to eliminate cost sharing for generic drugs for low-income patients. While any proposed measures will require Congress to pass legislation to become effective, these provisions reinforce the administration's focus on controlling drug prices. The majority of our medicines are purchased by private payers, and much of the focus of pending legislation is on government program reimbursement. However, we cannot know what form any such action may take, the likelihood it would be executed, enacted, effectuated or implemented or the market's perception of how such legislation would affect us. Any reduction in reimbursement from government programs may result in a similar reduction in payments

from private payers. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our current medicines and/or those for which we may receive regulatory approval in the future.

We are subject, directly or indirectly, to federal and state healthcare fraud and abuse and false claims laws, privacy and security laws and regulations. Prosecutions under such laws have increased in recent years and we may become subject to such litigation. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

In the United States, we are subject directly, or indirectly through our customers, to various state and federal fraud and abuse laws, including, without limitation, the federal Anti-Kickback Statute, the federal False Claims Act, civil monetary penalty statutes prohibiting beneficiary inducements, and similar state laws, federal and state privacy and security laws, sunshine laws, government price reporting laws, and other fraud laws. These laws may impact, among other things, our current and proposed sales, marketing and educational programs, as well as other possible relationships with customers, pharmacies, physicians, payers, and patients. We are subject to similar laws in the EU/EEA, including (effective as of May 25, 2018) the EU General Data Protection Regulation (2016/679), under which fines of up to €20.0 million or up to 4% of the annual global turnover of the infringer, whichever is greater, could be imposed for significant non-compliance.

Compliance with these laws, including the development of a comprehensive compliance program, is difficult, costly and time consuming. Because of the breadth of these laws and the narrowness of available statutory and regulatory exemptions, it is possible that some of our business activities could be subject to challenge under one or more of such laws. These risks may be increased where there are evolving interpretations of applicable regulatory requirements, such as those applicable to manufacturer co-pay initiatives. Pharmaceutical manufacturer co-pay initiatives and free medicine programs are the subject of ongoing litigation (involving other manufacturers and to which we are not a party) and evolving interpretations of applicable regulatory requirements and certain state laws, and any change in the regulatory or enforcement environment regarding such programs could impact our ability to offer such programs. If we are unsuccessful with our HorizonCares programs, any other co-pay initiatives or free medicine programs, we would be at a competitive disadvantage in terms of pricing versus preferred branded and generic competitors, or be subject to significant penalties. We are engaged in various business arrangements with current and potential customers, and we can give no assurance that such arrangements would not be subject to scrutiny under such laws, despite our efforts to properly structure such arrangements. Even if we structure our programs with the intent of compliance with such laws, there can be no certainty that we would not need to defend our business activities against enforcement or litigation. Further, we cannot give any assurances that prior business activities or arrangements of other companies that we acquire will not be scrutinized or subject to enforcement or litigation.

There has also been a trend of increased federal and state regulation of payments made to physicians and other healthcare providers. The ACA, among other things, imposed reporting requirements on drug manufacturers for payments made by them to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit required information may result in significant civil monetary penalties.

We are unable to predict whether we could be subject to actions under any of these or other healthcare laws, or the impact of such actions. If we are found to be in violation of, or to encourage or assist the violation by third parties of any of the laws described above or other applicable state and federal fraud and abuse laws, we may be subject to penalties, including administrative, civil and criminal penalties, damages, fines, withdrawal of regulatory approval, imprisonment, exclusion from government healthcare reimbursement programs, contractual damages, reputational harm, diminished profits and future earnings, injunctions and other associated remedies, or private "qui tam" actions brought by individual whistleblowers in the name of the government, and the curtailment or restructuring of our operations, all of which could have a material adverse effect on our business and results of operations. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business.

Our medicines or any other medicine candidate that we develop may cause undesirable side effects or have other properties that could delay or prevent regulatory approval or commercialization, result in medicine re-labeling or withdrawal from the market or have a significant impact on customer demand.

Undesirable side effects caused by any medicine candidate that we develop could result in the denial of regulatory approval by the FDA or other regulatory authorities for any or all targeted indications, or cause us to evaluate the future of our development programs. With respect to RAVICTI, the most common side effects are diarrhea, nausea, decreased appetite, gas, vomiting, high blood levels of ammonia, headache, tiredness and dizziness. With respect to PROCYSBI, the most common side effects include vomiting, nausea, abdominal pain, breath odor, diarrhea, skin odor, fatigue, rash and headache. The most common side effects observed in pivotal trials for ACTIMMUNE were "flu-like" or constitutional symptoms such as fever, headache, chills, myalgia and fatigue. With respect to BUPHENYL, the most common side effects are change in the frequency of breathing, lack of or irregular menstruation, lower back, side, or stomach pain, mood or mental changes, muscle pain or twitching, nausea or vomiting, nervousness or restlessness, swelling of the feet or lower legs, unpleasant taste and unusual tiredness or weakness. With respect to QUINSAIR, the most common side effects include itching, wheezing, hives, rash, swelling, pale skin color, fast heartbeat and faintness. With respect to KRYSTEXXA, the most commonly reported serious adverse reactions in the pivotal trial were gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis, exacerbation of pre-existing congestive heart failure and vomiting. The most commonly reported treatment-emergent adverse events in the Phase 3 clinical trials with RAYOS/LODOTRA included flare in rheumatoid arthritis related symptoms, abdominal pain, nasopharyngitis, headache, flushing, upper respiratory tract infection, back pain and weight gain. The most common adverse events reported in a Phase 2 clinical trial of PENNSAID 2% were application site reactions, such as dryness, exfoliation, erythema, pruritus, pain, induration, rash and scabbing. In our two Phase 3 clinical trials with DUEXIS, the most commonly reported treatment-emergent adverse events were nausea, dyspepsia, diarrhea, constipation and upper respiratory tract infection. In Phase 3 endoscopic registration clinical trials with VIMOVO, the most commonly reported treatment-emergent adverse events were erosive gastritis, dyspepsia, gastritis, diarrhea, gastric ulcer, upper abdominal pain, nausea and upper respiratory tract infection. With respect to MIGERGOT, the most commonly reported adverse reactions are ischemia, cyanosis, absence of pulse, cold extremities, gangrene, precordial distress and pain, electrocardiogram change, muscle pain, nausea and vomiting, rectal or anal ulcer, parathesias, numbness weakness, vertigo, localized edemas and itching.

The FDA or other regulatory authorities may also require, or we may undertake, additional clinical trials to support the safety profile of our medicines or medicine candidates.

In addition, if we or others identify undesirable side effects caused by our medicines or any other medicine candidate that we may develop that receives marketing approval, or if there is a perception that the medicine is associated with undesirable side effects:

- regulatory authorities may require the addition of labeling statements, such as a "black box" warning or a contraindication;
- regulatory authorities may withdraw their approval of the medicine or place restrictions on the way it is prescribed;
- we may be required to change the way the medicine is administered, conduct additional clinical trials or change the labeling of the medicine or implement a risk evaluation and mitigation strategy; and
- we may be subject to increased exposure to product liability and/or personal injury claims.

If any of these events occurred with respect to our medicines, our ability to generate significant revenues from the sale of these medicines would be significantly harmed.

We rely on third parties to conduct our pre-clinical and clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines or if they experience regulatory compliance issues, we may not be able to obtain regulatory approval for or commercialize our medicine candidates and our business could be substantially harmed.

We have agreements with third-party contract research organizations, or CROs, to conduct our clinical programs, including those required for post-marketing commitments, and we expect to continue to rely on CROs for the completion of on-going and planned clinical trials. We may also have the need to enter into other such agreements in the future if we were to develop other medicine candidates or conduct clinical trials in additional indications for our existing medicines. We have an agreement in place with Syneos Health, Inc., in connection with our Phase 3 confirmatory trial to evaluate teprotumumab

for the treatment of thyroid eye disease. In connection with the investigator-initiated study to evaluate ACTIMMUNE in combination with PD-1/PD-L1 inhibitors in various forms of cancer including advanced urothelial carcinoma (bladder cancer) and renal cell carcinoma, we are collaborating with Fox Chase Cancer Center. In connection with our ongoing study to evaluate RAYOS/LODOTRA on the fatigue experienced by SLE patients, we are collaborating with the ALR. We also rely heavily on these parties for the execution of our clinical studies and control only certain aspects of their activities. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol. We, our CROs and our academic research organizations are required to comply with current GCP or ICH regulations. The FDA enforces these GCP or ICH regulations through periodic inspections of trial sponsors, principal investigators and trial sites. If we or our CROs or collaborators fail to comply with applicable GCP or ICH regulations, the data generated in our clinical trials may be deemed unreliable and our submission of marketing applications may be delayed or the FDA may require us to perform additional clinical trials before approving our marketing applications. We cannot assure that, upon inspection, the FDA will determine that any of our clinical trials comply or complied with GCP or ICH regulations. In addition, our clinical trials must be conducted with medicine produced under cGMP regulations, and may require a large number of test subjects. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. Moreover, our business may be implicated if any of our CROs or collaborators violates federal or state fraud and abuse or false claims laws and regulations or healthcare privacy and security laws. We must also obtain certain third-party institutional review board, or IRB, and ethics committee approvals in order to conduct our clinical trials. Delays by IRBs and ethics committees in providing such approvals may delay our clinical trials.

If any of our relationships with these third-party CROs or collaborators terminate, we may not be able to enter into similar arrangements on commercially reasonable terms, or at all. If CROs or collaborators do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our medicines and medicine candidates. As a result, our results of operations and the commercial prospects for our medicines and medicine candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed.

Switching or adding additional CROs or collaborators can involve substantial cost and require extensive management time and focus. In addition, there is a natural transition period when a new CRO or collaborator commences work. As a result, delays may occur, which can materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our CROs and collaborators, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition or prospects.

Clinical development of drugs and biologics involves a lengthy and expensive process with an uncertain outcome, and results of earlier studies and trials may not be predictive of future trial results.

Clinical testing is expensive and can take many years to complete, and its outcome is uncertain. Failure can occur at any time during the clinical trial process. The results of pre-clinical studies and early clinical trials of potential medicine candidates may not be predictive of the results of later-stage clinical trials. Medicine candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through pre-clinical studies and initial clinical testing. For example, in December 2016, we announced that the Phase 3 trial, Safety, Tolerability and Efficacy of ACTIMMUNE Dose Escalation in Friedreich's Ataxia, evaluating ACTIMMUNE for the treatment of Friedreich's ataxia, or FA, did not meet its primary endpoint.

With respect to investigator-initiated studies for several of our products, and with respect to the Phase 3 pivotal clinical trial of teprotumumab in thyroid eye disease that we commenced in the fourth quarter of 2017, and to the extent that we are required to conduct additional clinical development of any of our existing or later acquired medicines or we conduct clinical development of earlier stage medicine candidates, we may experience delays in these clinical trials or investigator-initiated studies. We do not know whether any additional clinical trials will be initiated in the future, begin on time, need to be redesigned, enroll patients on time or be completed on schedule, if at all. Clinical trials can be delayed for a variety of reasons, including delays related to:

- obtaining regulatory approval to commence a trial;
- reaching agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;

- obtaining IRB or ethics committee approval at each site;
- recruiting suitable patients to participate in a trial;
- having patients complete a trial or return for post-treatment follow-up;
- clinical sites dropping out of a trial;
- adding new sites; or
- manufacturing sufficient quantities of medicine candidates for use in clinical trials.

Patient enrollment, a significant factor in the timing of clinical trials, is affected by many factors including the size and nature of the patient population, the proximity of patients to clinical sites, the eligibility criteria for the trial, the design of the clinical trial, competing clinical trials and clinicians' and patients' perceptions as to the potential advantages of the medicine candidate being studied in relation to other available therapies, including any new drugs or biologics that may be approved for the indications we are investigating. Furthermore, we rely and expect to rely on CROs and clinical trial sites to ensure the proper and timely conduct of our future clinical trials and while we have and intend to have agreements governing their committed activities, we will have limited influence over their actual performance.

We could encounter delays if prescribing physicians encounter unresolved ethical issues associated with enrolling patients in clinical trials of our medicine candidates in lieu of prescribing existing treatments that have established safety and efficacy profiles. Further, a clinical trial may be suspended or terminated by us, our collaborators, the FDA or other regulatory authorities due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a medicine candidate, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. If we experience delays in the completion of, or if we terminate, any clinical trial of our medicine candidates, the commercial prospects of our medicine candidates will be harmed, and our ability to generate medicine revenues from any of these medicine candidates will be delayed. In addition, any delays in completing our clinical trials will increase our costs, slow down our medicine development and approval process and jeopardize our ability to commence medicine sales and generate revenues.

Moreover, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and receive compensation in connection with such services. Under certain circumstances, we may be required to report some of these relationships to the FDA. The FDA may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected interpretation of the study. The FDA may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing applications by the FDA and may ultimately lead to the denial of marketing approval of one or more of our medicine candidates.

Any of these occurrences may harm our business, financial condition, results of operations and prospects significantly. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our medicine candidates.

Business interruptions could seriously harm our future revenue and financial condition and increase our costs and expenses.

Our operations could be subject to earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics and other natural or man-made disasters or business interruptions. While we carry insurance for certain of these events and have implemented disaster management plans and contingencies, the occurrence of any of these business interruptions could seriously harm our business and financial condition and increase our costs and expenses. We conduct significant management operations at both our global headquarters located in Dublin, Ireland and our U.S. office located in Lake Forest, Illinois. If our Dublin or Lake Forest offices were affected by a natural or man-made disaster or other business interruption, our ability to manage our domestic and foreign operations could be impaired, which could materially and adversely affect our results of operations and financial condition. We currently rely, and intend to rely in the future, on third-party manufacturers and suppliers to produce our medicines and third-party logistics partners to ship our medicines. Our ability to obtain commercial supplies of our medicines could be disrupted and our results of operations and financial condition could be materially and adversely affected if the operations of these third-party suppliers or logistics partners were affected by a man-made or natural disaster or other business interruption. The ultimate impact of such events on us, our significant suppliers and our general infrastructure is unknown.

We are dependent on information technology systems, infrastructure and data, which exposes us to data security risks.

We are dependent upon our own or third-party information technology systems, infrastructure and data, including mobile technologies, to operate our business. The multitude and complexity of our computer systems may make them vulnerable to service interruption or destruction, malicious intrusion, or random attack. Likewise, data privacy or security breaches by employees or others may pose a risk that sensitive data, including our intellectual property, trade secrets or personal information of our employees, patients, customers or other business partners may be exposed to unauthorized persons or to the public. Cyber-attacks are increasing in their frequency, sophistication and intensity. Cyber-attacks could include the deployment of harmful malware, denial-of-service, social engineering and other means to affect service reliability and threaten data confidentiality, integrity and availability. Our business partners face similar risks and any security breach of their systems could adversely affect our security posture. A security breach or privacy violation that leads to disclosure or modification of or prevents access to patient information, including personally identifiable information or protected health information, could harm our reputation, compel us to comply with federal and/or state breach notification laws and foreign law equivalents, subject us to mandatory corrective action, require us to verify the correctness of database contents and otherwise subject us to litigation or other liability under laws and regulations that protect personal data, any of which could disrupt our business and/or result in increased costs or loss of revenue. Moreover, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information, trade secrets or other intellectual property. While we have invested, and continue to invest, in the protection of our data and information technology infrastructure, there can be no assurance that our efforts will prevent service interruptions, or identify breaches in our systems, that could adversely affect our business and operations and/or result in the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm to us. In addition, our liability insurance may not be sufficient in type or amount to cover us against claims related to security breaches, cyber-attacks and other related breaches.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our medicines.

We face an inherent risk of product liability claims as a result of the commercial sales of our medicines and the clinical testing of our medicine candidates. For example, we may be sued if any of our medicines or medicine candidates allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the medicine, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our medicines and medicine candidates. Even a successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for our medicines or medicine candidates that we may develop;
- injury to our reputation;
- withdrawal of clinical trial participants;
- initiation of investigations by regulators;
- costs to defend the related litigation;
- a diversion of management's time and resources;
- substantial monetary awards to trial participants or patients;
- medicine recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- exhaustion of any available insurance and our capital resources; and
- the inability to commercialize our medicines or medicine candidates.

Our inability to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of medicines we develop. We currently carry product liability insurance covering our clinical studies and commercial medicine sales in the amount of $125.0 million in the aggregate. Although we maintain such insurance, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. If we determine that it is prudent to increase our product liability coverage due to the on-going commercialization of our current medicines in the United States, and/or the potential commercial launches of any of our medicines in additional markets or for additional indications, we may be unable to obtain such increased coverage on acceptable terms or at all. Our insurance policies also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We will have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts.

Our business involves the use of hazardous materials, and we and our third-party manufacturers must comply with environmental laws and regulations, which can be expensive and restrict how we do business.

Our third-party manufacturers' activities involve the controlled storage, use and disposal of hazardous materials owned by us, including the components of our medicine candidates and other hazardous compounds. We and our manufacturers are subject to federal, state and local as well as foreign laws and regulations governing the use, manufacture, storage, handling and disposal of these hazardous materials. Although we believe that the safety procedures utilized by our third-party manufacturers for handling and disposing of these materials comply with the standards prescribed by these laws and regulations, we cannot eliminate the risk of accidental contamination or injury from these materials. In the event of an accident, state, federal or foreign authorities may curtail the use of these materials and interrupt our business operations. We do not currently maintain hazardous materials insurance coverage. If we are subject to any liability as a result of our third-party manufacturers' activities involving hazardous materials, our business and financial condition may be adversely affected. In the future we may seek to establish longer-term third-party manufacturing arrangements, pursuant to which we would seek to obtain contractual indemnification protection from such third-party manufacturers potentially limiting this liability exposure.

Our employees, independent contractors, principal investigators, consultants, vendors, distributors and CROs may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk that our employees, independent contractors, principal investigators, consultants, vendors, distributors and CROs may engage in fraudulent or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct or unauthorized activities that violate FDA regulations, including those laws that require the reporting of true, complete and accurate information to the FDA, manufacturing standards, federal and state healthcare fraud and abuse laws and regulations, and laws that require the true, complete and accurate reporting of financial information or data. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Misconduct by our employees and other third parties may also include the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. We have adopted a Code of Business Conduct and Ethics, but it is not always possible to identify and deter misconduct by our employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs and imprisonment.

Risks Related to our Financial Position and Capital Requirements

In the past we have incurred significant operating losses.

We have a limited operating history and even less history operating as a combined organization following the acquisitions of Vidara, Hyperion, Crealta Holdings LLC, or Crealta, Raptor and River Vision Development Corp., or River Vision. We have financed our operations primarily through equity and debt financings and have incurred significant operating losses in the past. We had an operating loss of $392.4 million for the year ended December 31, 2017, an operating loss of $147.2 million for the year ended December 31, 2016 and operating income of $55.4 million for the year ended December 31, 2015. We had a net loss of $410.5 million for the year ended December 31, 2017, a net loss of $166.8 million for the year ended December 31, 2016 and net income of $39.5 million for the year ended December 31, 2015. As of December 31, 2017, we had an accumulated deficit of $1,252.3 million. Our prior losses have resulted principally from costs incurred in our development activities for our medicines and medicine candidates, commercialization activities related to our medicines, costs associated with our acquisition transactions and costs associated with derivative liability accounting. Our prior losses, combined with possible future losses, have had and will continue to have an adverse effect on our shareholders' equity and working capital. While we anticipate that we will generate operating profits in the future, whether we can sustain this will depend on the revenues we generate from the sale of our medicines being sufficient to cover our operating expenses.

We have limited sources of revenues and significant expenses. We cannot be certain that we will achieve or sustain profitability, which would depress the market price of our ordinary shares and could cause our investors to lose all or a part of their investment.

Our ability to achieve and sustain profitability depends upon our ability to generate sales of our medicines. We have a limited history of commercializing our medicines as a company, and commercialization has been primarily in the United States. We may never be able to successfully commercialize our medicines or develop or commercialize other medicines in the United States or in the EU, which we believe represents our most significant commercial opportunity. Our ability to generate future revenues depends heavily on our success in:

- continued commercialization of our existing medicines and any other medicine candidates for which we obtain approval;
- obtaining FDA approvals for teprotumumab, additional indications for ACTIMMUNE or an expanded indication for RAVICTI;
- securing additional foreign regulatory approvals for our medicines in territories where we have commercial rights; and
- developing, acquiring and commercializing a portfolio of other medicines or medicine candidates in addition to our current medicines.

Even if we do generate additional medicine sales, we may not be able to achieve or sustain profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the market price of our ordinary shares and could impair our ability to raise capital, expand our business, diversify our medicine offerings or continue our operations.

We may need to obtain additional financing to fund additional acquisitions.

Our operations have consumed substantial amounts of cash since inception. We expect to continue to spend substantial amounts to:

- commercialize our existing medicines in the United States, including the substantial expansion of our sales force in recent years;
- complete the regulatory approval process, and any future required clinical development related thereto, for our medicines and medicine candidates;
- potentially acquire other businesses or additional complementary medicines or medicines that augment our current medicine portfolio, including costs associated with refinancing debt of acquired companies; and
- conduct clinical trials with respect to potential additional indications, as well as conduct post-marketing requirements and commitments, with respect to our medicines and medicines we acquire.

While we believe that our existing cash and cash equivalents will be sufficient to fund our operations based on our current expectations of continued revenue growth, we may need to raise additional funds if we choose to expand our commercialization or development efforts more rapidly than presently anticipated, if we develop or acquire additional medicines or acquire companies, or if our revenue does not meet expectations.

We cannot be certain that additional funding will be available on acceptable terms, or at all. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of one or more of our medicines or medicine candidates or one or more of our other research and development initiatives, or delay, cut back or abandon our plans to grow the business through acquisitions. We also could be required to:

- seek collaborators for one or more of our current or future medicine candidates at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available; or
- relinquish or license on unfavorable terms our rights to technologies or medicine candidates that we would otherwise seek to develop or commercialize ourselves.

In addition, if we are unable to secure financing to support future acquisitions, our ability to execute on a key aspect of our overall growth strategy would be impaired.

Any of the above events could significantly harm our business, financial condition and prospects.

We have incurred a substantial amount of debt, which could adversely affect our business, including by restricting our ability to engage in additional transactions or incur additional indebtedness, and prevent us from meeting our debt obligations.

As of December 31, 2017, we had $1,901.7 million book value, or $2,020.8 million aggregate principal amount, of indebtedness, including $845.8 million in secured indebtedness. In March 2017, we borrowed $850.0 million in aggregate principal amount of secured loans pursuant to our credit agreement. In October 2017, we borrowed approximately $845.8 million aggregate principal amount of loans under our credit agreement pursuant to an amendment to our credit agreement to refinance the then outstanding senior secured term loans incurred in March 2017 under our credit agreement, which totaled approximately $845.8 million. In connection with the acquisition of Hyperion, we issued $475.0 million aggregate principal amount of 6.625% Senior Notes due 2023, or the 2023 Senior Notes, in April 2015. In connection with the acquisition of Raptor, we issued $300.0 million aggregate principal amount of 8.75% Senior Notes due 2024, or the 2024 Senior Notes, in October 2016. In March 2015, we issued $400.0 million aggregate principal amount of 2.50% Exchangeable Senior Notes due 2022, or the Exchangeable Senior Notes. Accordingly, we have a significant amount of debt outstanding on a consolidated basis.

This substantial level of debt could have important consequences to our business, including, but not limited to:

- reducing the benefits we expect to receive from our prior and any future acquisition transactions;
- making it more difficult for us to satisfy our obligations;
- requiring a substantial portion of our cash flows from operations to be dedicated to the payment of principal and interest on our indebtedness, therefore reducing our ability to use our cash flows to fund acquisitions, capital expenditures, and future business opportunities;
- exposing us to the risk of increased interest rates to the extent of any future borrowings, including borrowings under our credit agreement, at variable rates of interest;
- making it more difficult for us to satisfy our obligations with respect to our indebtedness, including our outstanding notes, our credit agreement, and any failure to comply with the obligations of any of our debt instruments, including restrictive covenants and borrowing conditions, could result in an event of default under the agreements governing such indebtedness;
- increasing our vulnerability to, and reducing our flexibility to respond to, changes in our business or general adverse economic and industry conditions;
- limiting our ability to obtain additional financing for working capital, capital expenditures, debt service requirements, acquisitions, and general corporate or other purposes and increasing the cost of any such financing;

- limiting our flexibility in planning for, or reacting to, changes in our business and the industry in which we operate; and placing us at a competitive disadvantage as compared to our competitors, to the extent they are not as highly leveraged and who, therefore, may be able to take advantage of opportunities that our leverage may prevent us from exploiting; and
- restricting us from pursuing certain business opportunities.

The credit agreement and the indentures governing the 2024 Senior Notes and the 2023 Senior Notes impose, and the terms of any future indebtedness may impose, various covenants that limit our ability and/or the ability of our restricted subsidiaries' (as designated under such agreements) to, among other things, pay dividends or distributions, repurchase equity, prepay junior debt and make certain investments, incur additional debt and issue certain preferred stock, incur liens on assets, engage in certain asset sales, consolidate with or merge or sell all or substantially all of our assets, enter into transactions with affiliates, designate subsidiaries as unrestricted subsidiaries, and allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to us.

Our ability to obtain future financing and engage in other transactions may be restricted by these covenants. In addition, any credit ratings will impact the cost and availability of future borrowings and our cost of capital. Our ratings at any time will reflect each rating organization's then opinion of our financial strength, operating performance and ability to meet our debt obligations. There can be no assurance that we will achieve a particular rating or maintain a particular rating in the future. A reduction in our credit ratings may limit our ability to borrow at acceptable interest rates. If our credit ratings were downgraded or put on watch for a potential downgrade, we may not be able to sell additional debt securities or borrow money in the amounts, at the times or interest rates or upon the more favorable terms and conditions that might otherwise be available. Any impairment of our ability to obtain future financing on favorable terms could have an adverse effect on our ability to refinance any of our then-existing debt and may severely restrict our ability to execute on our business strategy, which includes the continued acquisition of additional medicines or businesses.

We may not be able to generate sufficient cash to service all of our indebtedness and may be forced to take other actions to satisfy our obligations under our indebtedness, which may not be successful.

Our ability to make scheduled payments under or to refinance our debt obligations depends on our financial condition and operating performance, which is subject to prevailing economic, industry and competitive conditions and to certain financial, business and other factors beyond our control. Our ability to generate cash flow to meet our payment obligations under our debt may also depend on the successful implementation of our operating and growth strategies. Any refinancing of our debt could be at higher interest rates and may require us to comply with more onerous covenants, which could further restrict our business operations. We cannot assure that we will maintain a level of cash flows from operating activities sufficient to pay the principal, premium, if any, and interest on our indebtedness.

If our cash flows and capital resources are insufficient to fund our debt service obligations, we may be forced to reduce or delay capital expenditures, sell assets or business operations, seek additional capital or restructure or refinance our indebtedness. We cannot ensure that we would be able to take any of these actions, that these actions would be successful and permit us to meet our scheduled debt service obligations or that these actions would be permitted under the terms of existing or future debt agreements, including the indentures that govern the 2024 Senior Notes and the 2023 Senior Notes and the credit agreement. In addition, any failure to make payments of interest and principal on our outstanding indebtedness on a timely basis would likely result in a reduction of our credit rating, which could harm our ability to incur additional indebtedness.

If we cannot make scheduled payments on our debt, we will be in default and, as a result:

- our debt holders could declare all outstanding principal and interest to be due and payable;
- the administrative agent and/or the lenders under the credit agreement could foreclose against the assets securing the borrowings then outstanding; and
- we could be forced into bankruptcy or liquidation, which could result in you losing your investment.

We generally have broad discretion in the use of our cash and may not use it effectively.

Our management has broad discretion in the application of our cash, and investors will be relying on the judgment of our management regarding the use of our cash. Our management may not apply our cash in ways that ultimately increase the value of any investment in our securities. We expect to use our existing cash to fund commercialization activities for our medicines, to potentially fund additional medicine or business acquisitions, to potentially fund additional regulatory approvals of certain of our medicines, to potentially fund development, life cycle management or manufacturing activities of our medicines for other indications, to potentially fund share repurchases, and for working capital, capital expenditures and general corporate purposes. We may also invest our cash in short-term, investment-grade, interest-bearing securities. These investments may not yield a favorable return to our shareholders. If we do not invest or apply our cash in ways that enhance shareholder value, we may fail to achieve expected financial results, which could cause the price of our ordinary shares to decline.

Our ability to use net operating loss carryforwards and certain other tax attributes to offset U.S. income taxes may be limited.

Under Sections 382 and 383 of the Code, if a corporation undergoes an "ownership change" (generally defined as a greater than 50 percent change (by value) in its equity ownership over a three-year period), the corporation's ability to use pre-change net operating loss carryforwards and other pre-change tax attributes to offset post-change income may be limited. We continue to carry forward our annual limitation resulting from an ownership change date of August 2, 2012. The limitation on pre-change net operating losses incurred prior to the August 2, 2012 change date is approximately $7.7 million for 2018 through 2028. We continue to carry forward the annual limitation related to Hyperion of $50.0 million resulting from the last ownership change date in 2014 and the annual limitation related to Raptor of $0.2 million resulting from the last ownership change date in 2009. In addition, in the second quarter of 2017, we recognized $37.4 million of federal net operating losses, $43.2 million of state net operating losses and $5.8 million of federal tax credits following our acquisition of River Vision Development Corp. These acquired federal net operating losses and tax credits are subject to an annual limitation of $12.5 million from 2018 through 2021. The net operating loss carryforward limitation is cumulative such that any use of the carryforwards below the limitations in one year will result in a corresponding increase in the limitations for the subsequent tax year. Under the Tax Act, U.S. federal net operating losses incurred in 2018 and in future years may be carried forward indefinitely, but the deductibility of such federal net operating losses is limited. It is uncertain if and to what extent various U.S. states will conform to the Tax Act.

Following certain acquisitions of a U.S. corporation by a foreign corporation, Section 7874 of the Code limits the ability of the acquired U.S. corporation and its U.S. affiliates to utilize U.S. tax attributes such as net operating losses to offset U.S. taxable income resulting from certain transactions. Based on the limited guidance available, we expect this limitation is applicable following the Vidara Merger. As a result, it is not currently expected that we or our other U.S. affiliates will be able to utilize their U.S. tax attributes to offset their U.S. taxable income, if any, resulting from certain taxable transactions following the Vidara Merger. Notwithstanding this limitation, we expect that we will be able to fully use our U.S. net operating losses and tax credits prior to their expiration. As a result of this limitation, however, it may take HPI longer to use its net operating losses and tax credits. Moreover, contrary to these expectations, it is possible that the limitation under Section 7874 of the Code on the utilization of U.S. tax attributes could prevent us from fully utilizing our U.S. tax attributes prior to their expiration if we do not generate sufficient taxable income.

Any limitation on our ability to use our net operating loss and tax credit carryforwards, including the carryforwards of companies that we acquire, will likely increase the taxes we would otherwise pay in future years if we were not subject to such limitations.

Unstable market and economic conditions may have serious adverse consequences on our business, financial condition and share price.

From time to time, global credit and financial markets have experienced extreme disruptions, including severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates, and uncertainty about economic stability. Our general business strategy may be adversely affected by any such economic downturn, volatile business environment and continued unpredictable and unstable market conditions. If the equity and credit markets deteriorate, it may make any necessary debt or equity financing more difficult to complete, more costly, and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and share price and could require us to delay or abandon commercialization or development plans. There is a risk that one or more of our current service providers, manufacturers and other partners may not survive an economic down-turn, which could directly affect our ability to attain our operating goals on schedule and on budget.

The U.K.'s referendum to leave the EU or "Brexit," has caused and may continue to cause disruptions to capital and currency markets worldwide. The full impact of the Brexit decision, however, remains uncertain. A process of negotiation will determine the future terms of the U.K.'s relationship with the EU. During this period of negotiation, our results of operations and access to capital may be negatively affected by interest rate, exchange rate and other market and economic volatility, as well as regulatory and political uncertainty. The tax consequences of the U.K.'s withdrawal from the EU are uncertain as well. Brexit may also have a detrimental effect on our customers, distributors and suppliers, which would, in turn, adversely affect our revenues and financial condition.

At December 31, 2017, we had $751.4 million of cash and cash equivalents consisting of cash and money market funds. While we are not aware of any downgrades, material losses, or other significant deterioration in the fair value of our cash equivalents since December 31, 2017, no assurance can be given that deterioration in conditions of the global credit and financial markets would not negatively impact our current portfolio of cash equivalents or our ability to meet our financing objectives. Dislocations in the credit market may adversely impact the value and/or liquidity of marketable securities owned by us.

Changes in accounting rules or policies may affect our financial position and results of operations.

Accounting principles generally accepted in the United States, or GAAP, and related implementation guidelines and interpretations can be highly complex and involve subjective judgments. Changes in these rules or their interpretation, the adoption of new guidance or the application of existing guidance to changes in our business could significantly affect our financial position and results of operations. In addition, our operation as an Irish company with multiple subsidiaries in different jurisdictions adds additional complexity to the application of GAAP and this complexity will be exacerbated further if we complete additional strategic transactions. Changes in the application of existing rules or guidance applicable to us or our wholly owned subsidiaries could significantly affect our consolidated financial position and results of operations.

Covenants under the indentures governing our 2024 Senior Notes and 2023 Senior Notes and our credit agreement may restrict our business and operations in many ways, and if we do not effectively manage our covenants, our financial conditions and results of operations could be adversely affected.

The indentures governing the 2024 Senior Notes and the 2023 Senior Notes and the credit agreement impose various covenants that limit our ability and/or our restricted subsidiaries' ability to, among other things:

- pay dividends or distributions, repurchase equity, prepay, redeem or repurchase certain debt and make certain investments;
- incur additional debt and issue certain preferred stock;
- provide guarantees in respect of obligations of other persons;
- incur liens on assets;
- engage in certain asset sales;
- merge, consolidate with or sell all or substantially all of our assets to another person;
- enter into transactions with affiliates;
- sell assets and capital stock of our subsidiaries;
- enter into agreements that restrict distributions from our subsidiaries;
- designate subsidiaries as unrestricted subsidiaries; and
- allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to us.

These covenants may:

- limit our ability to borrow additional funds for working capital, capital expenditures, acquisitions or other general business purposes;
- limit our ability to use our cash flow or obtain additional financing for future working capital, capital expenditures, acquisitions or other general business purposes;

- require us to use a substantial portion of our cash flow from operations to make debt service payments;
- limit our flexibility to plan for, or react to, changes in our business and industry;
- place us at a competitive disadvantage compared to less leveraged competitors; and
- increase our vulnerability to the impact of adverse economic and industry conditions.

If we are unable to successfully manage the limitations and decreased flexibility on our business due to our significant debt obligations, we may not be able to capitalize on strategic opportunities or grow our business to the extent we would be able to without these limitations.

Our failure to comply with any of the covenants could result in a default under the credit agreement or the indentures governing the 2024 Senior Notes or the 2023 Senior Notes, which could permit the administrative agent or the trustee, as applicable, or permit the lenders or the holders of the 2024 Senior Notes or the 2023 Senior Notes to cause the administrative agent or the trustee, as applicable, to declare all or part of any outstanding senior secured term loans, the 2023 Senior Notes or the 2024 Senior Notes to be immediately due and payable or to exercise any remedies provided to the administrative agent or the trustee, including, in the case of the credit agreement proceeding against the collateral granted to secure our obligations under the credit agreement. An event of default under the credit agreement or the indentures governing the 2024 Senior Notes or the 2023 Senior Notes could also lead to an event of default under the terms of the other agreements and the indenture governing our Exchangeable Senior Notes. Any such event of default or any exercise of rights and remedies by our creditors could seriously harm our business.

If intangible assets that we have recorded in connection with our acquisition transactions become impaired, we could have to take significant charges against earnings.

In connection with the accounting for our various acquisition transactions, we have recorded significant amounts of intangible assets. Under GAAP, we must assess, at least annually and potentially more frequently, whether the value of goodwill and other indefinite-lived intangible assets has been impaired. Amortizing intangible assets will be assessed for impairment in the event of an impairment indicator. Any reduction or impairment of the value of goodwill or other intangible assets will result in a charge against earnings, which could materially adversely affect our results of operations and shareholders' equity in future periods.

Risks Related to Our Intellectual Property

If we are unable to obtain or protect intellectual property rights related to our medicines and medicine candidates, we may not be able to compete effectively in our markets.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our medicines and medicine candidates. The strength of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions and can be uncertain. The patent applications that we own may fail to result in issued patents with claims that cover our medicines in the United States or in other foreign countries. If this were to occur, early generic competition could be expected against our current medicines and other medicine candidates in development. There is no assurance that all potentially relevant prior art relating to our patents and patent applications has been found, which prior art can invalidate a patent or prevent a patent from issuing based on a pending patent application. In particular, because the APIs in RAYOS/LODOTRA, DUEXIS and VIMOVO have been on the market as separate medicines for many years, it is possible that these medicines have previously been used off-label in such a manner that such prior usage would affect the validity of our patents or our ability to obtain patents based on our patent applications. In addition, claims directed to dosing and dose adjustment may be substantially less likely to issue in light of the Supreme Court decision in Mayo Collaborative Services v. Prometheus Laboratories, Inc., where the court held that claims directed to methods of determining whether to adjust drug dosing levels based on drug metabolite levels in the red blood cells were not patent eligible because they were directed to a law of nature. This decision may have wide-ranging implications on the validity and scope of pharmaceutical method claims.

Even if patents do successfully issue, third parties may challenge their validity, enforceability or scope, which may result in such patents being narrowed or invalidated.

Patent litigation is currently pending in the United States District Court for the Eastern District of Texas against Par Pharmaceutical and in the United States District Court for the District of New Jersey against Lupin and against Par Pharmaceutical, who are each intending to market generic versions of RAVICTI prior to the expiration of certain of our patents listed in the Orange Book. These cases are collectively known as the RAVICTI cases, and arise from Paragraph IV Patent Certification notice letters from each of Par Pharmaceutical and Lupin advising each had filed an ANDA with the FDA seeking approval to market a generic version of RAVICTI before the expiration of the patents-in-suit. For a more detailed description of the RAVICTI litigation, see Note 19 of the Notes to consolidated financial statements, included in Item 15 of this Annual Report on Form 10-K.

Patent litigation is currently pending in the United States District Court for the District of New Jersey and the Court of Appeals for the Federal Circuit against several companies intending to market a generic version of VIMOVO before the expiration of certain of our patents listed in the Orange Book. These cases are collectively known as the VIMOVO cases, and involve the following sets of defendants: (i) Dr. Reddy's; (ii) Lupin; and (iii) Mylan. Patent litigation against a fourth generic company, Actavis, is currently pending in the Court of Appeals for the Federal Circuit. The cases arise from Paragraph IV Patent Certification notice letters from each of Dr. Reddy's, Lupin, Mylan and Actavis, advising each had filed an ANDA with the FDA seeking approval to market generic versions of VIMOVO before the expiration of the patents-in-suit. For a more detailed description of the VIMOVO litigation, see Note 19 of the Notes to consolidated financial statements, included in Item 15 of this Annual Report on Form 10-K.

Patent litigation is currently pending in the United States District Court for the District of New Jersey against two companies intending to market a generic version of PENNSAID 2% prior to the expiration of certain of our patents listed in the Orange Book. These cases are collectively known as the PENNSAID 2% cases, and involve the following sets of defendants: (i) Actavis and (ii) Lupin. These cases arise from Paragraph IV Patent Certification notice letters from each of Actavis and Lupin advising each had filed an ANDA with the FDA seeking approval to market a generic version of PENNSAID 2% before the expiration of the patents-in-suit. For a more detailed description of the PENNSAID 2% litigation, see Note 19 of the Notes to consolidated financial statements, included in Item 15 of this Annual Report on Form 10-K.

We intend to vigorously defend our intellectual property rights relating to our medicines, but we cannot predict the outcome of the RAVICTI cases, the PENNSAID 2% cases and the VIMOVO cases. Any adverse outcome in these matters or any new generic challenges that may arise could result in one or more generic versions of our medicines being launched before the expiration of the listed patents, which could adversely affect our ability to successfully execute our business strategy to increase sales of our medicines, and would negatively impact our financial condition and results of operations, including causing a significant decrease in our revenues and cash flows.

Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property or prevent others from designing around our claims. If the patent applications we hold with respect to our medicines fail to issue or if their breadth or strength of protection is threatened, it could dissuade companies from collaborating with us to develop them and threaten our ability to commercialize our medicines. We cannot offer any assurances about which, if any, patents will issue or whether any issued patents will be found not invalid and not unenforceable or will go unthreatened by third parties. Since patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we were the first to file any patent application related to our medicines or any other medicine candidates. Furthermore, if third parties have filed such patent applications, an interference proceeding in the United States can be provoked by a third-party or instituted by us to determine which party was the first to invent any of the subject matter covered by the patent claims of our applications.

With respect to RAVICTI, the composition of matter patent we hold would have expired in the United States in February 2015 without term extension. However, Hyperion applied for a term extension for this patent under the Drug Price Competition and Patent Term Restoration Act and received notice that the United States Patent and Trademark Office, or the U.S. PTO, extended the expiration date of the patent to July 28, 2018, and to 2022 with respect to orphan drug exclusivity. We cannot guarantee that pending patent applications related to RAVICTI will result in additional patents or that other existing and future patents related to RAVICTI will be held valid and enforceable or will be sufficient to deter generic competition in the United States. Therefore, it is possible that upon expiration of the RAVICTI composition of matter patent, we would need to rely on forms of regulatory exclusivity, to the extent available, to protect against generic competition.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable, processes for which patents are difficult to enforce and any other elements of our drug discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. Although we expect all of our employees to assign their inventions to us, and all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques.

Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. For example, if the issuance, in a given country, of a patent to us, covering an invention, is not followed by the issuance, in other countries, of patents covering the same invention, or if any judicial interpretation of the validity, enforceability, or scope of the claims in, or the written description or enablement in, a patent issued in one country is not similar to the interpretation given to the corresponding patent issued in another country, our ability to protect our intellectual property in those countries may be limited. Changes in either patent laws or in interpretations of patent laws in the United States and other countries may materially diminish the value of our intellectual property or narrow the scope of our patent protection. If we are unable to prevent material disclosure of the non-patented intellectual property related to our technologies to third parties, and there is no guarantee that we will have any such enforceable trade secret protection, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, results of operations and financial condition.

Third-party claims of intellectual property infringement may prevent or delay our development and commercialization efforts.

Our commercial success depends in part on us avoiding infringement of the patents and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions and inter party reexamination proceedings before the U.S. PTO. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which our collaborators are developing medicine candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our medicine candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our medicines and/or any other medicine candidates. Because patent applications can take many years to issue, there may be currently pending patent applications, which may later result in issued patents that our medicine candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our medicine candidates, any molecules formed during the manufacturing process or any final medicine itself, the holders of any such patents may be able to block our ability to commercialize such medicine candidate unless we obtained a license under the applicable patents, or until such patents expire. Similarly, if any third-party patent were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or methods of use, including combination therapy, the holders of any such patent may be able to block our ability to develop and commercialize the applicable medicine candidate unless we obtained a license or until such patent expires. In either case, such a license may not be available on commercially reasonable terms or at all.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our medicine candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties or redesign our infringing medicines, which may be impossible or require substantial time and monetary expenditure. We cannot predict whether any such license would be available at all or whether it would be available on commercially reasonable terms. Furthermore, even in the absence of litigation, we may need to obtain licenses from third parties to advance our research or allow commercialization of our medicine candidates, and we have done so from time to time. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. In that event, we would be unable to further

develop and commercialize one or more of our medicine candidates, which could harm our business significantly. We cannot provide any assurances that third-party patents do not exist which might be enforced against our medicines, resulting in either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties.

If we fail to comply with our obligations in the agreements under which we license rights to technology from third parties, we could lose license rights that are important to our business.

We are party to a number of technology licenses that are important to our business and expect to enter into additional licenses in the future. For example, we rely on a license from Ucyclyd with respect to technology developed by Ucyclyd in connection with the manufacturing of RAVICTI. The purchase agreement under which Hyperion purchased the worldwide rights to RAVICTI contains obligations to pay Ucyclyd regulatory and sales milestone payments relating to RAVICTI, as well as royalties on the net sales of RAVICTI. On May 31, 2013, when Hyperion acquired BUPHENYL under a restated collaboration agreement with Ucyclyd, Hyperion received a license to use some of the manufacturing technology developed by Ucyclyd in connection with the manufacturing of BUPHENYL. The restated collaboration agreement also contains obligations to pay Ucyclyd regulatory and sales milestone payments, as well as royalties on net sales of BUPHENYL. If we fail to make a required payment to Ucyclyd and do not cure the failure within the required time period, Ucyclyd may be able to terminate the license to use its manufacturing technology for RAVICTI and BUPHENYL. If we lose access to the Ucyclyd manufacturing technology, we cannot guarantee that an acceptable alternative method of manufacture could be developed or acquired. Even if alternative technology could be developed or acquired, the loss of the Ucyclyd technology could still result in substantial costs and potential periods where we would not be able to market and sell RAVICTI and/or BUPHENYL. We also license intellectual property necessary for commercialization of RAVICTI from an external party. This party may be entitled to terminate the license if we breach the agreement, including failure to pay required royalties on net sales of RAVICTI, or we do not meet specified diligence obligations in our development and commercialization of RAVICTI, and we do not cure the failure within the required time period. If the license is terminated, it may be difficult or impossible for us to continue to commercialize RAVICTI, which would have a material adverse effect on our business, financial condition and results of operations.

We also license rights to patents, know-how and trademarks for ACTIMMUNE from Genentech Inc., or Genentech, under an agreement that remains in effect for so long as we continue to commercialize and sell ACTIMMUNE. However, Genentech may terminate the agreement upon our material default, if not cured within a specified period of time. Genentech may also terminate the agreement in the event of our bankruptcy or insolvency. Upon such a termination of the agreement, all intellectual property rights conveyed to us under the agreement, including the rights to the ACTIMMUNE trademark, revert to Genentech. If we fail to comply with our obligations under this agreement, we could lose the ability to market and distribute ACTIMMUNE, which would have a material adverse effect on our business, financial condition and results of operations.

In addition, we are subject to contractual obligations under our agreements with Tripex and PARI related to QUINSAIR. Under the agreement with Tripex, we are required to pursue commercially reasonable efforts to initiate, and subsequently to complete, an additional clinical trial of QUINSAIR in a non-CF patient population within a specified period of time and an obligation to progress toward submitting an NDA for approval of QUINSAIR in the United States for use in all or part of the CF patient population. These obligations are subject to certain exceptions due to, for example, manufacturing delays not under our control, or delays caused by the FDA. If we fail to properly exercise such efforts to initiate and complete an appropriate clinical trial, or fail to submit an NDA for U.S. approval in the CF patient population, during the time periods specified in the agreement, we may be subject to various claims by Tripex and parties affiliated with Tripex. In addition, if we do not spend a minimum amount on QUINSAIR development in each of the three years following our acquisition of Raptor, we may also be obligated to pre-pay a milestone payment related to initiating a clinical trial for QUINSAIR in a non-CF indication. During October 2017, we triggered a milestone payment under this agreement, and we paid Tripex $20.0 million in November 2017. Under the license agreement with PARI, we are required to comply with diligence milestones related to development and commercialization of QUINSAIR in the United States and to spend a specified minimum amount per year on development activities in the United States until submission of the NDA for QUINSAIR in the United States. If we do not comply with these obligations, our licenses to certain intellectual property related to QUINSAIR may become non-exclusive in the United States or could be terminated. We are also subject to contractual obligations under our amended and restated license agreement with UCSD, with respect to PROCYSBI, including obligations to consider engaging in the development of PROCYSBI for the treatment of NASH and related diligence obligations if we undertake such development. Under the amended and restated license agreement with USCD, we also are subject to diligence obligations to identify a third party to undertake development of PROCYSBI for the treatment of Huntington's disease. To the extent that we fail to perform the diligence obligations under the agreement, UCSD may, with

respect to such indication, terminate the license or otherwise cause the license to become non-exclusive. If one or more of these licenses was terminated, we would have no further right to use or exploit the related intellectual property, which would limit our ability to develop PROCYSBI or QUINSAIR in other indications, and could impact our ability to continue commercializing PROCYSBI or QUINSAIR in their approved indications.

We also hold an exclusive license to patents and technology from Duke University, or Duke, and Mountain View Pharmaceuticals, Inc., or MVP, covering KRYSTEXXA. Duke and MVP may terminate the license if we commit fraud or for our willful misconduct or illegal conduct. Duke and MVP may also terminate the license upon our material breach of the agreement, if not cured within a specified period of time, or upon written notice if we have committed two or more material breaches under the agreement. Duke and MVP may also terminate the license in the event of our bankruptcy or insolvency. If the license is terminated, it may be impossible for us to continue to commercialize KRYSTEXXA, which would have a material adverse effect on our business, financial condition and results of operations.

We hold an exclusive license to Vectura Group plc's, or Vectura, proprietary technology and know-how covering the delayed-release of corticosteroids relating to RAYOS/LODOTRA. If we fail to comply with our obligations under our agreement with Vectura or our other license agreements, or if we are subject to a bankruptcy, the licensor may have the right to terminate the license, in which event we would not be able to market medicines covered by the license, including RAYOS/ LODOTRA.

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our patents or the patents of our licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that one of our patents, or a patent of one of our licensors, is not valid or is unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing.

There are numerous post grant review proceedings available at the U.S. PTO (including inter partes review, post-grant review and ex-parte reexamination) and similar proceedings in other countries of the world that could be initiated by a third-party that could potentially negatively impact our issued patents.

Interference proceedings provoked by third parties or brought by us may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our collaborators or licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our ordinary shares.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees on any issued patent are due to be paid to the U.S. PTO and foreign patent agencies in several stages over the lifetime of the patent. The U.S. PTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance

events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we or licensors that control the prosecution and maintenance of our licensed patents fail to maintain the patents and patent applications covering our medicine candidates, our competitors might be able to enter the market, which would have a material adverse effect on our business.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties.

We employ individuals who were previously employed at other biotechnology or pharmaceutical companies. We may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed confidential information of our employees' former employers or other third parties. We may also be subject to claims that former employers or other third parties have an ownership interest in our patents. Litigation may be necessary to defend against these claims. There is no guarantee of success in defending these claims, and even if we are successful, litigation could result in substantial cost and be a distraction to our management and other employees.

Risks Related to Ownership of Our Ordinary Shares

The market price of our ordinary shares historically has been volatile and is likely to continue to be volatile, and you could lose all or part of any investment in our ordinary shares.

The trading price of our ordinary shares has been volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. In addition to the factors discussed in this "Risk Factors" section and elsewhere in this report, these factors include:

- our failure to successfully execute our commercialization strategy with respect to our approved medicines, particularly our commercialization of our medicines in the United States;
- actions or announcements by third-party or government payers with respect to coverage and reimbursement of our medicines;
- disputes or other developments relating to intellectual property and other proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our medicines and medicine candidates;
- unanticipated serious safety concerns related to the use of our medicines;
- adverse regulatory decisions;
- changes in laws or regulations applicable to our business, medicines or medicine candidates, including but not limited to clinical trial requirements for approvals or tax laws;
- inability to comply with our debt covenants and to make payments as they become due;
- inability to obtain adequate commercial supply for any approved medicine or inability to do so at acceptable prices;
- developments concerning our commercial partners, including but not limited to those with our sources of manufacturing supply;
- our decision to initiate a clinical trial, not to initiate a clinical trial or to terminate an existing clinical trial;
- adverse results or delays in clinical trials;
- our failure to successfully develop and/or acquire additional medicine candidates or obtain approvals for additional indications for our existing medicine candidates;
- introduction of new medicines or services offered by us or our competitors;
- overall performance of the equity markets, including the pharmaceutical sector, and general political and economic conditions;
- failure to meet or exceed revenue and financial projections that we may provide to the public;
- actual or anticipated variations in quarterly operating results;
- failure to meet or exceed the estimates and projections of the investment community;

- inaccurate or significant adverse media coverage;
- publication of research reports about us or our industry or positive or negative recommendations or withdrawal of research coverage by securities analysts;
- our inability to successfully enter new markets;
- the termination of a collaboration or the inability to establish additional collaborations;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us or our competitors;
- our inability to maintain an adequate rate of growth;
- ineffectiveness of our internal controls or our inability to otherwise comply with financial reporting requirements;
- adverse U.S. and foreign tax exposure;
- additions or departures of key management, commercial or regulatory personnel;
- issuances of debt or equity securities;
- significant lawsuits, including patent or shareholder litigation;
- changes in the market valuations of similar companies to us;
- sales of our ordinary shares by us or our shareholders in the future;
- trading volume of our ordinary shares;
- effects of natural or man-made catastrophic events or other business interruptions; and
- other events or factors, many of which are beyond our control.

In addition, the stock market in general, and The NASDAQ Global Select Market and the stock of biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may adversely affect the market price of our ordinary shares, regardless of our actual operating performance.

We have never declared or paid dividends on our share capital and we do not anticipate paying dividends in the foreseeable future.

We have never declared or paid any cash dividends on our ordinary shares. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future, including due to limitations that are currently imposed by our credit agreement and the indentures governing the 2024 Senior Notes and the 2023 Senior Notes. Any return to shareholders will therefore be limited to the increase, if any, of our ordinary share price.

We have incurred and will continue to incur significant increased costs as a result of operating as a public company and our management will be required to devote substantial time to compliance initiatives.

As a public company, we have incurred and will continue to incur significant legal, accounting and other expenses that we did not incur as a private company. In particular, the Sarbanes-Oxley Act of 2000, or the Sarbanes-Oxley Act, as well as rules subsequently implemented by the SEC and the NASDAQ Stock Market, Inc., or NASDAQ, impose significant requirements on public companies, including requiring establishment and maintenance of effective disclosure and financial controls and changes in corporate governance practices. These rules and regulations have substantially increased our legal and financial compliance costs and have made some activities more time-consuming and costly. These effects are exacerbated by our transition to an Irish company and the integration of numerous acquired businesses and operations into our historical business and operating structure. If these requirements divert the attention of our management and personnel from other business concerns, they could have a material adverse effect on our business, financial condition and results of operations. The increased costs will continue to decrease our net income or increase our net loss, and may require us to reduce costs in other areas of our business or increase the prices of our medicines or services. For example, these rules and regulations make it more difficult and more expensive for us to obtain and maintain director and officer liability insurance.

We cannot predict or estimate the amount or timing of additional costs that we may incur to respond to these requirements. The impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers. If we fail to comply with the continued listing requirements of NASDAQ, our ordinary shares could be delisted from The NASDAQ Global Select Market, which would adversely affect the liquidity of our ordinary shares and our ability to obtain future financing.

The Sarbanes-Oxley Act requires, among other things, that we maintain effective internal controls for financial reporting and disclosure controls and procedures. In particular, we are required to perform annual system and process evaluation and testing of our internal controls over financial reporting to allow management to report on the effectiveness of our internal controls over financial reporting, as required by Section 404 of the Sarbanes-Oxley Act, or Section 404. Our independent registered public accounting firm is also required to deliver a report on the effectiveness of our internal control over financial reporting. Our testing, or the testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses. Our compliance with Section 404 requires that we incur substantial expense and expend significant management efforts, particularly because of our Irish parent company structure and international operations. If we are not able to comply with the requirements of Section 404 or if we or our independent registered public accounting firm identify deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses, the market price of our ordinary shares could decline and we could be subject to sanctions or investigations by NASDAQ, the SEC or other regulatory authorities, which would require additional financial and management resources.

New laws and regulations as well as changes to existing laws and regulations affecting public companies, including the provisions of the Sarbanes-Oxley Act and rules adopted by the SEC and by NASDAQ, would likely result in increased costs as we respond to their requirements.

Sales of a substantial number of our ordinary shares in the public market could cause our share price to decline.

If our existing shareholders sell, or indicate an intention to sell, substantial amounts of our ordinary shares in the public market, the trading price of such ordinary shares could decline. In addition, our ordinary shares that are either subject to outstanding options or reserved for future issuance under our employee benefit plans are or may become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules and Rule 144 under the Securities Act of 1933, as amended, or the Securities Act. If these additional ordinary shares are sold, or if it is perceived that they will be sold, in the public market, the trading price of our ordinary shares could decline.

In addition, any conversion or exchange of our Exchangeable Senior Notes, whether pursuant to their terms or pursuant to privately negotiated transactions between the issuer and/or us and a holder of such securities, could depress the market price for our ordinary shares.

Future sales and issuances of our ordinary shares, securities convertible into our ordinary shares or rights to purchase ordinary shares or convertible securities could result in additional dilution of the percentage ownership of our shareholders and could cause our share price to decline.

Additional capital may be needed in the future to continue our planned operations. To the extent we raise additional capital by issuing equity securities or securities convertible into or exchangeable for ordinary shares, our shareholders may experience substantial dilution. We may sell ordinary shares, and we may sell convertible or exchangeable securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell such ordinary shares, convertible or exchangeable securities or other equity securities in subsequent transactions, existing shareholders may be materially diluted. New investors in such subsequent transactions could gain rights, preferences and privileges senior to those of holders of ordinary shares. We also maintain equity incentive plans, including our Amended and Restated 2014 Equity Incentive Plan, 2014 Non-Employee Equity Plan and 2014 Employee Stock Purchase Plan, and intend to grant additional ordinary share awards under these and future plans, which will result in additional dilution to our existing shareholders.

Irish law differs from the laws in effect in the United States and may afford less protection to holders of our securities.

It may not be possible to enforce court judgments obtained in the United States against us in Ireland based on the civil liability provisions of the U.S. federal or state securities laws. In addition, there is some uncertainty as to whether the courts of Ireland would recognize or enforce judgments of U.S. courts obtained against us or our directors or officers based on the civil liabilities provisions of the U.S. federal or state securities laws or hear actions against us or those persons based on those laws. We have been advised that the United States currently does not have a treaty with Ireland providing for the reciprocal recognition and enforcement of judgments in civil and commercial matters. Therefore, a final judgment for the payment of money rendered by any U.S. federal or state court based on civil liability, whether or not based solely on U.S. federal or state securities laws, would not automatically be enforceable in Ireland.

As an Irish company, we are governed by the Irish Companies Acts, which differ in some material respects from laws generally applicable to U.S. corporations and shareholders, including, among others, differences relating to interested director and officer transactions and shareholder lawsuits. Likewise, the duties of directors and officers of an Irish company generally are owed to the company only. Shareholders of Irish companies generally do not have a personal right of action against directors or officers of the company and may exercise such rights of action on behalf of the company only in limited circumstances. Accordingly, holders of our securities may have more difficulty protecting their interests than would holders of securities of a corporation incorporated in a jurisdiction of the United States.

Provisions of our articles of association could delay or prevent a takeover of us by a third-party.

Our articles of association could delay, defer or prevent a third-party from acquiring us, despite the possible benefit to our shareholders, or otherwise adversely affect the price of our ordinary shares. For example, our articles of association:

- impose advance notice requirements for shareholder proposals and nominations of directors to be considered at shareholder meetings;
- stagger the terms of our board of directors into three classes; and
- require the approval of a supermajority of the voting power of the shares of our share capital entitled to vote generally at a meeting of shareholders to amend or repeal our articles of association.

In addition, several mandatory provisions of Irish law could prevent or delay an acquisition of us. For example, Irish law does not permit shareholders of an Irish public limited company to take action by written consent with less than unanimous consent. We are also subject to various provisions of Irish law relating to mandatory bids, voluntary bids, requirements to make a cash offer and minimum price requirements, as well as substantial acquisition rules and rules requiring the disclosure of interests in our ordinary shares in certain circumstances.

These provisions may discourage potential takeover attempts, discourage bids for our ordinary shares at a premium over the market price or adversely affect the market price of, and the voting and other rights of the holders of, our ordinary shares. These provisions could also discourage proxy contests and make it more difficult for you and our other shareholders to elect directors other than the candidates nominated by our board of directors, and could depress the market price of our ordinary shares.

A transfer of our ordinary shares may be subject to Irish stamp duty.

In certain circumstances, the transfer of shares in an Irish incorporated company will be subject to Irish stamp duty, which is a legal obligation of the buyer. This duty is currently charged at the rate of 1.0 percent of the price paid or the market value of the shares acquired, if higher. Because our ordinary shares are traded on a recognized stock exchange in the United States, an exemption from this stamp duty is available to transfers by shareholders who hold ordinary shares beneficially through brokers, which in turn hold those shares through the Depositary Trust Company, or DTC, to holders who also hold through DTC. However, a transfer by or to a record holder who holds ordinary shares directly in his, her or its own name could be subject to this stamp duty. We, in our absolute discretion and insofar as the Companies Acts or any other applicable law permit, may, or may provide that one of our subsidiaries will pay Irish stamp duty arising on a transfer of our ordinary shares on behalf of the transferee of such ordinary shares. If stamp duty resulting from the transfer of ordinary shares which would otherwise be payable by the transferee is paid by us or any of our subsidiaries on behalf of the transferee, then in those circumstances, we will, on our behalf or on behalf of such subsidiary (as the case may be), be entitled to (i) seek reimbursement of the stamp duty from the transferee, (ii) set-off the stamp duty against any dividends payable to the transferee of those ordinary shares and (iii) claim a first and permanent lien on the ordinary shares on which stamp duty has been paid by us or such subsidiary for the amount of stamp duty paid. Our lien shall extend to all dividends paid on those ordinary shares.

Dividends paid by us may be subject to Irish dividend withholding tax.

In certain circumstances, as an Irish tax resident company, we will be required to deduct Irish dividend withholding tax (currently at the rate of 20%) from dividends paid to our shareholders. Shareholders that are resident in the United States, EU countries (other than Ireland) or other countries with which Ireland has signed a tax treaty (whether the treaty has been ratified or not) generally should not be subject to Irish withholding tax so long as the shareholder has provided its broker, for onward transmission to our qualifying intermediary or other designated agent (in the case of shares held beneficially), or our or its transfer agent (in the case of shares held directly), with all the necessary documentation by the appropriate due date prior to payment of the dividend. However, some shareholders may be subject to withholding tax, which could adversely affect the price of our ordinary shares.

If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, our share price and trading volume could decline.

The trading market for our ordinary shares will depend in part on the research and reports that securities or industry analysts publish about us or our business. If one or more of the analysts who cover us downgrade our rating or publish inaccurate or unfavorable research about our business, our share price could decline. If one or more of these analysts cease coverage of our company or fail to publish reports on our company regularly, demand for our ordinary shares could decrease, which might cause our share price and trading volume to decline.

Securities class action litigation could divert our management's attention and harm our business and could subject us to significant liabilities.

The stock markets have from time to time experienced significant price and volume fluctuations that have affected the market prices for the equity securities of pharmaceutical companies. These broad market fluctuations may cause the market price of our ordinary shares to decline. In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology and biopharmaceutical companies have experienced significant stock price volatility in recent years. For example, following declines in our stock price, two federal securities class action lawsuits were filed in March 2016 against us and certain of our current and former officers alleging violations of the Securities Exchange Act of 1934, as amended. Subsequently, the two actions were consolidated (captioned Schaffer v. Horizon Pharma plc, et al., Case No. 1:16-cv-01763), and plaintiff added claims under the Securities Act and named additional defendants. On January 18, 2018, the District Court dismissed all plaintiffs' claims against all defendants, and denied the plaintiffs any further opportunity to amend their complaint. On February 16, 2018, plaintiffs filed a notice of appeal to the District Court's ruling. Even if we are successful in defending this appeal or any similar claims that may be brought in the future, such litigation could result in substantial costs and may be a distraction to our management, and may lead to an unfavorable outcome that could adversely impact our financial condition and prospects.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Location	Approximate Square Footage	Lease Expiry Date
Dublin, Ireland	18,900	November 3, 2029
Lake Forest, Illinois (1)	160,000	March 31, 2024
Novato, California (2)	61,000	August 31, 2021
Deerfield, Illinois (3)	32,300	June 30, 2018
Brisbane, California	20,100	November 30, 2019
Mannheim, Germany	14,300	December 31, 2018
Chicago, Illinois	6,500	December 31, 2018
Other	13,300	March 31, 2018 to May 31, 2020

(1) In connection with the Lake Forest lease, we have provided a $2.0 million letter of credit to the landlord, through a commercial bank.

(2) In March 2017, we vacated an area of the office space in Novato, California and in March and April 2017, we entered into sublease arrangements for this space with third parties.

(3) In January 2016, we vacated the premises in Deerfield, Illinois and began occupying the premises in Lake Forest, Illinois. In April 2017, we entered into a sublease arrangement for a portion of this space with a third party. In June 2017, we terminated a portion of the lease, resulting in 32,300 square feet remaining.

Item 3. Legal Proceedings

For a description of our legal proceedings, see Note 19 of the Notes to consolidated financial statements, included in Item 15 of this Annual Report on Form 10-K.

Item 4. Mine Safety Disclosures

None.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Information

Our ordinary shares trade on The NASDAQ Global Select Market under the trading symbol "HZNP".

The following table sets forth the high and low sales prices per share of our ordinary shares as reported on The NASDAQ Global Select Market for the periods indicated.

	High	Low
2017		
First quarter	$ 18.31	$ 14.20
Second quarter	15.90	9.45
Third quarter	14.22	11.17
Fourth quarter	15.40	12.66

	High	Low
2016		
First quarter	$ 22.02	$ 13.36
Second quarter	19.45	13.05
Third quarter	23.44	16.18
Fourth quarter	21.98	14.16

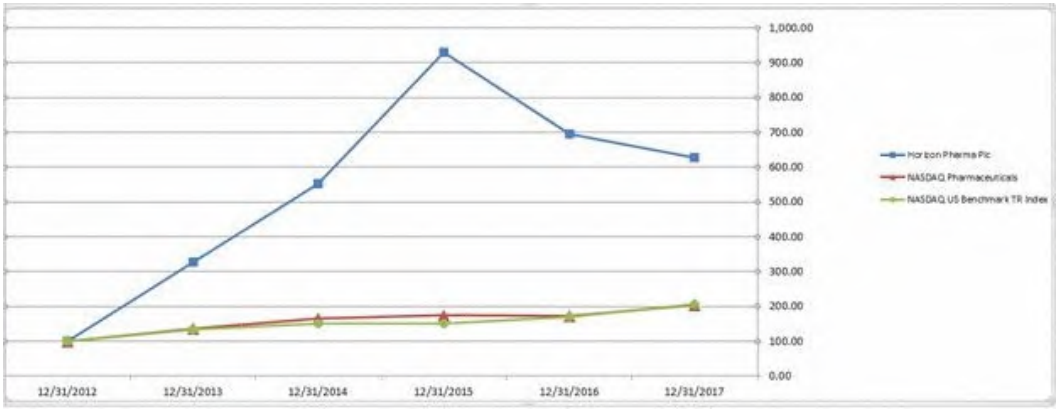
Holders of Record

The closing price of our ordinary shares on February 22, 2018 was $13.96. As of February 22, 2018, there were approximately thirteen holders of record of our ordinary shares. Because almost all of our ordinary shares are held by brokers, nominees and other institutions on behalf of shareholders, we are unable to estimate the total number of shareholders represented by these record holders.

Performance Graph

The following graph shows a comparison from December 31, 2012 through December 31, 2017 of the cumulative total return for (i) our ordinary shares, (ii) the NASDAQ U.S. Benchmark TR Index and (iii) NASDAQ Pharmaceuticals.

Information set forth in the graph below represents the performance of the Horizon Pharma, Inc. common stock from December 31, 2012 until September 18, 2014, the day before the consummation of the Vidara Merger, and the performance of our ordinary shares from September 19, 2014 through December 31, 2017. Our ordinary shares trade on the same exchange, the NASDAQ Global Select Market, and under the same trading symbol, "HZNP", as the Horizon Pharma, Inc. common stock prior to the Vidara Merger. The graph assumes an initial investment of $100 on December 31, 2012. The comparisons in the graph are required by the Securities and Exchange Commission and are not intended to forecast or be indicative of possible future performance of our ordinary shares.



	12/31/2012	12/31/2013	12/31/2014	12/31/2015	12/31/2016	12/31/2017
Cumulative Returns						
Horizon Pharma plc	$ 100.00	$ 327.04	$ 553.22	$ 930.04	$ 694.42	$ 626.61
NASDAQ Pharmaceuticals	100.00	135.68	165.28	174.27	172.37	205.33
NASDAQ U.S. Benchmark TR Index	100.00	133.48	150.12	150.84	170.46	206.91

The foregoing graph and table are furnished solely with this report, and are not filed with this report, and shall not be deemed incorporated by reference into any other filing under the Securities Act of 1933, as amended, or the Securities Act, or the Securities Exchange Act of 1934, as amended, whether made by us before or after the date hereof, regardless of any general incorporation language in any such filing, except to the extent we specifically incorporate this material by reference into any such filing.

Dividend Policy

We have never declared or paid cash dividends on our common equity. We currently intend to retain all available funds and any future earnings to support operations and finance the growth and development of our business and do not intend to pay cash dividends on our ordinary shares for the foreseeable future. Under Irish law, dividends may only be paid, and share repurchases and redemptions must generally be funded only out of, "distributable reserves". In addition, our ability to pay cash dividends is currently prohibited by the terms of our credit agreement with Citibank, N.A., as administrative and collateral agent, $475.0 million aggregate principal amount of 6.625% Senior Notes due 2023 and the $300.0 million aggregate principal amount of 8.75% Senior Notes due 2024, subject to customary exceptions. Any future determination as to the payment of dividends will, subject to Irish legal requirements, be at the sole discretion of our board of directors and will depend on our financial condition, results of operations, capital requirements and other factors our board of directors deems relevant.

Securities Authorized for Issuance under Equity Compensation Plans

See Item 12 of Part III of this Annual Report on Form 10-K regarding information about securities authorized for issuance under our equity compensation plans.

Recent Sales of Unregistered Securities

Except as previously reported in our Quarterly Reports on Form 10-Q and Current Reports on Form 8-K filed with the Securities and Exchange Commission there were no unregistered sales of equity securities by us during the year ended December 31, 2017.

Issuer Repurchases of Equity Securities

None.

Irish Law Matters

See *Irish Law Matters* included in Item 1 of Part I of this Annual Report on Form 10-K.

Item 6. Selected Financial Data

The selected statement of comprehensive (loss) income data and selected statement of cash flows data for the years ended December 31, 2017, 2016 and 2015, and the balance sheet data as of December 31, 2017 and 2016 have been derived from our audited financial statements included elsewhere in this Annual Report on Form 10-K. The selected statements of comprehensive loss data and selected statement of cash flows data for the years ended December 31, 2014 and 2013, and the balance sheet data as of December 31, 2015, 2014 and 2013 have been derived from audited financial statements which are not included in this Annual Report on Form 10-K.

Our historical results are not necessarily indicative of future results. The selected financial data should be read in conjunction with "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our financial statements and related notes included elsewhere in this Annual Report on Form 10-K. The selected financial data for the year ended December 31, 2013 is that of Horizon Pharma, Inc., or HPI, our predecessor, while the selected financial data for the years ended December 31, 2017, 2016, 2015 and 2014 is that of Horizon Pharma plc.

On September 19, 2014, the businesses of HPI and Vidara Therapeutics International Public Limited Company were combined in a merger transaction, on May 7, 2015, we completed our acquisition of Hyperion Therapeutics, Inc., on January 13, 2016, we completed our acquisition of Crealta Holdings LLC and on October 25, 2016, we completed our acquisition of Raptor Pharmaceutical Corp. The financial data presented below include the results of operations of the merged or acquired Vidara, Hyperion, Crealta and Raptor businesses from the applicable dates of merger or acquisition.

	As of December 31,				
	2017	2016	2015	2014	2013
			(in thousands)		
Selected Balance Sheet Data					
Cash and cash equivalents	$ 751,368	$ 509,055	$ 859,616	$ 218,807	$ 80,480
Working capital	473,199	440,430	748,595	106,024	67,455
Total assets (1)	4,166,092	4,292,059	3,058,588	1,123,133	246,328
Total debt, net (1)	1,901,655	1,807,493	1,136,756	334,012	104,494
Accumulated deficit (2)	(1,252,329)	(848,021)	(681,187)	(720,719)	(457,116)
Total shareholders' equity (deficit) (2)	991,098	1,263,779	1,313,145	540,204	(49,082)

	For the Years Ended December 31,				
	2017	2016	2015	2014	2013
	(in thousands, except per share data)				
Selected Statement of Comprehensive (Loss) Income Data					
Net sales	$ 1,056,231	$ 981,120	$ 757,044	$ 296,955	$ 74,016
Cost of goods sold	546,275	393,272	219,502	78,753	14,625
Gross profit	509,956	587,848	537,542	218,202	59,391
Loss before benefit for income taxes	(513,275)	(228,085)	(132,712)	(269,687)	(150,126)
Net (loss) income	(410,526)	(166,834)	39,532	(263,603)	(149,005)
Net (loss) income per ordinary share - basic	(2.52)	(1.04)	0.27	(3.15)	(2.34)
Net (loss) income per ordinary share - diluted	(2.52)	(1.04)	0.25	(3.15)	(2.34)
Selected Statement of Cash Flows Data					
Net cash provided by (used in) operating activities	$ 280,208	$ 369,456	$ 194,166	$ 27,549	$ (54,287)
Net cash used in investing activities	(121,619)	(1,375,881)	(995,048)	(227,720)	(36,135)
Net cash provided by financing activities	78,408	657,074	1,442,481	338,285	66,716
Payments for acquisitions, net of cash acquired	(187,220)	(1,356,271)	(1,022,361)	(224,220)	(35,000)
Proceeds from divestiture, net of cash divested	69,371	—	—	—	—
Net proceeds from the issuance of ordinary shares/common stock	4,505	4,884	500,454	41,934	6,637
Net proceeds from the issuance of debt	1,693,512	656,190	1,241,027	286,966	143,598
Repayment of debt	(1,618,617)	(4,000)	(299,000)	—	(64,884)

(1) In 2016, we retrospectively adopted Accounting Standards Update, or ASU, No. 2015-03, *Interest-Imputation of Interest (Subtopic 835-30): Simplifying the Presentation of Debt Issuance Costs*, simplifying the presentation of debt issuance costs. As a result, deferred financing costs of $11.5 million and $6.3 million that were classified within "total assets" at December 31, 2014 and 2013, respectively, were reclassified to "total debt, net" in the above table to conform prior-period classifications as a result of the new guidance.

(2) On January 1, 2017, we adopted ASU No. 2016-09, *Improvements to Employee Share-Based Payment Accounting*, on a modified retrospective basis and recorded a decrease of $7.2 million in net deferred tax liabilities and a corresponding decrease in accumulated deficit during the year ended December 31, 2017.

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and the related notes appearing at the end of this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. You should read the "Risk Factors" section of this Annual Report on Form 10-K for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

The discussion below contains "forward-looking statements," as defined in Section 21E of the Securities Exchange Act of 1934, as amended, that reflect our current expectations regarding our future growth, results of operations, cash flows, performance and business prospects and opportunities, as well as assumptions made by, and information currently available to, our management. We have tried to identify forward-looking statements by using words such as "anticipate," "believe," "plan," "expect," "intend," "will," and similar expressions, but these words are not the exclusive means of identifying forward-looking statements. These statements are based on information currently available to us and are subject to various risks, uncertainties, and other factors, including, but not limited to, those matters discussed in Item 1A. "Risk Factors" in Part I of this Annual Report on Form 10-K, that could cause our actual growth, results of operations, cash flows, performance and business prospects and opportunities to differ materially from those expressed in, or implied by, these statements. Except as expressly required by the federal securities laws, we undertake no obligation to update such factors or to publicly announce the results of any of the forward-looking statements contained herein to reflect future events, developments, or changed circumstances, or for any other reason.

OVERVIEW

Unless otherwise indicated or the context otherwise requires, references to "we", "us" and "our" refer to Horizon Pharma plc and its consolidated subsidiaries.

Beginning in the first quarter of 2017, we modified our presentation of certain operating expenses. Previously, we presented "general and administrative" expenses as one line item in our consolidated statement of comprehensive (loss) income, and "selling and marketing" expenses as another. For the year ended December 31, 2017 presentation and prior-period comparisons, we now combine these two line items into one line item, titled "selling, general and administrative" expenses.

Our Business

We are a biopharmaceutical company focused on researching, developing and commercializing innovative medicines that address unmet treatment needs for rare and rheumatic diseases. By fostering a growing pipeline of medicines in development and exploring all potential uses for currently marketed medicines, we strive to make a powerful difference for patients, their caregivers and physicians.

Our marketed medicines are:

Orphan Business Unit
RAVICTI® (glycerol phenylbutyrate) Oral Liquid
PROCYSBI® (cysteamine bitartrate) delayed-release capsules
ACTIMMUNE® (interferon gamma-1b); marketed as IMUKIN® outside the United States, Canada and Japan
BUPHENYL® (sodium phenylbutyrate) Tablets and Powder; marketed as AMMONAPS® in certain European countries and Japan
QUINSAIR™ (levofloxacin inhalation solution)
Rheumatology Business Unit
KRYSTEXXA® (pegloticase)
RAYOS® (prednisone) delayed-release tablets; marketed as LODOTRA® outside the United States
Primary Care Business Unit
PENNSAID® (diclofenac sodium topical solution) 2% w/w, or PENNSAID 2%
DUEXIS® (ibuprofen/famotidine)
VIMOVO® (naproxen/esomeprazole magnesium)
MIGERGOT® (ergotamine tartrate & caffeine suppositories)

During the years ended December 31, 2017, 2016 and 2015, we completed the following acquisitions and divestitures:

- On June 30, 2017, we completed our acquisition of certain rights to interferon gamma-1b from Boehringer Ingelheim International GmbH, or Boehringer Ingelheim International, in all territories outside of the United States, Canada and Japan.
- On June 23, 2017, we sold our European subsidiary that owned the marketing rights to PROCYSBI® (cysteamine bitartrate) delayed-release capsules and QUINSAIR™ (levofloxacin inhalation solution) in Europe, the Middle East and Africa, or EMEA, regions, or the Chiesi divestiture, to Chiesi Farmaceutici S.p.A., or Chiesi.
- On May 8, 2017, we completed our acquisition of River Vision Development Corp., or River Vision, which added the late development-stage rare disease biologic medicine candidate teprotumumab to our research and development pipeline.
- On October 25, 2016, we completed our acquisition of Raptor Pharmaceutical Corp., or Raptor, which added the rare disease medicines PROCYSBI and QUINSAIR to our medicine portfolio.
- On January 13, 2016, we completed our acquisition of Crealta Holdings LLC, or Crealta, which added the rare disease medicine KRYSTEXXA and the primary care medicine MIGERGOT to our medicine portfolio.
- On May 7, 2015, we completed our acquisition of Hyperion Therapeutics, Inc., or Hyperion, which added the rare disease medicines RAVICTI and BUPHENYL to our medicine portfolio.

The consolidated financial statements presented herein include the results of operations of the acquired Hyperion, Crealta and Raptor businesses from the applicable dates of acquisition. See Note 4 of the Notes to consolidated financial statements, included in Item 15 of this Annual Report on Form 10-K, for further details of our acquisitions and divestitures.

Strategy

Our strategy is to continue the transformation of Horizon Pharma plc into a balanced, diversified, sustainable-growth biopharmaceutical company predominantly focused on rare disease medicines. We are executing on our strategy by accelerating the growth of our rare disease medicine portfolio through differentiated commercial strategies, business development efforts, and the expansion of our pipeline with post-marketing and development-stage programs. We are strongly committed to helping ensure patient access to their medicines and support services, and by investing in the further development of medicines for patients with rare or underserved diseases.

Orphan Business Unit

The rare disease medicines in our orphan business unit are RAVICTI, PROCYSBI, ACTIMMUNE, BUPHENYL and QUINSAIR. Our strategy for RAVICTI is to drive growth through increased awareness and diagnosis of urea cycle disorders, and to drive conversion from older-generation nitrogen scavengers, such as generic forms of sodium phenylbutyrate, to RAVICTI, based on the medicine's differentiated benefits. With respect to PROCYSBI, our strategy is to drive conversion of patients from older-generation immediate-release capsules of cysteamine bitartrate to PROCYSBI, increase the uptake of diagnosed but untreated patients and identify previously undiagnosed patients who are suitable for treatment. Our strategy with respect to ACTIMMUNE includes driving growth by increasing awareness and diagnosis of chronic granulomatous disease and increasing the length and persistence of treatment.

With our May 2017 acquisition of River Vision, we added the late-stage rare disease biologic medicine candidate teprotumumab to our pipeline. Teprotumumab, which successfully completed a Phase 2 clinical trial and is currently enrolling patients in a Phase 3 confirmatory trial, targets the treatment of moderate-to-severe thyroid eye disease, a debilitating autoimmune condition that presents in patients with Graves' disease. Our strategy for teprotumumab is to support its continued clinical development and pursue regulatory approval. The River Vision acquisition further demonstrates our commitment to rare disease medicines and expands and diversifies our rare disease medicine pipeline to support sustainable longer-term growth. Our Phase 3 clinical trial evaluating teprotumumab for the treatment of moderate-to-severe active thyroid eye disease was initiated during the fourth quarter of 2017, and we anticipate that data from the trial will be available during the second half of 2019.

Rheumatology Business Unit

The rare disease medicine KRYSTEXXA is the primary marketed medicine in our rheumatology business unit. We are focused on optimizing and maximizing the peak sales potential of KRYSTEXXA by expanding our commercialization efforts, as well as investing in education, patient and physician outreach, and investigation programs that demonstrate KRYSTEXXA as an effective treatment of chronic refractory gout, or, uncontrolled gout, which is refractory (unresponsive) to conventional therapies. We believe that KRYSTEXXA represents a significant opportunity and potential growth driver for our rheumatology business unit. The rheumatology business unit also includes RAYOS/LODOTRA.

Primary Care Business Unit

Our strategy for the primary care business unit, which includes PENNSAID 2%, DUEXIS, VIMOVO and MIGERGOT, is to educate physicians about these clinically differentiated medicines and the benefits they offer. Patients are able to fill prescriptions for these medicines through pharmacies participating in our HorizonCares patient access program, as well as other pharmacies. In addition, we have evolved our commercial strategy to enter into business arrangements with pharmacy benefit managers, or PBMs, and other payers to secure formulary status and reimbursement of our medicines. The business arrangements with the PBMs generally require us to pay administrative fees and rebates to the PBMs and other payers for qualifying prescriptions.

For all of our business units we market our medicines in the United States through our field sales force, which numbered approximately 430 representatives as of December 31, 2017.

RESULTS OF OPERATIONS

Year Ended December 31, 2017 Compared to Year Ended December 31, 2016

	For the Years Ended December 31,		Change
	2017	2016	
	(in thousands)		
Net sales	$ 1,056,231	$ 981,120	$ 75,111
Cost of goods sold	546,275	393,272	153,003
Gross profit	**509,956**	**587,848**	**(77,892)**
Operating expenses			
Research and development	224,962	60,707	164,255
Selling, general and administrative	677,363	608,308	69,055
Impairment of in-process research and development	—	66,000	(66,000)
Total operating expenses	**902,325**	**735,015**	**167,310**
Operating (loss) income	**(392,369)**	**(147,167)**	**(245,202)**
Other expense, net:			
Interest expense, net	(126,523)	(86,610)	(39,913)
Foreign exchange loss	(260)	(1,005)	745
Gain on divestiture	6,267	—	6,267
Loss on debt extinguishment	(978)	—	(978)
Other income (expense), net	588	6,697	(6,109)
Total other expense, net	**(120,906)**	**(80,918)**	**(39,988)**
Loss before benefit for income taxes	**(513,275)**	**(228,085)**	**(285,190)**
Benefit for income taxes	(102,749)	(61,251)	(41,498)
Net loss	**$ (410,526)**	**$ (166,834)**	**$ (243,692)**

Net sales. Net sales increased $75.1 million, or 8%, to $1,056.2 million during the year ended December 31, 2017, from $981.1 million during the year ended December 31, 2016, primarily due to lower net sales during the year ended December 31, 2016, as a result of the $65.0 million litigation settlement with Express Scripts, Inc., or Express Scripts.

The following table presents a summary of total net sales attributed to geographic sources for the years ended December 31, 2017 and 2016 (in thousands):

	Year Ended December 31, 2017		Year Ended December 31, 2016	
	Amount	% of Total Net Sales	Amount	% of Total Net Sales
United States	$ 1,026,527	97%	$ 964,041	98%
Rest of world	29,704	3%	17,079	2%
Total net sales	**$ 1,056,231**		**$ 981,120**	

The following table reflects the components of net sales for the years ended December 31, 2017 and 2016 (in thousands):

	Year Ended December 31,		Change	Change
	2017	2016	$	%
RAVICTI	$ 193,918	$ 151,532	$ 42,386	28%
PENNSAID 2%	191,050	304,433	(113,383)	(37)%
KRYSTEXXA	156,483	91,102	65,381	72%
PROCYSBI	137,740	25,268	112,472	445%
DUEXIS	121,161	173,728	(52,567)	(30)%
ACTIMMUNE	110,993	104,624	6,369	6%
VIMOVO	57,666	121,315	(63,649)	(52)%
RAYOS	52,125	47,356	4,769	10%
BUPHENYL	20,792	16,879	3,913	23%
MIGERGOT	5,468	4,651	817	18%
LODOTRA	5,393	4,193	1,200	29%
QUINSAIR	3,442	1,039	2,403	231%
Litigation settlement	—	(65,000)	65,000	100%
Total net sales	**$ 1,056,231**	**$ 981,120**	**$ 75,111**	**8%**

Net sales were higher during the year ended December 31, 2017 compared to the year ended December 31, 2016, primarily due to lower net sales during the year ended December 31, 2016 as a result of the $65.0 million litigation settlement with Express Scripts, the recognition of PROCYSBI sales following the acquisition of Raptor in October 2016 and higher net sales of KRYSTEXXA and RAVICTI, offset by lower net sales of PENNSAID 2%, VIMOVO and DUEXIS.

RAVICTI. Net sales increased $42.4 million, or 28%, to $193.9 million during the year ended December 31, 2017, from $151.5 million during the year ended December 31, 2016. Net sales in the United States increased by approximately $39.4 million, which was composed of $31.5 million resulting from prescription volume growth and $7.9 million due to higher net pricing. Net sales outside the United States increased by approximately $3.0 million primarily due to higher sales volume.

PENNSAID 2%. Net sales decreased $113.4 million, or 37%, to $191.1 million during the year ended December 31, 2017, from $304.5 million during the year ended December 31, 2016. Net sales decreased by approximately $90.2 million due to lower net pricing, as further described after the next table, and approximately $23.2 million resulting from lower prescription volume.

KRYSTEXXA. Net sales increased $65.4 million, or 72%, to $156.5 million during the year ended December 31, 2017, from $91.1 million during the year ended December 31, 2016. Net sales increased by approximately $40.1 million resulting from prescription volume growth and approximately $25.3 million due to higher net pricing.

PROCYSBI. Net sales increased $112.5 million, or 445%, to $137.7 million during the year ended December 31, 2017, from $25.2 million during the year ended December 31, 2016. Net sales increased by approximately $101.8 million resulting from prescription volume growth and approximately $10.7 million due to higher net pricing. We began recognizing PROCYSBI sales following our acquisition of Raptor in October 2016.

DUEXIS. Net sales decreased $52.6 million, or 30%, to $121.2 million during the year ended December 31, 2017, from $173.8 million during the year ended December 31, 2016. Net sales decreased by approximately $59.4 million due to lower net pricing, as further described after the next table, partially offset by an increase of $6.8 million resulting from prescription volume growth.

ACTIMMUNE. Net sales increased $6.4 million, or 6%, to $111.0 million during the year ended December 31, 2017, from $104.6 million during the year ended December 31, 2016. Net sales increased by approximately $12.9 million due to higher net pricing, partially offset by a decrease of approximately $6.5 million resulting from lower prescription volume.

VIMOVO. Net sales decreased $63.6 million, or 52%, to $57.7 million during the year ended December 31, 2017, from $121.3 million during the year ended December 31, 2016. Net sales decreased by approximately $47.1 million due to lower net pricing, as further described after the next table, and approximately $16.5 million resulting from lower prescription volume.

RAYOS. Net sales increased $4.8 million, or 10%, to $52.1 million during the year ended December 31, 2017, from $47.3 million during the year ended December 31, 2016. Net sales increased by approximately $17.2 million resulting from prescription volume growth, partially offset by a decrease of approximately $12.4 million due to lower net pricing.

BUPHENYL. Net sales increased $3.9 million, or 23%, to $20.8 million during the year ended December 31, 2017, from $16.9 million during the year ended December 31, 2016. Net sales increased by approximately $7.3 million due to higher net pricing, partially offset by a decrease of approximately $3.4 million resulting from lower prescription volume.

MIGERGOT. Net sales increased $0.8 million, or 18%, to $5.5 million during the year ended December 31, 2017, from $4.7 million during the year ended December 31, 2016. Net sales increased by approximately $1.1 million due to higher net pricing, partially offset by a decrease of approximately $0.3 million resulting from lower prescription volume.

LODOTRA. Net sales increased $1.2 million, or 29%, to $5.4 million during the year ended December 31, 2017, from $4.2 million during the year ended December 31, 2016. The increase was due to increased shipments to our European distribution partner, Mundipharma International Corporation Limited, or Mundipharma. LODOTRA sales to Mundipharma occur at the time we ship, based on Mundipharma's estimated requirements. Accordingly, LODOTRA sales are not linear or directly tied to Mundipharma's in-market sales and can therefore fluctuate significantly from period to period.

QUINSAIR. Net sales increased $2.4 million, or 231%, to $3.4 million during the year ended December 31, 2017, from $1.0 million during the year ended December 31, 2016. Net sales increased by approximately $2.7 million resulting from prescription volume growth, partially offset by a decrease of approximately $0.3 million due to lower net pricing. We began recognizing QUINSAIR sales following our acquisition of Raptor in October 2016. In June 2017, following the Chiesi divestiture, our QUINSAIR sales in EMEA ceased, and post-June 2017 sales were in Canada and Latin America.

In September 2016, we entered into a settlement agreement and mutual release with Express Scripts pursuant to which we and Express Scripts were released from any and all claims relating to our then ongoing litigation without admitting any fault or wrongdoing and we agreed to pay Express Scripts $65.0 million. This settlement was accounted for as a reduction of net sales in the consolidated statement of comprehensive loss for the year ended December 31, 2016.

The table below reconciles our gross to net sales for the years ended December 31, 2017 and 2016 (in millions):

	Year Ended December 31, 2017		Year Ended December 31, 2016	
	Amount	% of Gross Sales	Amount	% of Gross Sales
Gross sales	$ 4,057.8	100.0%	$ 3,234.2	100.0%
Adjustments to gross sales:				
Prompt pay discounts	(80.2)	(2.0)%	(64.0)	(2.0)%
Medicine returns	(45.6)	(1.1)%	(17.1)	(0.5)%
Co-pay and other patient assistance	(1,907.6)	(47.0)%	(1,701.3)	(52.6)%
Wholesaler fees and commercial rebates	(641.5)	(15.8)%	(133.7)	(4.2)%
Government rebates and chargebacks	(326.7)	(8.1)%	(272.0)	(8.4)%
Litigation settlement	—	—	(65.0)	(2.0)%
Total adjustments	**(3,001.6)**	**(74.0)%**	**(2,253.1)**	**(69.7)%**
Net sales	**$ 1,056.2**	**26.0%**	**$ 981.1**	**30.3%**

During the year ended December 31, 2017, wholesaler fees and commercial rebates, as a percentage of gross sales, increased to 15.8% from 4.2% during the year ended December 31, 2016, and co-pay and other patient assistance, as a percentage of gross sales, decreased to 47.0% from 52.6% during the year ended December 31, 2016. During the second half of 2016, we entered into business arrangements with PBMs and other payers in an effort to secure formulary status and reimbursement of our medicines, such as our arrangements with Express Scripts, CVS Caremark and Prime Therapeutics LLC, which resulted in lower co-pay and other patient assistance costs as a percentage of gross sales during the year ended December 31, 2017. The mix of PBM healthcare plans that adopted our primary care medicines onto their formulary during 2017 was more heavily weighted towards those plans for which we pay a higher commercial rebate. In addition, we also experienced a higher rate of managed care control in our non-contracted business, which resulted in significantly lower net pricing during the year ended December 31, 2017, when compared to the year ended December 31, 2016.

On a quarter-to-quarter basis, our net sales have traditionally been lower in first half of the year, particularly in the first quarter, with the second half of the year representing a greater share of overall net sales each year. This is due to annual managed care plan changes and the re-setting of patients' medical insurance deductibles at the beginning of each year, resulting in higher co-pay and other patient assistance costs as patients meet their annual medical insurance deductibles during the first and second quarters, and higher net sales in the second half of the year after patients meet their deductibles and healthcare plans reimburse a greater portion of the total cost of our medicines.

Cost of Goods Sold. Cost of goods sold increased $153.0 million to $546.3 million during the year ended December 31, 2017, from $393.3 million during the year ended December 31, 2016. As a percentage of net sales, cost of goods sold was 51.7% during the year ended December 31, 2017, compared to 40.1% during the year ended December 31, 2016. Costs of goods sold as a percentage of net sales was higher during the year ended December 31, 2016 due to the one-time reduction in net sales in the year ended December 31, 2016 as a result of the litigation settlement with Express Scripts. Additionally, we recorded an increase in cost of goods sold in the year ended December 31, 2017. The increase in cost of goods sold was primarily attributable to a $59.9 million increase in intangible amortization expense, a $48.0 million increase in inventory step-up expense, a $20.7 million increase in royalty remeasurement expense, a $10.7 million increase in drug substance harmonization costs, a $10.5 million increase in royalty accretion expense and a $9.6 million increase in employee costs, which reflects the increase in manufacturing activities resulting from the growth of our medicine portfolio. During the year ended December 31, 2016 we recorded a loss of $14.3 million in relation to purchase commitments with Boehringer Ingelheim, which related to additional units of ACTIMMUNE following the cancellation of the Phase 3 trial, Safety, Tolerability and Efficacy of ACTIMMUNE Dose Escalation in Friedreich's Ataxia study, or the FA program. During the year ended December 31, 2017, we updated our forecast for future demand and renegotiated our purchase commitments with Boehringer Ingelheim and recorded additional net expense of $1.7 million to cost of goods sold.

The increase in intangible amortization of $59.9 million during the year ended December 31, 2017 compared to the prior year was primarily due to an increase of $59.1 million in amortization of developed technology related to PROCYSBI (acquired in October 2016).

Because inventory step-up expense is acquisition-related, will not continue indefinitely and has a significant effect on our gross profit, gross margin percentage and net income (loss) for all affected periods, we disclose balance sheet and income statement amounts related to inventory step-up within the Notes to the consolidated financial statements. The increase in inventory step-up expense of $48.0 million recorded to cost of goods sold during the year ended December 31, 2017 compared to the prior year was primarily due to KRYSTEXXA inventory step-up expense of $78.3 million (acquired in January 2016) and PROCYSBI and QUINSAIR inventory step-up expense of $40.8 million (acquired in October 2016) recorded during the year ended December 31, 2017, compared to $48.8 million recorded during the year ended December 31, 2016 related to KRYSTEXXA and MIGERGOT inventory step-up expense and $22.3 million recorded related to PROCYSBI and QUINSAIR inventory step-up expense.

Research and Development Expenses. Research and development expenses increased $164.3 million to $225.0 million during the year ended December 31, 2017, from $60.7 million during the year ended December 31, 2016. The increase was primarily attributable to $150.3 million related to the acquisition of River Vision during the year ended December 31, 2017. Pursuant to Accounting Standards Codification Topic 805*, Business Combinations*, or ASC 805, as amended by ASU No. 2017-01, we accounted for the River Vision acquisition as the purchase of an in-process research and development, or IPR&D, asset and, pursuant to ASC Topic 730, *Research and Development,* recorded the purchase price as a research and development expense during the year ended December 31, 2017. Additionally, during the year ended December 31, 2017, we entered into an agreement to license HZN-003 (formerly MEDI4945), a rheumatology pipeline program with the objective of enhancing our leadership position in the uncontrolled gout market, from MedImmune LLC, or MedImmune, and we paid MedImmune an upfront cash payment of $12.0 million which we recorded as a "research and development" expense in the consolidated statement of comprehensive loss during the year ended December 31, 2017 and included in "accrued expenses" as of December 31, 2017. The upfront payment was subsequently paid in January 2018.

Selling, General and Administrative Expenses. Selling, general and administrative expenses increased $69.1 million to $677.4 million during the year ended December 31, 2017, from $608.3 million during the year ended December 31, 2016. The increase was primarily attributable to an increase of $22.9 million in employee costs related to our growth in headcount following the Raptor acquisition in October 2016, an increase of $24.2 million in marketing program costs and the impairment of $22.3 million paid to Boehringer Ingelheim International upon closing of the acquisition of certain rights to interferon gamma-1b during the year ended December 31, 2017, compared to $5.3 million recorded as an impairment during the year ended December 31, 2016.

Impairment of In-Process Research and Development. At the time of the merger of the businesses of Horizon Pharma, Inc., or HPI, and Vidara on September 19, 2014, or the Vidara Merger, IPR&D was considered separable from the business as the project could be sold to a third party, and we assigned a fair value of $66.0 million to an intangible asset. On December 8, 2016, we announced the discontinuation of the FA program. Following this announcement, we determined that the IPR&D has no alternative use or economic value, and we recorded an impairment charge during the year ended December 31, 2016 to fully write off the value of the asset on our consolidated balance sheet.

Interest Expense, Net. Interest expense, net, increased $39.9 million to $126.5 million during the year ended December 31, 2017, from $86.6 million during the year ended December 31, 2016. The increase was primarily due to higher borrowings, including our $300.0 million aggregate principal amount of 8.75% Senior Notes due 2024, or the 2024 Senior Notes, in connection with our acquisition of Raptor in October 2016, and our $850.0 million principal amount of secured loans under our 2017 term loan facility, of which $375.0 million was in connection with our acquisition of Raptor, compared to the $397.0 million principal amount of secured loans from previous borrowings under our senior secured loan facility.

Gain on divestiture. During the year ended December 31, 2017, we completed the Chiesi divestiture for an upfront payment of $72.5 million, which reflects $3.1 million of cash divested, with additional potential milestone payments based on sales thresholds, and we recorded a gain of $6.3 million on the divestiture.

Foreign Exchange Loss. During the year ended December 31, 2017, we reported a foreign exchange loss of $0.3 million.

Loss on Debt Extinguishment. During the year ended December 31, 2017, we entered into two refinancing amendments for our term loans. We accounted for a portion of the repayments under these refinancing amendments as a debt extinguishment and recorded a loss on debt extinguishment of $1.0 million in the consolidated statements of comprehensive loss, which reflected the write-off of the unamortized portion of debt discount and deferred financing costs previously incurred and a one percent prepayment penalty fee.

Benefit for Income Taxes. During the year ended December 31, 2017, we recorded a benefit for income taxes of $102.7 million compared to $61.3 million during the year ended December 31, 2016. The increase in benefit for income taxes during the year ended December 31, 2017, compared to year ended December 31, 2016, was primarily due to a provisional $74.9 million net benefit recorded following the enactment in the United States of H.R. 1, "An Act to provide for reconciliation pursuant to titles II and V of the concurrent resolution on the budget for fiscal year 2018", informally titled the Tax Cuts and Jobs Act, or the Tax Act, in December 2017, which net benefit included a $134.2 million tax benefit from the revaluation of our U.S. net deferred tax liability based on the new U.S. federal tax rate of 21 percent, partially offset by the write-off of the $59.2 million deferred tax asset related to our U.S. interest expense carryforwards under Section 163(j) of the Internal Revenue Code of 1986, as amended, or the Code. Additionally, during the year ended December 31, 2017, we recorded an increase in pre-tax losses which resulted in an increase in the benefit for income taxes during the year.

During the year ended December 31, 2017, the first of three tranches of our outstanding performance stock unit awards, or PSUs, expired without payout as the minimum total compounded annual shareholder rate of return was not achieved. As a result, we wrote off to income tax expense $16.4 million of deferred tax assets related to previously recognized share-based compensation. During the years ended December 31, 2017, 2016 and 2015, we recorded share-based compensation expense of $49.6 million, $48.6 million and $37.7 million, respectively, related to these PSUs.

In relation to the remaining outstanding PSUs, if our share price is lower than $32.70 and $33.86 for the twenty trading days ending March 22, 2018 and June 22, 2018, respectively, approximately $9.3 million and $8.4 million, respectively, of deferred tax assets at December 31, 2017, related to previously recognized share-based compensation expense will be charged to income tax expense.

Year Ended December 31, 2016 Compared to Year Ended December 31, 2015

	For the Years Ended December 31,		
	2016	2015	Change
	(in thousands)		
Net sales	$ 981,120	$ 757,044	$ 224,076
Cost of goods sold	393,272	219,502	173,770
Gross profit	**587,848**	**537,542**	**50,306**
Operating expenses			
Research and development	60,707	41,865	18,842
Selling, general and administrative	608,308	440,305	168,003
Impairment of in-process research and development	66,000	—	66,000
Total operating expenses	**735,015**	**482,170**	**252,845**
Operating (loss) income	**(147,167)**	**55,372**	**(202,539)**
Other income (expense), net:			
Interest expense, net	(86,610)	(69,900)	(16,710)
Foreign exchange loss	(1,005)	(1,237)	232
Loss on induced conversion of debt and debt extinguishment	—	(77,624)	77,624
Loss on sale of long-term investments	—	(29,032)	29,032
Other income (expense), net:	6,697	(10,291)	16,988
Total other expense, net	**(80,918)**	**(188,084)**	**107,166**
Loss before benefit for income taxes	**(228,085)**	**(132,712)**	**(95,373)**
Benefit for income taxes	(61,251)	(172,244)	110,993
Net (loss) income	**$ (166,834)**	**$ 39,532**	**$ (206,366)**

Net sales. Net sales increased $224.1 million, or 30%, to $981.1 million during the year ended December 31, 2016, from $757.0 million during the year ended December 31, 2015.

The following table presents a summary of total net sales attributed to geographic sources for the years ended December 31, 2016 and 2015 (in thousands):

	Year Ended December 31, 2016		Year Ended December 31, 2015	
	Amount	% of Total Net Sales	Amount	% of Total Net Sales
United States	$ 964,041	98%	$ 744,036	98%
Rest of world	17,079	2%	13,008	2%
Total net sales	**$ 981,120**		**$ 757,044**	

The following table reflects the components of net sales for the years ended December 31, 2016 and 2015 (in thousands):

	Year Ended December 31,		Change	Change
	2016	2015	$	%
PENNSAID 2%	$ 304,433	$ 147,010	$ 157,423	107%
DUEXIS	173,728	190,357	(16,629)	(9)%
RAVICTI	151,532	86,875	64,657	74%
VIMOVO	121,315	166,672	(45,357)	(27)%
ACTIMMUNE	104,624	107,444	(2,820)	(3)%
KRYSTEXXA	91,102	—	91,102	*
RAYOS	47,356	40,329	7,027	17%
PROCYSBI	25,268	—	25,268	*
BUPHENYL	16,879	13,458	3,421	25%
MIGERGOT	4,651	—	4,651	*
LODOTRA	4,193	4,899	(706)	(14)%
QUINSAIR	1,039	—	1,039	*
Litigation settlement	(65,000)	—	(65,000)	*
Total net sales	**$ 981,120**	**$ 757,044**	**$ 224,076**	**30%**

* Percentage change is not meaningful.

The increase in net sales during the year ended December 31, 2016 was primarily due to the growth in net sales of PENNSAID 2%, the full-period recognition of RAVICTI sales in 2016, compared to a partial period recognition in 2015 following the acquisition of Hyperion in May 2015, the recognition of KRYSTEXXA sales following the acquisition of Crealta in January 2016 and the recognition of PROCYSBI sales following the acquisition of Raptor in October 2016, offset by the $65.0 million litigation settlement with Express Scripts along with lower net sales of VIMOVO and DUEXIS.

PENNSAID 2%. Net sales increased $157.4 million, or 107%, to $304.4 million during the year ended December 31, 2016, from $147.0 million during the year ended December 31, 2015. Net sales increased by approximately $87.5 million due to higher net pricing and $69.9 million resulting from prescription volume growth.

DUEXIS. Net sales decreased $16.6 million, or 9%, to $173.7 million during the year ended December 31, 2016, from $190.3 million during the year ended December 31, 2015. Net sales decreased by approximately $50.4 million due to lower net pricing resulting from higher co-pay and other patient assistance, offset by an increase of approximately $33.8 million resulting from prescription volume growth.

RAVICTI. Net sales increased $64.7 million, or 74%, to $151.5 million during the year ended December 31, 2016, from $86.8 million during the year ended December 31, 2015. Net sales increased by approximately $55.7 million resulting from prescription volume growth and $9.0 million due to higher net pricing. We began recognizing RAVICTI sales following the acquisition of Hyperion in May 2015, therefore only a partial period of RAVICTI sales were recognized during the year ended December 31, 2015, compared with full-period recognition of sales during the year ended December 31, 2016.

VIMOVO. Net sales decreased $45.4 million, or 27%, to $121.3 million during the year ended December 31, 2016, from $166.7 million during the year ended December 31, 2015. Net sales decreased by approximately $35.9 million due to lower net pricing resulting from higher co-pay and other patient assistance and approximately $9.5 million resulting from lower prescription volumes.

ACTIMMUNE. Net sales decreased $2.8 million, or 3%, to $104.6 million during the year ended December 31, 2016, from $107.4 million during the year ended December 31, 2015. Net sales decreased by approximately $8.8 million resulting from prescription volume decreases, offset by an increase of approximately $6.0 million due to higher net pricing.

KRYSTEXXA. Net sales were $91.1 million during the year ended December 31, 2016. We began recognizing KRYSTEXXA sales following the acquisition of Crealta in January 2016.

RAYOS. Net sales increased $7.0 million, or 17%, to $47.4 million during the year ended December 31, 2016, from $40.4 million during the year ended December 31, 2015. Net sales increased by approximately $8.4 million resulting from prescription volume growth, offset by a decrease of approximately $1.4 million due to lower net pricing.

PROCYSBI. Net sales were $25.3 million during the year ended December 31, 2016. We began recognizing PROCYSBI sales following the acquisition of Raptor in October 2016.

BUPHENYL. Net sales increased $3.4 million, or 25%, to $16.9 million during the year ended December 31, 2016, from $13.5 million during the year ended December 31, 2015. We began recognizing BUPHENYL sales following the acquisition of Hyperion in May 2015, therefore only a partial period of BUPHENYL sales were recognized during the year ended December 31, 2015, compared with full-period recognition of sales during the year ended December 31, 2016.

MIGERGOT. Net sales were $4.7 million during the year ended December 31, 2016. We began recognizing MIGERGOT sales following the acquisition of Crealta in January 2016.

LODOTRA. Net sales decreased $0.7 million, or 14%, to $4.2 million during the year ended December 31, 2016, from $4.9 million during the year ended December 31, 2015. The decrease was due to fewer shipments to our European distribution partner, Mundipharma International Corporation Limited, or Mundipharma. LODOTRA sales to Mundipharma occur at the time we ship, based on Mundipharma's estimated requirements. Accordingly, LODOTRA sales are not linear or directly tied to Mundipharma's in-market sales and can therefore fluctuate significantly.

QUINSAIR. Net sales were $1.0 million during the year ended December 31, 2016. We began recognizing QUINSAIR sales following the acquisition of Raptor in October 2016.

In September 2016, we entered into a settlement agreement and mutual release with Express Scripts pursuant to which we and Express Scripts were released from any and all claims relating to our then ongoing litigation without admitting any fault or wrongdoing and we agreed to pay Express Scripts $65.0 million. This settlement has been accounted for as a reduction of "net sales" in the consolidated statement of comprehensive loss for the year ended December 31, 2016.

The table below reconciles our gross to net sales for the years ended December 31, 2016 and 2015 (in millions):

	Year Ended December 31, 2016		Year Ended December 31, 2015	
	Amount	% of Gross Sales	Amount	% of Gross Sales
Gross sales	$ 3,234.2	100.0%	$ 2,057.3	100.0%
Adjustments to gross sales:				
Prompt pay discounts	(64.0)	(2.0)%	(41.3)	(2.0)%
Medicine returns	(17.1)	(0.5)%	(14.4)	(0.7)%
Co-pay and other patient assistance	(1,701.3)	(52.6)%	(1,020.2)	(49.6)%
Wholesaler fees and commercial rebates	(133.7)	(4.2)%	(66.1)	(3.2)%
Government rebates and chargebacks	(272.0)	(8.4)%	(158.3)	(7.7)%
Litigation settlement	(65.0)	(2.0)%	—	—
Total adjustments	**(2,253.1)**	**(69.7)%**	**(1,300.3)**	**(63.2)%**
Net sales	**$ 981.1**	**30.3%**	**$ 757.0**	**36.8%**

During the year ended December 31, 2016, co-pay and other patient assistance, as a percentage of gross sales, increased to 52.6% from 49.6% during the year ended December 31, 2015. The increase was primarily due to the expansion of our HorizonCares program during 2016.

Cost of Goods Sold. Cost of goods sold increased $173.8 million to $393.3 million during the year ended December 31, 2016, from $219.5 million during the year ended December 31, 2015. As a percentage of net sales, cost of goods sold was 40.0% during the year ended December 31, 2016, compared to 29.0% during the year ended December 31, 2015. The large increase in costs of goods sold as a percentage of net sales was due to the one-time reduction in net sales in the year ended December 31, 2016 as a result of the litigation settlement with Express Scripts and an increase in cost of goods sold in the year ended December 31, 2016. The increase in cost of goods sold was primarily a result of higher intangible amortization expense of $84.0 million and increased inventory step-up expense of $59.6 million. Other factors that caused cost of goods sold to increase during the year included a $14.3 million expense related to a loss on inventory purchase commitments, higher royalty accretion expense of $20.5 million and a $16.2 million increase in direct and indirect costs associated with higher sales, offset by a $20.8 million decrease in charges relating to the remeasurement of contingent royalty liabilities.

The increase in intangible amortization of $84.0 million during the year ended December 31, 2016 compared to the prior year was due to a $33.9 million increase in amortization expense related to RAVICTI and BUPHENYL intangible assets (acquired in May 2015), $35.9 million amortization of developed technology related to KRYSTEXXA and MIGERGOT (acquired in January 2016), $14.0 million amortization of developed technology related to PROCYSBI (acquired in October 2016) and $0.2 million increase in amortization related to ACTIMMUNE.

Because inventory step-up expense is acquisition-related, will not continue indefinitely and has a significant effect on our gross profit, gross margin percentage and net income (loss) for all affected periods, we disclose balance sheet and income statement amounts related to inventory step-up within the Notes to the consolidated financial statements. The increase in inventory step-up expense of $59.6 million during the year ended December 31, 2016 compared to the prior year was due to $48.8 million recorded during the year ended December 31, 2016 related to KRYSTEXXA and MIGERGOT inventory step-up (acquired in January 2016) and $22.4 million related to PROCYSBI and QUINSAIR inventory step-up (acquired in October 2016), compared to $8.4 million recorded during the year ended December 31, 2015 related to RAVICTI and BUPHENYL inventory step-up (acquired in May 2015) and $3.2 million related to ACTIMMUNE inventory step-up (acquired in September 2014).

Research and Development Expenses. Research and development expenses increased $18.8 million to $60.7 million during the year ended December 31, 2016, from $41.9 million during the year ended December 31, 2015. The increase in research and development expenses during the year ended December 31, 2016 was primarily attributable to $2.8 million of higher share-based compensation, an increase of $5.5 million in other employee costs resulting from growth in our headcount following the Hyperion, Crealta and Raptor acquisitions, $4.0 million related to costs to be incurred in the winding down of the FA program, an increase of $3.0 million in general research and development costs, a $2.0 million upfront fee paid for a license of a patent and an increase of $1.5 million in regulatory submission fees.

Selling, General and Administrative Expenses. Selling, general and administrative expenses increased $168.0 million to $608.3 million during the year ended December 31, 2016, from $440.3 million during the year ended December 31, 2015. The increase in selling, general and administrative expenses was in line with the significant growth in gross sales and the increase in the number of employees over the same period, and was primarily attributable to an increase of $59.3 million in employee costs resulting from increasing our headcount, a $30.5 million increase in professional costs, a $25.5 million increase in share-based compensation expense and a $19.3 million increase in marketing expenses.

Impairment of In-Process Research and Development. At the time of the Vidara Merger, IPR&D was considered separable from the business as the project could be sold to a third party, and we assigned a fair value of $66.0 million to the intangible asset. Following the FA announcement, we determined that the IPR&D has no alternative use or economic value, and we recorded an impairment charge during the year ended December 31, 2016 to fully write off the value of the asset on our consolidated balance sheet.

Interest Expense, Net. Interest expense, net, increased $16.7 million to $86.6 million during the year ended December 31, 2016, from $69.9 million during the year ended December 31, 2015. The increased interest expense, net, was primarily due to full-period recognition during the year ended December 31, 2016 of the interest on higher borrowings to fund the acquisition of Hyperion in May 2015, including our $475.0 million aggregate principal amount of 6.625% Senior Notes due 2023, or the 2023 Senior Notes, prior six-year $400.0 million term loan facility, or the 2015 Term Loan Facility, and $400.0 million aggregate principal amount of 2.50% Exchangeable Senior Notes due 2022, or the Exchangeable Senior Notes, as compared to partial period recognition of the interest on these borrowings during the year ended December 31, 2015 and our lower prior year borrowings under our prior five-year $300.0 million term loan facility, or 2014 Term Loan Facility. We also incurred additional interest expense following our borrowings to fund the acquisition of Raptor in October 2016, including our additional $375.0 million additional borrowings under the 2015 Term Loan Facility, or the 2016 Incremental Loan Facility, and the 2024 Senior Notes.

Foreign Exchange Loss. During the year ended December 31, 2016, we reported a foreign exchange loss of $1.0 million.

Loss on Induced Conversion of Debt and Debt Extinguishment. The loss on induced conversion of debt and debt extinguishment during the year ended December 31, 2015 of $77.6 million was composed of $20.7 million related to the induced conversions of our 5.00% Convertible Senior Notes due 2018, including $10.0 million for cash inducement payments, a $10.1 million charge for the extinguishment of debt and $0.6 million of expenses, and $56.9 million related to the extinguishment of the 2014 Term Loan Facility, consisting of a $45.4 million early redemption premium and a $11.5 million charge for the extinguishment of debt. The number of shares issued equaled the number of shares based on the underlying conversion option. The aggregate cash payments to the holders for additional exchange consideration were recorded as part of the extinguishment loss. There were no induced conversions in 2016.

Loss on Sale of Long-Term Investments. The loss on sale of long-term investments during the year ended December 31, 2015 was $29.0 million. During the third quarter of 2015, we purchased 2,250,000 shares of common stock of Depomed, Inc., or Depomed, representing 3.75% of Depomed's then outstanding common stock. The shares were acquired at a cost of $71.8 million. During the fourth quarter of 2015, following our decision to withdraw our offer to acquire Depomed, we sold all of our shares in Depomed, receiving sales proceeds of $42.8 million and recognized a realized loss of $29.0 million. There were no sales of long-term investments in 2016.

Other Income (Expense) net. Other income, net during the year ended December 31, 2016 was primarily related to the release of a contingent liability of $6.9 million which was assumed as part of the Crealta acquisition. In December 2015, Crealta considered it probable that the manufacture of the active pharmaceutical ingredient, or API, for KRYSTEXXA would be moved out of Israel based on a notice of termination provided by its contract manufacturer, therefore triggering a repayment obligation to Israel's Office of the Chief Scientist. As a result, Crealta established a $6.9 million contingent liability reserve in its December 31, 2015 financial statements. As of the date of our acquisition of Crealta, the $6.9 million repayment obligation was still probable. Therefore, it was recorded as an assumed liability in "other long-term liabilities" as part of the acquisition accounting for Crealta. During the third quarter of 2016, Horizon management negotiated a new amendment to the manufacturing agreement and it was determined that the manufacture of the KRYSTEXXA API would not be moved outside of Israel and thus the repayment of the $6.9 million would not be triggered. The contingent liability was released to "other income (expense)" during the year ended December 31, 2016 as it was a reversal of an assumed liability and therefore did not represent income from operations. Other expense, net, during the year ended December 31, 2015 totaled $10.3 million, which primarily included the fees related to the Hyperion acquisition financing commitment.

Benefit for Income Taxes. During the year ended December 31, 2016, we recorded an income tax benefit of $61.3 million compared to $172.2 million during the year ended December 31, 2015. The recognition of income tax benefit during the year ended December 31, 2016 was primarily attributable to the mix of income and losses amongst jurisdictions, a notional interest deduction and the change in our U.S. state effective tax rate. The recognition of an income tax benefit during the year ended December 31, 2015 was primarily attributable to the release of $103.1 million in valuation allowances in the U.S. tax consolidation group due to the recognition of significant deferred tax liabilities as a result of the Hyperion acquisition as well as the ability to recognize a tax benefit on losses incurred in the United States.

Non-GAAP Financial Measures

Non-GAAP adjusted net sales, EBITDA, or earnings before interest, taxes, depreciation and amortization, adjusted EBITDA, non-GAAP net income and non-GAAP earnings per share are used and provided by us as non-GAAP financial measures. These non-GAAP financial measures are intended to provide additional information on our performance, operations and profitability. Adjustments to our GAAP figures as well as EBITDA exclude acquisition/divestiture-related costs, upfront and milestone payments related to license agreements, drug substance harmonization costs, fees related to term loan refinancing, restructuring and realignment costs, the Express Scripts litigation settlement amount, loss on sale of long-term investments and charges related to discontinuation of the Friedreich's ataxia program, as well as non-cash items such as share-based compensation, inventory step-up expense, depreciation and amortization, remeasurement of royalties for medicines acquired through business combinations, royalty accretion, non-cash interest expense, non-current asset impairment charges, gain on divestiture, loss on debt extinguishment, reversal of pre-acquisition reserve upon signing of contract and other non-cash adjustments. Certain other special items or substantive events may also be included in the non-GAAP adjustments periodically when their magnitude is significant within the periods incurred. We maintain an established non-GAAP cost policy that guides the determination of what costs will be excluded in non-GAAP measures. We believe that these non-GAAP financial measures, when considered together with the GAAP figures, can enhance an overall understanding of our financial and operating performance. The non-GAAP financial measures are included with the intent of providing investors with a more complete understanding of our historical financial results and trends and to facilitate comparisons between periods. In addition, these non-GAAP financial measures are among the indicators our management uses for planning and forecasting purposes and measuring our performance. For example, adjusted EBITDA is used by us as one measure of management performance under certain incentive compensation arrangements. These non-GAAP financial measures should be considered in addition to, and not as a substitute for, or superior to, financial measures calculated in accordance with GAAP. The non-GAAP financial measures used by us may be calculated differently from, and therefore may not be comparable to, non-GAAP financial measures used by other companies.

Beginning in the second quarter of 2016, we modified the method of calculating non-GAAP income tax expense to align with guidance issued by the Securities and Exchange Commission on May 17, 2016. The modified methodology calculates the income tax component of non-GAAP net income for each period by adjusting the GAAP tax benefit for the estimated tax impact of each non-GAAP adjustment based on the statutory income tax rate of the applicable jurisdictions for each non-GAAP adjustment. This modified methodology does not reflect any use of net operating loss carryforwards that we potentially may have been able to use if our actual earnings for these periods had been the non-GAAP net income. Previously, we had calculated the income tax component of non-GAAP net income by using the estimated cash taxes that we expected to pay for the period. The non-GAAP net income and diluted net income per share amounts shown in the GAAP to non-GAAP reconciliation tables below are based on the modified methodology.

Reconciliations of reported GAAP net sales to non-GAAP adjusted net sales and reported GAAP net (loss) income to EBITDA, adjusted EBITDA and non-GAAP net income, and the related per share amounts, are as follows (in thousands, except share and per share amounts):

	For the Years Ended December 31,		
	2017	2016	2015
GAAP Net Sales	**$ 1,056,231**	**$ 981,120**	**$ 757,044**
Litigation settlement	—	65,000	—
Non-GAAP Adjusted Net Sales	**$ 1,056,231**	**$ 1,046,120**	**$ 757,044**

	For the Years Ended December 31,		
	2017	2016	2015
GAAP Net (Loss) Income	**$ (410,526)**	**$ (166,834)**	**$ 39,532**
Non-GAAP adjustments:			
Remeasurement of royalties for medicines acquired through business combinations	21,774	386	21,151
Acquisition/divestiture-related costs	177,035	52,874	72,221
Restructuring and realignment costs	4,883	—	—
Amortization, accretion and inventory step-up:			
Intangible amortization expense	276,784	216,875	132,923
Accretion of royalty liabilities	51,263	40,616	20,088
Amortization of debt discount and deferred financing costs	21,619	18,546	18,810
Inventory step-up expense	119,151	71,137	11,495
Share-based compensation	121,553	114,144	85,786
Depreciation expense	6,631	4,962	5,420
Gain on divestiture	(6,267)	—	—
Charges relating to discontinuation of the Friedreich's ataxia program (1)	22,509	23,513	—
Drug substance harmonization costs (2)	10,651	—	—
Upfront and milestone payments related to license agreements	12,186	2,000	—
Fees related to term loan refinancing	5,220	—	—
Loss on debt extinguishment	978	—	77,624
Royalties for medicines acquired through business combinations	(47,003)	(37,593)	(29,834)
Litigation settlement	—	65,000	—
Impairment of in-process research and development	—	66,000	—
Reversal of pre-acquisition reserve upon signing of contract	—	(6,900)	—
Loss on sale of long-term investments	—	—	29,032
Total of pre-tax non-GAAP adjustments	**798,967**	**631,560**	**444,716**
Income tax effect of pre-tax non-GAAP adjustments (3)	(118,704)	(110,290)	(122,214)
Other non-GAAP income tax adjustments (4)	(74,939)	—	(105,133)
Total of non-GAAP adjustments	**605,324**	**521,270**	**217,369**
Non-GAAP Net Income	**$ 194,798**	**$ 354,436**	**$ 256,901**
Non-GAAP Earnings Per Share:			
Weighted average ordinary shares – Basic	**163,122,663**	**160,699,543**	**148,788,020**
Non-GAAP Earnings Per Share – Basic			
GAAP (loss) earnings per share - Basic	**$ (2.52)**	**$ (1.04)**	**$ 0.27**
Non-GAAP adjustments	3.71	3.25	1.46
Non-GAAP earnings per share – Basic	**$ 1.19**	**$ 2.21**	**$ 1.73**
Weighted average ordinary shares – Diluted			
Weighted average ordinary shares – Basic	163,122,663	160,699,543	148,788,020
Ordinary share equivalents	2,582,576	3,626,570	7,135,231
Weighted average ordinary shares – Diluted	**165,705,239**	**164,326,113**	**155,923,251**
Non-GAAP Earnings Per Share – Diluted			
GAAP (loss) earnings per share – Diluted	**$ (2.52)**	**$ (1.04)**	**$ 0.25**
Non-GAAP adjustments	3.71	3.25	1.40
Diluted earnings per share effect of ordinary share equivalents	(0.01)	(0.05)	—
Non-GAAP earnings per share – Diluted	**$ 1.18**	**$ 2.16**	**$ 1.65**

	For the Years Ended December 31,		
	2017	2016	2015
GAAP Net (Loss) Income	**$ (410,526)**	**$ (166,834)**	**$ 39,532**
Depreciation	6,631	4,962	5,420
Amortization, accretion and inventory step-up:			
Intangible amortization expense	276,784	216,875	132,923
Accretion of royalty liabilities	51,263	40,616	20,088
Amortization of deferred revenue	(860)	(836)	(962)
Inventory step-up expense	119,151	71,137	11,495
Interest expense, net (including amortization of debt discount and deferred financing costs)	126,523	86,610	69,900
Benefit for income taxes	(102,749)	(61,251)	(172,244)
EBITDA	**66,217**	**191,279**	**106,152**
Other non-GAAP adjustments:			
Remeasurement of royalties for medicines acquired through business combinations	21,774	386	21,151
Acquisition/divestiture-related costs	177,035	52,874	72,221
Restructuring and realignment costs	4,883	—	—
Share-based compensation	121,553	114,144	85,786
Gain on divestiture	(6,267)	—	—
Charges relating to discontinuation of the Friedreich's ataxia program (1)	22,509	23,513	—
Drug substance harmonization costs (2)	10,651	—	—
Upfront and milestone payments related to license agreements	12,186	2,000	—
Fees related to term loan refinancing	5,220	—	—
Loss on debt extinguishment	978	—	77,624
Royalties for medicines acquired through business combinations	(47,003)	(37,593)	(29,834)
Litigation settlement	—	65,000	—
Impairment of in-process research and development	—	66,000	—
Reversal of pre-acquisition reserve upon signing of contract	—	(6,900)	—
Loss on sale of long-term investments	—	—	29,032
Total of other non-GAAP adjustments	**323,519**	**279,424**	**255,980**
Adjusted EBITDA	**$ 389,736**	**$ 470,703**	**$ 362,132**

(1) Charges relating to discontinuation of the FA program of $22.5 million for the year ended December 31, 2017 include $22.3 million relating to the impairment of a non-current asset, additional net expense of $1.7 million for excess purchase commitments and a reduction of $1.5 million to "research and development expenses" reflecting lower costs than previously estimated to be incurred to discontinue the FA program. Charges relating to the discontinuation of the FA program for the year ended December 31, 2016 include a $14.3 million loss on inventory purchase commitments, a $5.3 million impairment of a non-current asset and $4.0 million of clinical trial wind-down costs.

(2) During the year ended December 31, 2016, we committed to spend $14.9 million related to the harmonization of the manufacturing processes for ACTIMMUNE and IMUKIN drug substance. During the year ended December 31, 2017, we incurred $12.1 million of this spend, including costs of $10.7 million that qualify for exclusion in our non-GAAP financial measures under our non-GAAP cost policy.

(3) Adjustment to the GAAP tax benefit for the estimated tax impact of each non-GAAP adjustment is based on the statutory tax rate of the applicable jurisdictions for each non-GAAP adjustment.

(4) Other non-GAAP income tax adjustments during the year ended December 31, 2017 reflect the provisional $74.9 million net benefit recorded following the enactment of the Tax Act, which net benefit included a $134.2 million tax benefit from the revaluation of our U.S. net deferred tax liability based on the new U.S. federal tax rate of 21 percent, partially offset by the write-off of the $59.2 million deferred tax asset related to our U.S. interest expense carryforwards under Section 163(j) of the Code.

Other non-GAAP income tax adjustments during the year ended December 31, 2015 of $105.1 million related to the release of certain valuation allowances in connection with the Hyperion acquisition.

Liquidity, Financial Position and Capital Resources

We have incurred losses since our inception in June 2005 and, as of December 31, 2017, we had an accumulated deficit of $1,252.3 million. We expect that our sales and marketing expenses will continue to increase as a result of the commercialization of our medicines but we believe these cost increases will be more than offset by higher net sales and gross profits. Additionally, we expect that our research and development costs will increase as we acquire more development-stage medicine candidates.

We have financed our operations to date through equity financings, debt financings and the issuance of convertible notes, along with cash flows from operations during the last several years. As of December 31, 2017, we had $751.4 million in cash and cash equivalents and total debt with a book value of $1,901.7 million and face value of $2,020.8 million. Cash at December 31, 2017 reflects our use of cash on hand of approximately $144.0 million, net of $6.3 million of cash acquired, to fund our acquisition of River Vision on May 8, 2017, $32.5 million paid during the year ended December 31, 2017 in relation to the litigation settlement in 2016 with Express Scripts and $22.3 million paid to Boehringer Ingelheim International following the completion of the acquisition of certain rights to interferon gamma-1b, and includes $69.4 million received following the Chiesi divestiture in June 2017, net of cash divested. We believe our existing cash and cash equivalents and our expected cash flows from our operations will be sufficient to fund our business needs for at least the next twelve months from the issuance of the financial statements in this Annual Report on Form 10-K. Part of our strategy is to expand and leverage our commercial capabilities and to develop a pipeline of rare disease medicine candidates by researching, developing and commercializing innovative medicines that address unmet treatment needs for rare and rheumatic diseases. To the extent we enter into transactions to acquire medicines or businesses in the future, we will most likely need to finance a significant portion of those acquisitions through additional debt, equity or convertible debt financings, or through the use of cash on hand.

On October 23, 2017, HPI, our wholly owned subsidiary, and Horizon Pharma USA, Inc., our wholly owned subsidiary, or HPUSA, and together with HPI in such capacity, the Borrowers, borrowed approximately $845.8 million aggregate principal amount of loans, or the October 2017 Refinancing Loans, pursuant to an amendment, or the October 2017 Refinancing Amendment, to the Credit Agreement, dated as of May 7, 2015, by and among the Borrowers, us and certain of our subsidiaries as guarantors, the lenders party thereto from time to time and Citibank, N.A., as administrative agent and collateral agent, as amended by Amendment No. 1, dated as of October 25, 2016 , or the 2016 Credit Agreement, and Amendment No. 2, dated March 29, 2017, or the March 2017 Credit Agreement. As used herein, all references to the "Credit Agreement" are references to the March 2017 Credit Agreement, as amended by the October 2017 Refinancing Amendment.

The October 2017 Refinancing Loans were incurred as a separate new class of term loans under the Credit Agreement with substantially the same terms as the previously outstanding senior secured term loans incurred on March 29, 2017 under the March 2017 Credit Agreement, or the October 2017 Refinanced Loans, to effectuate a repricing of the October 2017 Refinanced Loans. The Borrowers used the proceeds of the October 2017 Refinancing Loans to repay the October 2017 Refinanced Loans, which totaled approximately $845.8 million. The October 2017 Refinancing Loans bear interest, at the Borrowers' option, at a rate equal to either the London Inter-Bank Offer Rate, or LIBOR, plus an applicable margin of 3.25% per year (subject to a LIBOR floor of 1.0%), or the adjusted base rate plus 2.25%. The adjusted base rate is defined as the greater of (a) LIBOR (using one-month interest period) plus 1%, (b) prime rate, (c) fed funds plus 0.5%, and (d) 2%. The Credit Agreement provides for (i) the October 2017 Refinancing Loans, (ii) one or more uncommitted additional incremental loan facilities subject to the satisfaction of certain financial and other conditions, and (iii) one or more uncommitted refinancing loan facilities with respect to loans thereunder. The Credit Agreement allows for us and certain of our subsidiaries to become borrowers under incremental or refinancing facilities.

The obligations under the Credit Agreement (including obligations in respect of the October 2017 Refinancing Loans) and any swap obligations and cash management obligations owing to a lender (or an affiliate of a lender) thereunder are guaranteed by us and each of our existing and subsequently acquired or formed direct and indirect subsidiaries (other than certain immaterial subsidiaries, subsidiaries whose guarantee would result in material adverse tax consequences and subsidiaries whose guarantee is prohibited by applicable law). The obligations under the Credit Agreement (including obligations in respect of the October 2017 Refinancing Loans) and any such swap and cash management obligations are secured, subject to customary permitted liens and other agreed upon exceptions, by a perfected security interest in (i) all tangible and intangible assets of the Borrowers and the guarantors, except for certain customary excluded assets, and (ii) all of the capital stock owned by the Borrowers and guarantors thereunder (limited, in the case of the stock of certain non-U.S.

subsidiaries of the Borrowers, to 65% of the capital stock of such subsidiaries). The Borrowers and the guarantors under the Credit Agreement are individually and collectively referred to herein as a "Loan Party" and the "Loan Parties," as applicable.

Borrowers under the Credit Agreement are permitted to make voluntary prepayments of the loans under the Credit Agreement at any time without payment of a premium, except that with respect to the October 2017 Refinancing Loans, a 1% premium will apply to a repayment of the October 2017 Refinancing Loans in connection with a repricing of, or any amendment to the Credit Agreement in a repricing of, such loans effected on or prior to the date that is six months following October 23, 2017. The Borrowers are required to make mandatory prepayments of loans under the Credit Agreement (without payment of a premium) with (a) net cash proceeds from certain non-ordinary course asset sales (subject to reinvestment rights and other exceptions), (b) casualty proceeds and condemnation awards (subject to reinvestment rights and other exceptions), (c) net cash proceeds from issuances of debt (other than certain permitted debt), and (d) 50% of our excess cash flow (subject to decrease to 25% or 0% if our first lien leverage ratio is less than 2.25:1 or 1.75:1, respectively). The October 2017 Refinancing Loans will amortize in equal quarterly installments beginning on December 31, 2017 in an aggregate annual amount equal to 1% of the original principal amount of the October 2017 Refinanced Loans (i.e. $850.0 million), with any remaining balance payable on March 29, 2024, the final maturity date of the October 2017 Refinancing Loans.

We elected to exercise our reinvestment rights under the mandatory prepayment provisions of the March 2017 Credit Agreement with respect to the net proceeds from the Chiesi divestiture. To the extent we do not apply such net proceeds to permitted acquisitions (including the acquisition of rights to products and products lines) and/or the acquisition of capital assets within 365 days of the receipt thereof (or commit to so apply and then apply within 180 days after the end of such 365-day period), we would be required to make a mandatory prepayment under the Credit Agreement in an amount equal to the unapplied net proceeds. Until such time, the net proceeds are not legally restricted for use. As of December 31, 2017, we had applied a portion of such net proceeds to the acquisition of additional rights to interferon gamma-1b and to our agreement to license HZN-003.

We were, as of December 31, 2017, and currently are in compliance with the Credit Agreement.

On October 25, 2016, HPI and HPUSA, or the 2024 Issuers, completed a private placement of $300.0 million aggregate principal amount of 2024 Senior Notes to certain investment banks acting as initial purchasers who subsequently resold the 2024 Senior Notes to qualified institutional buyers as defined in Rule 144A under the Securities Act.

The obligations under the 2024 Senior Notes are the 2024 Issuers' general unsecured senior obligations and are fully and unconditionally guaranteed on a senior unsecured basis by us and all of our direct and indirect subsidiaries that are guarantors from time to time under the Credit Agreement.

We used the net proceeds from the offering of the 2024 Senior Notes as well as $375.0 million principal amount of senior secured term loans incurred in October 2016 under the 2016 Credit Agreement to fund a portion of the acquisition of Raptor, repay Raptor's outstanding debt, and pay any prepayment premiums, fees and expenses in connection with the foregoing.

The 2024 Senior Notes accrue interest at an annual rate of 8.75% payable semiannually in arrears on May 1 and November 1 of each year, beginning on May 1, 2017. The 2024 Senior Notes will mature on November 1, 2024, unless earlier repurchased or redeemed.

Except as described below, the 2024 Senior Notes may not be redeemed before November 1, 2019. Thereafter, some or all of the 2024 Senior Notes may be redeemed at any time at specified redemption prices, plus accrued and unpaid interest to the redemption date. At any time prior to November 1, 2019, some or all of the 2024 Senior Notes may be redeemed at a price equal to 100% of the aggregate principal amount thereof, plus a make-whole premium and accrued and unpaid interest to the redemption date. Also prior to November 1, 2019, up to 35% of the aggregate principal amount of the 2024 Senior Notes may be redeemed at a redemption price of 108.75% of the aggregate principal amount thereof, plus accrued and unpaid interest, with the net proceeds of certain equity offerings. In addition, the 2024 Senior Notes may be redeemed in whole but not in part at a redemption price equal to 100% of the principal amount plus accrued and unpaid interest and additional amounts, if any, to, but excluding, the redemption date, if on the next date on which any amount would be payable in respect of the 2024 Senior Notes, the 2024 Issuers or any guarantor is or would be required to pay additional amounts as a result of certain tax-related events.

If we undergo a change of control, the 2024 Issuers will be required to make an offer to purchase all of the 2024 Senior Notes at a price in cash equal to 101% of the aggregate principal amount thereof plus accrued and unpaid interest to, but not

including, the repurchase date. If we or certain of our subsidiaries engage in certain asset sales, the 2024 Issuers will be required under certain circumstances to make an offer to purchase the 2024 Senior Notes at 100% of the principal amount thereof, plus accrued and unpaid interest to the repurchase date.

On April 29, 2015, Horizon Pharma Financing Inc., our wholly owned subsidiary, or Horizon Financing, completed a private placement of $475.0 million aggregate principal amount of 2023 Senior Notes to certain investment banks acting as initial purchasers who subsequently resold the 2023 Senior Notes to qualified institutional buyers as defined in Rule 144A under the Securities Act, and in offshore transactions to non-U.S. persons in reliance on Regulation S under the Securities Act.

In connection with the closing of the Hyperion acquisition on May 7, 2015, Horizon Financing merged with and into HPI and, as a result, the 2023 Senior Notes became HPI's general unsecured senior obligations. The obligations under the 2023 Senior Notes are fully and unconditionally guaranteed by on a senior unsecured basis us and all of our direct and indirect subsidiaries that are guarantors from time to time under the Credit Agreement.

The 2023 Senior Notes accrue interest at an annual rate of 6.625% payable semiannually in arrears on May 1 and November 1 of each year, beginning on November 1, 2015. The 2023 Senior Notes will mature on May 1, 2023, unless earlier repurchased or redeemed.

Except as described below, the 2023 Senior Notes may not be redeemed before May 1, 2018. Thereafter, some or all of the 2023 Senior Notes may be redeemed at any time at specified redemption prices, plus accrued and unpaid interest to the redemption date. At any time prior to May 1, 2018, some or all of the 2023 Senior Notes may be redeemed at a price equal to 100% of the aggregate principal amount thereof, plus a make-whole premium and accrued and unpaid interest to the redemption date. Also prior to May 1, 2018, up to 35% of the aggregate principal amount of the 2023 Senior Notes may be redeemed at a redemption price of 106.625% of the aggregate principal amount thereof, plus accrued and unpaid interest, with the net proceeds of certain equity offerings. In addition, the 2023 Senior Notes may be redeemed in whole but not in part at a redemption price equal to 100% of the principal amount plus accrued and unpaid interest and additional amounts, if any, to, but excluding, the redemption date, if on the next date on which any amount would be payable in respect of the 2023 Senior Notes, HPI or any guarantor is or would be required to pay additional amounts as a result of certain tax-related events.

If we undergo a change of control, HPI will be required to make an offer to purchase all of the 2023 Senior Notes at a price in cash equal to 101% of the aggregate principal amount thereof plus accrued and unpaid interest to, but not including, the repurchase date. If we or certain of our subsidiaries engage in certain asset sales, HPI will be required under certain circumstances to make an offer to purchase the 2023 Senior Notes at 100% of the principal amount thereof, plus accrued and unpaid interest to the repurchase date.

On March 13, 2015, Horizon Pharma Investment Limited, our wholly owned subsidiary, or Horizon Investment, completed a private placement of $400.0 million aggregate principal amount of Exchangeable Senior Notes to several investment banks acting as initial purchasers who subsequently resold the Exchangeable Senior Notes to qualified institutional buyers as defined in Rule 144A under the Securities Act. The net proceeds from the offering of the Exchangeable Senior Notes were approximately $387.2 million, after deducting the initial purchasers' discount and offering expenses payable by Horizon Investment.

We have fully and unconditionally guaranteed the Exchangeable Senior Notes on a senior unsecured basis, or the Guarantee. The Exchangeable Senior Notes and the Guarantee are Horizon Investment's and our senior unsecured obligations. The Exchangeable Senior Notes accrue interest at an annual rate of 2.50% payable semiannually in arrears on March 15 and September 15 of each year, beginning on September 15, 2015. The Exchangeable Senior Notes will mature on March 15, 2022, unless earlier exchanged, repurchased or redeemed. The initial exchange rate is 34.8979 of our ordinary shares per $1,000 principal amount of the Exchangeable Senior Notes (equivalent to an initial exchange price of approximately $28.66 per ordinary share).

We have a significant amount of debt outstanding on a consolidated basis. This substantial level of debt could have important consequences to our business, including, but not limited to: making it more difficult for us to satisfy our obligations; requiring a substantial portion of our cash flows from operations to be dedicated to the payment of principal and interest on our indebtedness, therefore reducing our ability to use our cash flows to fund acquisitions, capital expenditures, and future business opportunities; limiting our ability to obtain additional financing, including borrowing additional funds; increasing our vulnerability to, and reducing our flexibility to respond to, general adverse economic and industry conditions; limiting our flexibility in planning for, or reacting to, changes in our business and the industry in which we operate; and

placing us at a disadvantage as compared to our competitors, to the extent that they are not as highly leveraged. We may not be able to generate sufficient cash to service all of our indebtedness and may be forced to take other actions to satisfy our obligations under our indebtedness.

In addition, the indentures governing the 2024 Senior Notes and 2023 Senior Notes and the Credit Agreement impose various covenants that limit our ability and/or our restricted subsidiaries' ability to, among other things, pay dividends or distributions, repurchase equity, prepay junior debt and make certain investments, incur additional debt and issue certain preferred stock, incur liens on assets, engage in certain asset sales or merger transactions, enter into transactions with affiliates, designate subsidiaries as unrestricted subsidiaries; and allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to us.

We were, as of December 31, 2017, and currently are in compliance with the indenture governing the 2024 Senior Notes and 2023 Senior Notes.

During the year ended December 31, 2017, we issued an aggregate of 2.0 million of our ordinary shares in connection with stock option exercises, the vesting of restricted stock units, employee share purchase plan purchases and the vesting of performance stock units. We received a total of $9.3 million in net proceeds in connection with such issuances.

During the year ended December 31, 2017, we issued an aggregate of 391,500 ordinary shares upon the cash exercise of warrants and received proceeds of $1.8 million representing the aggregate exercise price for such warrants. In addition, warrants to purchase an aggregate of 704,285 of our ordinary shares were exercised in cashless exercises, resulting in the issuance of 523,520 ordinary shares.

In May 2016, our board of directors authorized a share repurchase program pursuant to which we may repurchase up to 5,000,000 of our ordinary shares. In May 2017, our board of directors reauthorized a share repurchase program pursuant to which we may repurchase up to 16,000,000 of our ordinary shares. As of December 31, 2017, we had repurchased 100,000 of our ordinary shares under this repurchase program, for total consideration of $1.0 million. The timing and amount of future repurchases, if any, will depend on a variety of factors, including the price of our ordinary shares, alternative investment opportunities, our cash resources, restrictions under the Credit Agreement and market conditions.

Sources and Uses of Cash

The following table provides a summary of our cash position and cash flows for the years ended December 31, 2017, 2016 and 2015 (in thousands):

	For the Years Ended December 31,		
	2017	2016	2015
Cash and cash equivalents	$ 751,368	$ 509,055	$ 859,616
Cash provided by (used in):			
Operating activities	280,208	369,456	194,166
Investing activities	(101,619)	(1,375,881)	(995,048)
Financing activities	58,408	657,074	1,442,481

Net Cash Provided by Operating Activities

During the years ended December 31, 2017, 2016 and 2015, net cash provided by operating activities was $280.2 million, $369.5 million and $194.2 million, respectively.

Net cash provided by operating activities during the year ended December 31, 2017 was primarily attributable to cash collections from net sales. Cash provided by operating activities was negatively impacted during the year ended December 31, 2017 by cash payments of $113.8 million for interest, $32.5 million outlay for the remaining fifty percent of the litigation settlement amount with Express Scripts, cash payments of $54.0 million for acquisition/divestiture-related costs, cash payments relating to term loan refinancing of $9.1 million, cash payments related to the discontinuation of the FA program of $7.2 million, cash payments relating to our drug substance harmonization program of $5.2 million and cash payments related to our restructuring and realignment activities of $4.7 million.

Net cash provided by operating activities during 2016 was primarily attributable to cash collections from net sales. Cash provided by operating activities was negatively impacted during the year ended December 31, 2016, by $32.5 million outlay for fifty percent of the litigation settlement amount with Express Scripts, cash payments of $48.9 million for acquisition-related expenses and $60.8 million for interest payments made on our 2015 Term Loan Facility, 2016 Incremental Loan Facility, 2023 Senior Notes and Exchangeable Senior Notes.

Net cash provided by operating activities during 2015 was primarily attributable to cash collections from net sales. Cash provided by operating activities was negatively impacted during the year ended December 31, 2015, due to cash payments of $68.2 million for acquisition-related expenses, including the payment in April 2015 of approximately $11.2 million of employee and director excise taxes due to the Vidara Merger. Cash payments during the year ended December 31, 2015 also included a $45.4 million early redemption premium related to the 2014 Term Loan Facility, $42.0 million of interest payments made on our 2014 Term Loan Facility, 2015 Term Loan Facility, 2023 Senior Notes and Exchangeable Senior Notes, and $10.0 million of cash payments related to induced debt conversions.

Net Cash Used in Investing Activities

During the years ended December 31, 2017, 2016 and 2015, net cash used in investing activities was $101.6 million, $1,375.9 million and $995.0 million, respectively.

Net cash used in investing activities during the year ended December 31, 2017 was primarily associated with $144.9 million of payments for the acquisition of River Vision, net of cash acquired, and associated transaction costs, and $22.3 million relating to the payment for certain rights for interferon gamma-1b. This was partially offset by $69.4 million of proceeds received from the Chiesi divestiture, net of cash divested.

Net cash used in investing activities during 2016 was primarily related to $835.9 million of payments for the acquisition of Raptor, net of cash acquired, $514.8 million of payments for the acquisition of Crealta, net of cash acquired, a $5.6 million (€5.0 million) initial payment for certain non-U.S. intellectual property rights to interferon gamma-1b and $15.7 million of payments for purchases of property and equipment.

Net cash used in investing activities during 2015 was primarily associated with $1,022.4 million of payments for the acquisition of Hyperion, net of cash acquired, and payments of $71.8 million made in relation to the purchase of 2,250,000 shares of common stock of Depomed. This was offset by proceeds of $42.8 million from the sale of such Depomed shares and proceeds from the liquidation of available-for-sale investments of $64.6 million.

Net Cash Provided by Financing Activities

During the years ended December 31, 2017, 2016 and 2015, net cash provided by financing activities was $58.4 million, $657.1 million and $1,442.5 million, respectively.

Net cash provided by financing activities during the year ended December 31, 2017 was primarily attributable to the net proceeds of $1,693.5 million from term loans, offset in part by repayment of term loans of $1,618.6 million. We refinanced our term loans during March 2017 and October 2017. The March 2017 refinancing loans replaced the $394.0 million 2015 term loan facility and the $375.0 million 2016 incremental loan facility and the October 2017 Refinancing Loans replaced the October 2017 Refinanced Loans. The March 2017 Credit Agreement resulted in an increase of $81.0 million of principal amount of our outstanding debt and the October 2017 Refinancing Loans did not result in any changes to the principal amount outstanding. Additionally, during the year ended December 31, 2017, we paid $20.0 million relating to milestones in connection with a contingent consideration liability assumed in our acquisition of Raptor.

Net cash provided by financing activities during 2016 was primarily related to $364.3 million of net proceeds received from borrowings under our 2016 Incremental Loan Facility and $291.9 million of net proceeds received from borrowings under our 2024 Senior Notes.

Net cash provided by financing activities during 2015 was primarily attributable to $387.2 million of net proceeds received from borrowings under the Exchangeable Senior Notes, $391.5 million net proceeds from the 2015 Term Loan Facility, $462.3 million net proceeds from the 2023 Senior Notes and $475.7 million of net proceeds from the issuance of 17,652,500 ordinary shares in our 2015 public offering, partially offset by the repayment of the 2014 Term Loan Facility and a partial repayment of the 2015 Term Loan Facility, which resulted in a financing outflow of $299.0 million.

Financial Condition as of December 31, 2017 compared to December 31, 2016

Accounts receivable, net. Accounts receivable, net, increased $61.7 million, from $305.7 million as of December 31, 2016 to $367.4 million as of December 31, 2017. The increase is due to growth in gross sales of our medicines.

Inventories, net. Inventories, net, decreased $113.1 million, from $174.8 million as of December 31, 2016 to $61.7 million as of December 31, 2017. The decrease was primarily due to $119.1 million of inventory step-up expense recorded during the year ended December 31, 2017, of which $78.3 million related to KRYSTEXXA and $40.8 million related to PROCYSBI and QUINSAIR. Additionally, during the year ended December 31, 2017, we recorded $3.2 million of inventory step-up expense to the gain on divestiture following the sale of inventory to Chiesi in connection with the Chiesi divestiture.

Developed technology, net. Developed technology, net, decreased $323.2 million, from $2,767.2 million as of December 31, 2016 to $2,443.9 million as of December 31, 2017. The decrease was primarily due to the amortization of developed technology of $276.0 million during the year ended December 31, 2017 and developed technology with a net book value of $47.2 million disposed of in the Chiesi divestiture.

Goodwill. Goodwill decreased $19.2 million from $445.6 million as of December 31, 2016 to $426.4 million as of December 31, 2017. The decrease was due to $16.3 million written off in connection with the Chiesi divestiture and $2.9 million in measurement period adjustments related to the Raptor acquisition, which were recorded during the year ended December 31, 2017.

Other assets. Other assets increased $33.7 million from $2.4 million as of December 31, 2016 to $36.1 million as of December 31, 2017. The increase was primarily due to a royalty reimbursement asset recorded in connection with the Chiesi divestiture during the year ended December 31, 2017, which represents the future estimated amount receivable from Chiesi in respect of PROCYSBI and QUINSAIR contingent royalty liabilities.

Accrued expenses. Accrued expenses decreased $45.0 million, from $182.8 million as of December 31, 2016 to $137.8 million as of December 31, 2017. This was primarily due to the payment of $32.5 million during the year ended December 31, 2017 pursuant to our settlement agreement with Express Scripts, a decrease of $10.1 million in payroll-related expenses and a decrease of $4.8 million in accrued interest.

Accrued trade discounts and rebates. Accrued trade discounts and rebates increased $204.2 million, from $297.6 million as of December 31, 2016 to $501.8 million as of December 31, 2017. This was primarily due to a $142.8 million increase in accrued wholesaler fees and commercial rebates, a $42.0 million increase in accrued co-pay and other patient assistance costs and a $19.4 million increase in accrued government rebates and chargebacks.

Long-term debt, net, net of current. Long-term debt, net, net of current increased $74.9 million from $1,501.7 million as of December 31, 2016 to $1,576.6 million as of December 31, 2017. The increase was primarily related to the $845.8 million aggregate principal amount of October 2017 Refinancing Loans which replaced the October 2017 Refinanced Loans. The October 2017 Refinanced Loans originally replaced the $394.0 million 2015 term loan facility and the $375.0 million 2016 incremental loan facility. The October 2017 Refinanced Loans and October 2017 Refinancing Loans resulted in an increase of $81.0 million of principal amount of our outstanding debt. This increase was offset in part by certain charges related to the refinancing loans and amortization of debt discount and deferred financing fees and a repayment of $4.2 million during the year ended December 31, 2017.

Deferred tax liabilities, net. Deferred tax liabilities, net, decreased $138.7 million, from $296.6 million as of December 31, 2016 to $157.9 million as of December 31, 2017. This was primarily due to a provisional $74.9 million net benefit recorded following the enactment of the Tax Act, which net benefit included a $134.2 million tax benefit from the revaluation of our U.S. net deferred tax liability based on the new U.S. federal tax rate of 21 percent, partially offset by the write-off of the $59.2 million deferred tax asset related to our U.S. interest expense carryforwards under Section 163(j) of the Code. We also recorded a decrease in net deferred tax liabilities resulting from the acquisition of deferred tax assets of $19.9 million in connection with the River Vision acquisition and a decrease during the year ended December 31, 2017 in net deferred tax liabilities primarily resulting from the tax effect of the amortization of intangible assets during the year of $61.6 million, partially offset by $34.5 million due to the use of losses during the year. Additionally, we adopted ASU No. 2016-09, Improvements to Employee Share-Based Payment Accounting, or ASU No. 2016-09, on a modified retrospective basis on January 1, 2017 and recorded a decrease of $7.2 million in net deferred tax liabilities and a corresponding decrease in accumulated deficit during the year ended December 31, 2017.

Contractual Obligations

As of December 31, 2017, minimum future cash payments due under contractual obligations, including, among others, our debt agreements, minimum purchase agreements and non-cancelable operating lease agreements, were as follows (in thousands):

	2018	2019	2020	2021	2022	2023 & Thereafter	Total
Debt agreements – principal (1)	10,625	8,500	8,500	8,500	406,375	1,578,250	2,020,750
Debt agreements - interest (1)	109,095	105,391	108,072	108,378	102,411	116,086	649,433
Purchase commitments (2)	45,098	14,523	10,336	7,116	10,635	27,044	114,752
Operating lease obligations (3)	7,356	6,659	5,951	5,350	4,092	11,994	41,402
Total contractual cash obligations	**172,174**	**135,073**	**132,859**	**129,344**	**523,513**	**1,733,374**	**2,826,337**

(1) Represents the minimum contractual obligation due under the following debt agreements:

- $845.8 million under the October 2017 Refinancing Loans, which includes estimated quarterly interest payments based on the applicable interest rate at December 31, 2017 of 4.75% and quarterly payments of 1.0% of the principal, and repayment of the remaining principal in March 2024.
- $475.0 million 2023 Senior Notes, which includes bi-annual interest payments and repayment of the principal in May 2023.
- $400.0 million Exchangeable Senior Notes, which includes bi-annual interest payments and repayment of the principal in March 2022.
- $300.0 million 2024 Senior Notes, which includes bi-annual interest payments and repayment of the principal in November 2024.

(2) These amounts reflect the following purchase commitments with our third-party manufacturers:

- Purchase commitment for RAVICTI through 2022.
- Purchase commitment for PROCYSBI and QUINSAIR through December 2020.
- Minimum annual order quantities required to be placed with Boehringer Ingelheim for final packaged ACTIMMUNE through July 2024 and additional units we also committed to purchase which were intended to cover anticipated demand if the results of the FA program of ACTIMMUNE for the treatment of FA had been successful. As of December 31, 2017, the minimum binding purchase commitment to Boehringer Ingelheim Biopharmaceuticals GmbH, or Boehringer Ingelheim Biopharmaceuticals, was $24.3 million (converted using a Dollar-to-Euro exchange rate of 1.2003) through July 2024.
- A commitment to spend $3.4 million with Boehringer Ingelheim related to the harmonization of the manufacturing process for ACTIMMUNE drug substance.
- Purchase commitment for BUPHENYL through 2020.
- Minimum purchase commitment for KRYSTEXXA through 2026.
- Minimum purchase commitment for RAYOS/LODOTRA tablets from Jagotec AG through December 2023 (the end of the minimum term), which is the firm commitment term under the contract.
- Purchase commitment for final packaged PENNSAID 2% from Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.) through February 2018.
- Purchase commitment for final packaged DUEXIS tablets from Sanofi-Aventis U.S. through June 2018.
- Minimum purchase commitment for VIMOVO tablets from Patheon Pharmaceuticals Inc. through March 2018.
- Purchase commitments for process validation activities for teprotumumab through 2018.

(3) These amounts reflect payments due under our operating leases, which are principally for our facilities. For further details regarding these properties, see Item 2 of Part I, *Properties,* of this Annual Report on Form 10-K.

As of December 31, 2017, our contingent liability for uncertain tax positions amounted to $23.4 million (excluding interest and penalties). Due to the nature and timing of the ultimate outcome of these uncertain tax positions, we cannot make a reasonably reliable estimate of the amount and period of related future payments, if any. Therefore, our contingent liability has been excluded from the above contractual obligations table. We do not expect a significant tax payment related to these obligations within the next year.

In addition to the obligations set out in the above table, we have assumed material obligations to make royalty and milestone payments to certain third parties on net sales of certain of our medicines. See Note 18 of the Notes to consolidated financial statements, included in Item 15 of this Annual Report on Form 10-K, for details of these material obligations.

Off-Balance Sheet Arrangements

Since our inception, we have not engaged in any off-balance sheet arrangements, including the use of structured finance, special purpose entities or variable interest entities, other than the indemnification agreements discussed in Note 18 in the Notes to our consolidated financial statements included in this report.

Critical Accounting Policies and Significant Judgments and Estimates

The methods, estimates and judgments that we use in applying our critical accounting policies have a significant impact on the results that we report in our financial statements. Some of our accounting policies require us to make difficult and subjective judgments, often as a result of the need to make estimates regarding matters that are inherently uncertain.

We have identified the accounting policies and estimates listed below as those that we believe require management's most subjective and complex judgments in estimating the effect of inherent uncertainties. This section should also be read in conjunction with Note 2 in the Notes to our consolidated financial statements included in this report, which includes a discussion of these and other significant accounting policies.

Revenue Recognition

Revenue is recognized when all of the following criteria are met: persuasive evidence of an arrangement exists; delivery has occurred or services have been rendered; the price is fixed or determinable; and collectability is reasonably assured. Some of our agreements contain multiple elements and in accordance with these agreements, we may be eligible for upfront license fees, marketing or commercial milestones and payment for medicine deliveries.

Revenue From Medicine Deliveries

Revenue from medicine deliveries comprises substantially all of our gross sales. We recognize revenue from the sale of our medicines when delivery has occurred, title has transferred, the selling price is fixed or determinable, the right of return no longer exists (which is the earlier of medicine being dispensed through patient prescriptions or the expiration of the right of return) or medicine returns can be reasonably estimated, collectability is reasonably assured and we have no further performance obligations. Due to our ability to reasonably estimate and determine allowances for co-pay and other patient assistance, medicine returns, rebates and discounts based on our own internal data for DUEXIS and RAYOS or data relating to prior sales of our acquired medicines which was received in connection with the acquisition of those medicines, we recognize revenue at the point of sale to wholesale pharmaceutical distributors and pharmacies for all currently distributed medicines.

Revenue From Upfront License Fees

We recognize revenues from the receipt of non-refundable, upfront license fees. In situations where the licensee is able to obtain stand-alone value from the license and no further performance obligations exist on our part, revenues are recognized on the earlier of when payments are received or collection is assured. Where continuing involvement by us is required in the form of technology transfer, medicine manufacturing or technical support, revenues are deferred and recognized over the term of the agreement.

Revenue From Milestone Receipts

Milestone payments are recognized as revenue based on achievement of the associated milestones, as defined in the relevant agreements. Revenue from a milestone achievement is recognized when earned, as evidenced by acknowledgment from our partner, provided that (1) the milestone event is substantive and its achievability was not reasonably assured at the inception of the agreement, (2) the milestone represents the culmination of an earnings process and (3) the milestone payment is non-refundable. If any of these criteria are not met, revenue from the milestone achievement is recognized over the remaining minimum period of our performance obligations under the agreement.

As of December 31, 2017 and 2016, deferred revenues related to milestone and upfront payments received were $16.6 million and $11.1 million, respectively.

Following the adoption of ASU No. 2014-09*, Revenue from Contracts with Customers*, we expect to reclassify approximately $11.0 million of deferred revenue directly to retained earnings in the first quarter of 2018.

Medicine Sales Discounts and Allowances

We record allowances for medicine returns, rebates and discounts at the time of sale to wholesale pharmaceutical distributors and pharmacies. We are also required to make significant judgments and estimates in determining some of these allowances. If actual results differ from our estimates, we will be required to make adjustments to these allowances in the future.

Commercial Rebates

We participate in certain commercial rebate programs. Under these rebate programs, we pay a rebate to the commercial entity or third-party administrator of the program. We accrue estimated rebates based on contract prices, estimated percentages of medicine sold to qualified patients and estimated levels of inventory in the distribution channel and record the rebate as a reduction of revenue. Accrued commercial rebates are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Distribution Service Fees

We include distribution service fees paid to our wholesalers for distribution and inventory management services as a reduction to revenue. We accrue estimated distribution fees based on contractually determined amounts, typically as a percentage of revenue, and record the fees as a reduction of revenue. Accrued distribution service fees are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Patient Access Programs

We offer discount card and other programs such as our HorizonCares program to patients under which the patient receives a discount on his or her prescription. In certain circumstances when a patient's prescription is rejected by a managed care vendor, we will pay for the full cost of the prescription. We reimburse pharmacies for this discount through third-party vendors. We reduce gross sales by the amount of actual co-pay and other patient assistance in the period based on the invoices received. We also record an accrual to reduce gross sales for estimated co-pay and other patient assistance on units sold to distributors that have not yet been prescribed/dispensed to a patient. The estimate is based on contract prices, estimated percentages of medicine that will be prescribed to qualified patients, average assistance paid based on reporting from the third-party vendors and estimated levels of inventory in the distribution channel. Accrued co-pay and other patient assistance fees are included in "accrued trade discounts and rebates" on the consolidated balance sheet. Patient assistance programs include both co-pay assistance and fully bought down prescriptions.

Sales Returns

Consistent with industry practice, we maintain a return policy that allows customers to return medicine within a specified period prior to and subsequent to the medicine expiration date. Generally, medicine may be returned for a period beginning six months prior to its expiration date and up to one year after its expiration date. The right of return expires on the earlier of one year after the medicine expiration date or the time that the medicine is dispensed to the patient. The majority of our medicine returns are the result of medicine dating, which falls within the range set by our policy, and are settled through the issuance of a credit to the customer. Our estimate of the provision for returns is based upon our historical experience with actual returns, which is applied to the level of sales for the period that corresponds to the period during which our customer may return medicine. This period is known to us based on the shelf lives of our medicines at the time of shipment. We record sales returns as an allowance against accounts receivable and a reduction of revenue.

Prompt Pay Discounts

As an incentive for prompt payment, we offer a two percent cash discount to customers. We expect that all customers will comply with the contractual terms to earn the discount. We record the discount as an allowance against accounts receivable and a reduction of revenue.

Government Rebates

We participate in certain federal government rebate programs, such as Medicare and Medicaid. We accrue estimated rebates based on estimated percentages of medicine sold to qualified patients, estimated rebate percentages and estimated levels of inventory in the distribution channel that will be sold to qualified patients and record the rebates as a reduction of revenue. Accrued government rebates are included in “accrued trade discounts and rebates” on the consolidated balance sheet.

Government Chargebacks

We provide discounts to federal government qualified entities with whom we have contracted. These federal entities purchase medicines from the wholesale pharmaceutical distributors at a discounted price, and the wholesale pharmaceutical distributors then charge back to us the difference between the current retail price and the contracted price that the federal entities paid for the medicine. We accrue estimated chargebacks based on contract prices and sell-through sales data obtained from third-party information and record the chargeback as a reduction of revenue. Accrued government chargebacks are included in “accrued trade discounts and rebates” on the consolidated balance sheet.

Cost of Goods Sold

We recognize cost of goods sold in connection with our sales of each of our distributed medicines. Cost of goods sold includes all costs directly related to the acquisition of our medicines from our third-party manufacturers, including freight charges and other direct expenses such as insurance and supply chain costs. Cost of goods sold also includes amortization of intellectual property as described in the intangible assets and goodwill accounting policy below, inventory step-up expense, royalty payments to third parties, royalty accretion expense, changes in estimates associated with the contingent royalty liability as described in the accrued contingent royalty accounting policy below and loss on inventory purchase commitments.

Intangible Assets

Definite-lived intangible assets are amortized over their estimated useful lives. We review our intangible assets when events or circumstances may indicate that the carrying value of these assets exceeds their fair value. We measure fair value based on the estimated future discounted cash flows associated with our assets in addition to other assumptions and projections that we deem to be reasonable and supportable. The estimated useful lives, from the date of acquisition, for all identified intangible assets that are subject to amortization are between five and thirteen years.

We determined that no impairment of the above intangible assets existed as of December 31, 2017.

Indefinite-lived intangible assets consist of capitalized IPR&D. IPR&D assets represent capitalized incomplete research projects that we acquired through business combinations. Such assets are initially measured at their acquisition date fair values and are tested for impairment, until completion or abandonment of research and development efforts associated with the projects. An IPR&D asset is considered abandoned when research and development efforts associated with the asset have ceased, and there are no plans to sell or license the asset or derive value from the asset. At that point, the asset is considered to be impaired and is written off. Upon successful completion of each project, we will make a determination about the then remaining useful life of the intangible asset and begin amortization. We test our indefinite-lived intangibles, including IPR&D assets, for impairment annually during the fourth quarter and more frequently if events or changes in circumstances indicate that it is more likely than not that the asset is impaired.

Following an impairment charge recorded in the fourth quarter of 2016, we had no indefinite-lived intangible assets as of December 31, 2017 and 2016.

Business Combinations

We account for business combinations in accordance with the pronouncement guidance in ASC 805, in which acquired assets and liabilities are measured at their respective estimated fair values as of the acquisition date. We may be required, as in the case of intangible assets or contingent royalties, to determine the fair value associated with these amounts by estimating the fair value using an income approach under the discounted cash flow method, which may include revenue projections and other assumptions made by us to determine the fair value. We recorded goodwill of $9.9 million and $186.2 million in connection with our acquisitions of Crealta and Raptor, respectively. Additionally, as part of the Chiesi divestiture, we recorded a reduction to goodwill of $16.3 million.

Goodwill

Goodwill represents the excess of the purchase price of acquired businesses over the estimated fair value of the identifiable net assets acquired. Goodwill is not amortized but is tested for impairment at least annually at the reporting unit level or more frequently if events or changes in circumstances indicate that the asset might be impaired. Impairment loss, if any, is recognized based on a comparison of the fair value of the asset to its carrying value, without consideration of any recoverability. We test goodwill for impairment annually during the fourth quarter and whenever indicators of impairment exist by first assessing qualitative factors to determine whether it is more likely than not that the fair value is less than its carrying amount. If we conclude it is more likely than not that the fair value of a reporting unit is less than its carrying amount, a quantitative impairment test is performed. If we conclude that goodwill is impaired, we will record an impairment charge in our consolidated statement of comprehensive (loss) income. Based upon our most recent annual impairment test performed in the fourth quarter of 2017, we concluded goodwill was not impaired.

Provision for Income Taxes

We account for income taxes based upon an asset and liability approach. Deferred tax assets and liabilities represent the future tax consequences of the differences between the financial statement carrying amounts of assets and liabilities versus the tax basis of assets and liabilities. Under this method, deferred tax assets are recognized for deductible temporary differences, and operating loss and tax credit carryforwards. Deferred tax liabilities are recognized for taxable temporary differences. Deferred tax assets are reduced by a valuation allowance when, in the opinion of management, it is more likely than not that some portion or all of the deferred tax assets will not be realized. The impact of tax rate changes on deferred tax assets and liabilities is recognized in the year that the change is enacted. We also account for the uncertainty in income taxes by utilizing a comprehensive model for the recognition, measurement, presentation and disclosure in financial statements of any uncertain tax positions that have been taken or are expected to be taken on an income tax return. Deferred tax assets and deferred tax liabilities are netted by jurisdiction on our consolidated balance sheets.

On December 22, 2017, the SEC staff issued Staff Accounting Bulletin No. 118, or SAB 118, which provides guidance on accounting for the tax effects of the Tax Act. SAB 118 provides a measurement period that should not extend beyond one year from the date of enactment for companies to complete the accounting under ASC 740, *Income Taxes*. In accordance with SAB 118, we reflect the income tax effects of those aspects of the Tax Act for which the accounting under ASC 740 is complete. To the extent that our accounting for certain income tax effects of the Tax Act is incomplete but we can determine a reasonable estimate, we record a provisional estimate in the consolidated financial statements. As of December 31, 2017, we have not completed our accounting for the effects of the Tax Act. However, we have made reasonable estimates of the effects on our income tax provision with respect to certain items, primarily the revaluation of our existing U.S. deferred tax balances and the write-off of our U.S. deferred tax assets resulting from interest expense carryforwards under Section 163(j)

of the Code. In other cases, we have not been able to make reasonable estimates and continue to account for those items based on our existing accounting under the provisions of the tax laws that were in effect prior to enactment. We recognized a net income tax benefit of $74.9 million for the year ended December 31, 2017, associated with the items we could reasonably estimate; refer to Note 22 of the Notes to consolidated financial statements. This benefit reflects the revaluation of our U.S. net deferred tax liability based on the new U.S. federal tax rate of 21 percent, partially offset by the write-off of the deferred tax asset related to our U.S. interest expense carryforwards. We are still analyzing the Tax Act and refining our calculations and the results of this analysis which could potentially impact the measurement of our income tax balances and income tax expense for the year ended December 31, 2017.

Share-Based Compensation

We account for employee share-based compensation by measuring and recognizing compensation expense for all share-based payments based on estimated grant date fair values. We use the straight-line method to allocate compensation cost to reporting periods over each awardee's requisite service period, which is generally the vesting period. We adopted ASU No. 2016-09 on January 1, 2017 and we have elected to retain a forfeiture rate after adoption.

Accrued Contingent Royalties

Our accrued contingent royalties consist of the contingent royalty obligations assumed by us related to our acquisitions of rights to certain of our medicines. At the time of each acquisition, we assigned a fair value to the liability for royalties. The royalty liability was based on anticipated revenue streams utilizing the income approach under the discounted cash flow method. The estimated liability for royalties is increased or decreased over time to reflect the change in its present value, and accretion expense is recorded as part of cost of goods sold. We evaluate the adequacy of the estimated contingent royalty liability at least annually in the fourth quarter, or whenever events or changes in circumstances indicate that an evaluation of the estimate is necessary. As part of our evaluation, we adjust the carrying value of the liability to the present value of the revised estimated cash flows using the original discount rate.

Any adjustment to the liability is recorded as an increase or reduction in cost of goods sold. The royalty liability is included in current and long-term accrued royalties on the consolidated balance sheets.

New Accounting Pronouncements Impacting Critical Accounting Policies

Refer to Note 2 in the Notes to our consolidated financial statements included in this report, which includes a discussion of the new accounting pronouncements impacting critical accounting policies.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

We are exposed to various market risks, which include potential losses arising from adverse changes in market rates and prices, such as interest rates and foreign exchange fluctuations. We do not enter into derivatives or other financial instruments for trading or speculative purposes.

Interest Rate Risk. We are subject to interest rate fluctuation exposure through our borrowings under the Credit Agreement and our investment in money market accounts which bear a variable interest rate. Loans under the Credit Agreement bear interest, at our option, at a rate equal to either the LIBOR rate, plus an applicable margin of 3.25% per annum (subject to a 1.00% LIBOR floor), or the adjusted base rate plus 2.25%. The adjusted base rate is defined as the greater of (a) LIBOR (using one-month interest period) plus 1%, (b) prime rate, (c) fed funds plus 0.5% and (d) 2%. Our approximately $845.8 million of October 2017 Refinancing Loans are based on LIBOR. The one month LIBOR rate at the date of filing of this Annual Report on Form 10-K is 1.625%, and as a result, the interest rate on our borrowings is currently 4.875% per annum.

An increase in the LIBOR of 100 basis points above the LIBOR rate at the date of filing of this Annual Report on Form 10-K would increase our interest expense related to the Credit Agreement by $8.4 million per year.

The goals of our investment policy are associated with the preservation of capital, fulfillment of liquidity needs and fiduciary control of cash. To achieve our goal of maximizing income without assuming significant market risk, we maintain our excess cash and cash equivalents in money market funds. Because of the short-term maturities of our cash equivalents, we do not believe that a decrease in interest rates would have any material negative impact on the fair value of our cash equivalents.

Foreign Currency Risk. Our purchase cost of ACTIMMUNE and our sales contracts relating to LODOTRA are principally denominated in Euros and are subject to foreign currency risk. We have contracts relating to RAVICTI, QUINSAIR and PROCYSBI for sales in Canada which sales are subject to foreign currency risk. We also incur certain operating expenses in currencies other than the U.S. dollar in relation to our Irish operations and foreign subsidiaries. Therefore, we are subject to volatility in cash flows due to fluctuations in foreign currency exchange rates, particularly changes in the Euro and the Canadian dollar.

Inflation Risk. We do not believe that inflation has had a material impact on our business or results of operations during the periods for which the consolidated financial statements are presented in this report.

Credit Risk. Historically, our accounts receivable balances have been highly concentrated with a select number of customers, consisting primarily of large wholesale pharmaceutical distributors who, in turn, sell the medicines to pharmacies, hospitals and other customers. As of December 31, 2017, and 2016, our top three customers accounted for approximately 79% and 78%, respectively, of our total outstanding accounts receivable balances.

Item 8. Financial Statements and Supplementary Data

The financial information required by Item 8 is contained in Part IV, Item 15 of this Annual Report on Form 10-K.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our Chief Executive Officer and Chief Financial Officer, after evaluating the effectiveness of our "disclosure controls and procedures" (as defined in Rule 13a-15(e) promulgated under the Securities Exchange Act of 1934, as amended, or the Exchange Act), have concluded that, as of December 31, 2017, our disclosure controls and procedures were effective to provide reasonable assurance that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the Securities and Exchange Commission's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by an issuer in the reports that it files or submits under the Exchange Act is accumulated and communicated to the issuer's management, including its principal executive officer or officers and principal financial officer or officers, or persons performing similar functions, as appropriate to allow timely decisions regarding required disclosure.

Management Report on Internal Control over Financial Reporting

Our management, under the supervision of our chief executive officer and our chief financial officer, is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined under Rule 13a-15(f) of the Exchange Act. Internal control over financial reporting is designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate. Therefore, even those systems determined to be effective can provide only reasonable assurance with respect to financial statement preparation and presentation.

Our management has assessed the effectiveness of our internal control over financial reporting as of December 31, 2017. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in *Internal Control – Integrated Framework (2013).* Management's assessment included an evaluation of the design of our internal control over financial reporting and testing of the operational effectiveness of our internal control over financial reporting. Based on management's assessment, management has concluded that, as of December 31, 2017, our internal control over financial reporting was effective based on those criteria.

The effectiveness of our internal control over financial reporting as of December 31, 2017, has been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm, as stated in their report which appears herein.

Changes in Internal Control Over Financial Reporting

During the three months ended December 31, 2017, we implemented a new payroll and human capital management system in the United States. In connection with the implementation, we changed certain processes and procedures which resulted in material changes to our internal controls over financial reporting. While we expect this new system implementation to strengthen our internal controls, management will continue to evaluate and monitor our internal controls as processes and procedures in the affected areas evolve.

There have been no other material changes to our internal control over financial reporting, as defined in Exchange Act Rules 13a-15(f) and 15d-15(f), during the three months ended December 31, 2017, that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The information required by this item is incorporated herein by reference to our definitive Proxy Statement to be filed in connection with our 2018 Annual General Meeting of Shareholders, or our 2018 Proxy Statement, which will be filed with the Securities and Exchange Commission within 120 days after December 31, 2017.

We have adopted a written Code of Business Conduct and Ethics, or Ethics Code, that applies to all officers, directors and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. The Ethics Code is available on our website at www.horizonpharma.com. If we make any substantive amendments to the Ethics Code or grant any waiver from a provision of the Ethics Code to any executive officer or director, we will promptly disclose the nature of the amendment or waiver on our website or in a Current Report on Form 8-K.

Item 11. Executive Compensation

The information required by this item is incorporated herein by reference to our 2018 Proxy Statement.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this item is incorporated herein by reference to our 2018 Proxy Statement.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this item is incorporated herein by reference to our 2018 Proxy Statement.

Item 14. Principal Accounting Fees and Services

The information required by this item is incorporated herein by reference to our 2018 Proxy Statement.

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a) Documents filed as part of this report.

1. Financial Statements

The financial statements listed on the Index to Financial Statements F-1 to F-65 are filed as part of this Annual Report on Form 10-K.

2. Financial Statement Schedules

Schedule II – Valuation and Qualifying Accounts and Reserves for each of the three fiscal years ended December 31, 2017, 2016 and 2015 appearing on page F-66. Other financial statement schedules have been omitted because the required information is included in the consolidated financial statements or notes thereto or because they are not applicable or not required.

3. Exhibits

INDEX TO EXHIBITS

Exhibit Number	Description of Document
2.1	Transaction Agreement and Plan of Merger, dated March 18, 2014, by and among Horizon Pharma, Inc., Vidara Therapeutics Holdings LLC, Vidara Therapeutics International Ltd. (now known as Horizon Pharma Public Limited Company), Hamilton Holdings (USA), Inc. and Hamilton Merger Sub, Inc. (incorporated by reference to Exhibit 2.1 to Horizon Pharma, Inc.'s Current Report on Form 8-K, filed on March 20, 2014).†
2.2	First Amendment to Transaction Agreement and Plan of Merger, dated June 12, 2014, by and between Horizon Pharma, Inc. and Vidara Therapeutics Holdings LLC (incorporated by reference to Exhibit 99.1 to Horizon Pharma, Inc.'s Current Report on Form 8-K, filed on June 18, 2014).
2.3	Agreement and Plan of Merger, dated March 29, 2015, by and among Horizon Pharma, Inc., Ghrian Acquisition Inc. and Hyperion Therapeutics, Inc. (incorporated by reference to Exhibit 2.1 to Horizon Pharma Public Limited Company's Amendment No. 1 to Current Report on Form 8-K, filed on April 9, 2015).†
2.4*	Agreement and Plan of Merger, dated December 10, 2015, by and among Horizon Pharma USA, Inc., HZNP Limited, Criostail LLC, Crealta Holdings LLC and the other parties thereto (incorporated by reference to Exhibit 2.4 to Horizon Pharma Public Limited Company's Amendment No. 1 to Annual Report on Form 10-K, filed on May 26, 2017).††
2.5	Agreement and Plan of Merger, dated September 12, 2016, by and among Horizon Pharma Public Limited Company, Misneach Corporation and Raptor Pharmaceutical Corp. (incorporated by reference to Exhibit 2.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on September 12, 2016).†
3.1	Memorandum and Articles of Association of Horizon Pharma Public Limited Company, as amended (incorporated by reference to Exhibit 3.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on May 4, 2017).
4.1	Indenture, dated March 13, 2015, by and among Horizon Pharma Public Limited Company, Horizon Pharma Investment Limited and U.S. Bank National Association (incorporated by reference to Exhibit 4.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on March 13, 2015).
4.2	Form of 2.50% Exchangeable Senior Note due 2022 (incorporated by reference to Exhibit 4.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on March 13, 2015).
4.3	Indenture, dated April 29, 2015, by and between Horizon Pharma Financing Inc. and U.S. Bank National Association (incorporated by reference to Exhibit 4.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on April 29, 2015).
4.4	Form of 6.625% Senior Note due 2023 (incorporated by reference to Exhibit 4.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on April 29, 2015).

4.5	First Supplemental Indenture, dated May 7, 2015, by and among Horizon Pharma Public Limited Company, certain subsidiaries of Horizon Pharma Public Limited Company and U.S. Bank National Association (incorporated by reference to Exhibit 10.2 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on May 11, 2015).
4.6	Indenture, dated October 25, 2016, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and U.S. Bank National Association, as trustee (incorporated by reference to Exhibit 4.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on October 25, 2016).
4.7	Form of 8.75% Senior Note due 2024 (incorporated by reference to Exhibit 4.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on October 25, 2016).
10.1+	Form of Indemnification Agreement entered into by and between Horizon Pharma Public Limited Company and certain of its directors, officers and employees (incorporated by reference to Exhibit 10.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on September 19, 2014).
10.2+	Form of Indemnification Agreement entered into by and between Horizon Pharma, Inc. and certain directors, officers and employees of Horizon Pharma Public Limited Company (incorporated by reference to Exhibit 10.2 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on September 19, 2014).
10.3+	Horizon Pharma Public Limited Company Non-Employee Director Compensation Policy, as amended (incorporated by reference to Exhibit 10.3 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 29, 2016).
10.4+**	Horizon Pharma, Inc. 2005 Stock Plan and Form of Stock Option Agreement thereunder (incorporated by reference to Exhibit 10.2 to Horizon Pharma, Inc.'s Registration Statement on Form S-1 (No. 333-168504), as amended).
10.5+**	Horizon Pharma, Inc. 2011 Equity Incentive Plan, as amended, and Form of Option Agreement and Form of Stock Option Grant Notice thereunder (incorporated by reference to Exhibit 99.1 to Horizon Pharma, Inc.'s Current Report on Form 8-K, filed on July 2, 2014).
10.6+	Horizon Pharma Public Limited Company 2014 Equity Incentive Plan, as amended, and Form of Option Agreement, Form of Stock Option Grant Notice, Forms of Restricted Stock Unit Agreement and Forms of Restricted Stock Unit Grant Notice thereunder.
10.7+	Horizon Pharma Public Limited Company 2014 Non-Employee Equity Plan, as amended, and Form of Option Agreement, Form of Stock Option Grant Notice, Form of Restricted Stock Unit Agreement and Form of Restricted Stock Unit Grant Notice thereunder (incorporated by reference to Exhibit 99.3 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on May 4, 2016).
10.8+	Horizon Pharma Public Limited Company 2014 Employee Share Purchase Plan, as amended (incorporated by reference to Exhibit 99.2 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on May 4, 2016).
10.9+	Form of Employee Proprietary Information and Inventions Agreement (incorporated by reference to Exhibit 10.15 to Horizon Pharma, Inc.'s Registration Statement on Form S-1 (No. 333-168504), as amended).
10.10+	Amended and Restated Executive Employment Agreement, dated July 27, 2010, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Timothy P. Walbert (incorporated by reference to Exhibit 10.22 to Horizon Pharma, Inc.'s Registration Statement on Form S-1 (No. 333-168504), as amended).
10.11+	Amended and Restated Executive Employment Agreement, dated July 27, 2010, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Jeffrey W. Sherman, M.D. FACP (incorporated by reference to Exhibit 10.24 to Horizon Pharma, Inc.'s Registration Statement on Form S-1 (No. 333-168504), as amended).
10.12*	Manufacturing and Supply Agreement, dated May 25, 2011, by and between Horizon Pharma USA, Inc. and Sanofi-Aventis U.S. LLC (incorporated by reference to Exhibit 10.35 to Horizon Pharma, Inc.'s Registration Statement on Form S-1 (No. 333-168504), as amended).
10.13*	Sales Contract, dated July 1, 2010, by and between Horizon Pharma USA, Inc. and BASF Corporation (incorporated by reference to Exhibit 10.29 to Horizon Pharma, Inc.'s Registration Statement on Form S-1 (No. 333-168504), as amended).

10.14*	Amendment to Manufacturing and Supply Agreement, effective as of September 25, 2013, by and between Horizon Pharma USA, Inc. and Sanofi-Aventis U.S. LLC (incorporated by reference to Exhibit 10.3 to Horizon Pharma, Inc.'s Quarterly Report on Form 10-Q, filed on November 8, 2013).
10.15+	First Amendment to Amended and Restated Executive Employment Agreement, dated January 16, 2014, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Timothy P. Walbert (incorporated by reference to Exhibit 99.1 to Horizon Pharma, Inc.'s Current Report on Form 8-K, filed on January 16, 2014).
10.16+	First Amendment to Amended and Restated Executive Employment Agreement, dated January 16, 2014, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Jeffrey W. Sherman, M.D., FACP (incorporated by reference to Exhibit 99.3 to Horizon Pharma, Inc.'s Current Report on Form 8-K, filed on January 16, 2014).
10.17+	Executive Employment Agreement, effective as of March 5, 2014, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Robert F. Carey (incorporated by reference to Exhibit 10.56 to Horizon Pharma, Inc.'s Annual Report on Form 10-K, filed on March 13, 2014).
10.18+	Executive Employment Agreement, effective as of June 23, 2014, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Paul W. Hoelscher (incorporated by reference to Exhibit 99.4 to Horizon Pharma, Inc.'s Current Report on Form 8-K, filed on June 18, 2014).
10.19*	Supply Agreement, dated October 17, 2014, by and between Horizon Pharma Ireland Limited and Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.) (incorporated by reference to Exhibit 10.57 to Horizon Pharma Public Limited Company's Amendment No. 2 to Annual Report on Form 10-K, filed on April 10, 2015).
10.20	Lease, dated November 4, 2014, by and among Horizon Pharma Public Limited Company, Horizon Pharma Services Limited and John Ronan and Castle Cove Property Developments Limited (incorporated by reference to Exhibit 10.58 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).
10.21*	License Agreement for Interferon Gamma, dated May 5, 1998, by and between Genentech, Inc. and Connetics Corporation (incorporated by reference to Exhibit 10.62 to Horizon Pharma Public Limited Company's Amendment No. 3 to Annual Report on Form 10-K, filed on May 26, 2017).
10.22	Amendment No. 1 to License Agreement for Interferon Gamma, dated December 28, 1998, by and between Genentech, Inc. and Connetics Corporation (incorporated by reference to Exhibit 10.63 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).
10.23*	Amendment No. 2 to License Agreement for Interferon Gamma, dated January 15, 1999, by and between Genentech, Inc. and Connetics Corporation (incorporated by reference to Exhibit 10.64 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).
10.24*	Amendment No. 3 to License Agreement for Interferon Gamma, dated April 27, 1999, by and between Genentech, Inc. and Connetics Corporation (incorporated by reference to Exhibit 10.65 to Horizon Pharma Public Limited Company's Amendment No. 3 to Annual Report on Form 10-K, filed on May 26, 2017).
10.25	Consent to Assignment Agreement, dated June 23, 2000 (Amendment No. 4), by and among Genentech, Inc., Connetics Corporation and InterMune Pharmaceuticals, Inc. (incorporated by reference to Exhibit 10.66 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).
10.26	Amendment No. 5 to License Agreement for Interferon Gamma, dated January 25, 2001, by and between Genentech, Inc. and InterMune Pharmaceuticals, Inc. (incorporated by reference to Exhibit 10.67 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).
10.27*	Amendment No. 6 to License Agreement for Interferon Gamma, dated February 27, 2006, by and between Genentech, Inc. and InterMune, Inc. (incorporated by reference to Exhibit 10.68 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).
10.28*	Amendment No. 7 to License Agreement for Interferon Gamma, dated December 17, 2013, by and between Genentech, Inc. and Vidara Therapeutics International Public Limited Company (incorporated by reference to Exhibit 10.69 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).

10.29+	Executive Employment Agreement, effective as of September 18, 2014, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Barry Moze (incorporated by reference to Exhibit 10.74 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).
10.30+	Horizon Pharma, Inc. Deferred Compensation Plan.
10.31+	Horizon Pharma Public Limited Company Equity Long Term Incentive Program (incorporated by reference to Exhibit 10.2 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on May 8, 2015).
10.32+	Executive Employment Agreement, dated May 7, 2015, by and among Horizon Pharma Inc., Horizon Pharma USA, Inc. and Brian Beeler (incorporated by reference to Exhibit 10.4 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on May 8, 2015).
10.33	Credit Agreement, dated May 7, 2015, by and among Horizon Pharma, Inc., as borrower, Horizon Pharma Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 10.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on May 11, 2015).
10.34*	License Agreement, dated April 16, 1999, by and among Saul Brusilow, M.D., Brusilow Enterprises, Inc. and Medicis Pharmaceutical Corporation (incorporated by reference to Exhibit 10.8 to Horizon Pharma Public Limited Company's Amendment No. 2 to Quarterly Report on Form 10-Q, filed on May 26, 2017).
10.35*	Settlement Agreement and First Amendment to License Agreement, dated August 21, 2007, by and among Saul Brusilow, M.D., Brusilow Enterprises, Inc., Medicis Pharmaceutical Corporation and Ucyclyd Pharma, Inc. (incorporated by reference to Exhibit 10.22 to Hyperion Therapeutics, Inc.'s Amendment No. 1 to the Registration Statement on Form S-1, filed on May 24, 2012).
10.36+	Horizon Pharma Public Limited Company Share Clog Program Trust Deed, as amended, and Form of Clog Letter (incorporated by reference to Exhibit 10.6 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on August 8, 2016).
10.37+	Executive Employment Agreement, dated August 6, 2015, by and among Horizon Pharma Inc., Horizon Pharma USA, Inc. and George P. Hampton (incorporated by reference to Exhibit 10.2 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on November 6, 2015).
10.38*	License Agreement, dated August 12, 1998, by and among Mountain View Pharmaceuticals, Inc., Duke University and Crealta Pharmaceuticals LLC (as successor in interest to Bio-Technology General Corporation), as amended November 12, 2001, August 30, 2010, March 12, 2014 and July 16, 2015 (incorporated by reference to Exhibit 10.61 to Horizon Pharma Public Limited Company's Amendment No. 1 to Annual Report on Form 10-K, filed on May 26, 2017).
10.39*	Commercial Supply Agreement, dated March 20, 2007, by and between Crealta Pharmaceuticals LLC (as successor in interest to Savient Pharmaceuticals, Inc.) and Bio-Technology General (Israel) Ltd., as amended September 24, 2007, January 24, 2009, July 1, 2010 and March 21, 2012 (incorporated by reference to Exhibit 10.62 to Horizon Pharma Public Limited Company's Amendment No. 1 to Annual Report on Form 10-K, filed on May 26, 2017).
10.40*	Supply Agreement, dated August 3, 2015, by and between NOF Corporation and Crealta Pharmaceuticals LLC (incorporated by reference to Exhibit 10.63 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 29, 2016).
10.41	Sublease, dated August 21, 2015, by and between Solo Cup Operating Corporation and Horizon Pharma USA, Inc. and Sublease Consent and Recognition Agreement, dated October 2, 2015, by and among Lake Forest Landmark II, LLC, Solo Cup Operating Corporation and Horizon Pharma USA, Inc. (incorporated by reference to Exhibit 10.64 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 29, 2016).
10.42*	Asset Purchase Agreement, dated March 22, 2012, by and between Hyperion Therapeutics, Inc. and Ucyclyd Pharma, Inc. (incorporated by reference to Exhibit 2.1 to Hyperion Therapeutics, Inc.'s Amendment No. 1 to the Registration Statement on Form S-1, filed on May 24, 2012).

10.43*	Amendment No. 1 to Supply Agreement, dated February 4, 2016, by and between Horizon Pharma Ireland Limited and Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.) (incorporated by reference to Exhibit 10.66 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 29, 2016).
10.44*	Commercial Supply Agreement, dated October 16, 2008, by and between Exelead, Inc. (formerly known as Sigma-Tau PharmaSource, Inc. (as successor in interest to Enzon Pharmaceuticals, Inc.)) and Crealta Pharmaceuticals LLC (as successor in interest to Savient Pharmaceuticals, Inc.), as amended October 5, 2009, October 22, 2009 and July 29, 2014 (incorporated by reference to Exhibit 10.68 to Horizon Pharma Public Limited Company's Amendment No. 1 to Annual Report on Form 10-K, filed on May 26, 2017).
10.45*	Fifth Amendment to Commercial Supply Agreement, effective as of August 31, 2016, by and between Horizon Pharma Ireland Limited and Bio-Technology General (Israel) Ltd. (incorporated by reference to Exhibit 10.1 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on November 7, 2016).
10.46	Amendment No. 1, dated October 25, 2016, to Credit Agreement, dated May 7, 2015, by and among Horizon Pharma, Inc., as borrower, Horizon Pharma Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 99.1 to Horizon Pharma Public Limited Company's Amendment No. 1 to Current Report on Form 8-K, filed on October 25, 2016).
10.47*	API Supply Agreement, dated November 3, 2010, by and among Cambrex Profarmaco Milano, Horizon Orphan LLC (as successor in interest to Raptor Therapeutics Inc.) and Horizon Pharma Europe B.V. (as successor in interest to Raptor Pharmaceuticals Europe B.V.), as amended April 9, 2013 (incorporated by reference to Exhibit 10.4 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on November 7, 2016).
10.48*	Manufacturing Services Agreement, dated November 15, 2010, by and among Patheon Pharmaceuticals Inc., Horizon Orphan LLC (as successor in interest to Raptor Therapeutics Inc.) and Horizon Pharma Europe B.V. (as successor in interest to Raptor Pharmaceuticals Europe B.V.), as amended April 5, 2012 and June 21, 2013 (incorporated by reference to Exhibit 10.5 to Horizon Pharma Public Limited Company's Amendment No. 1 to Quarterly Report on Form 10-Q, filed on May 26, 2017).
10.49*	Amendment No. 1 to Sales Contract, effective as of January 1, 2016, by and between Horizon Pharma USA, Inc. and BASF Corporation (incorporated by reference to Exhibit 10.74 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2017).
10.50+	Horizon Pharma Public Limited Company Equity Long Term Incentive Program (incorporated by reference to Exhibit 99.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on January 11, 2018).
10.51+	Horizon Pharma Public Limited Company Cash Incentive Program (incorporated by reference to Exhibit 99.2 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on January 11, 2018).
10.52+	Horizon Pharma Public Limited Company Incentive Compensation Recoupment Policy (incorporated by reference to Exhibit 99.4 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on January 11, 2018).
10.53+	Executive Employment Agreement, effective as of January 4, 2018, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Shao-Lee Lin, M.D., Ph.D.
10.54+	Executive Employment Agreement, effective as of September 11, 2017, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Irina Konstantinovsky (incorporated by reference to Exhibit 10.2 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on November 6, 2017).
10.55+	Executive Employment Agreement, effective as of August 21, 2017, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Eric Mosbrooker (incorporated by reference to Exhibit 10.3 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on November 6, 2017).
10.56	Amendment No. 2, dated March 29, 2017, to Credit Agreement, dated May 7, 2015, by and among Horizon Pharma, Inc., as Borrower, Horizon Pharma USA, Inc., as an Additional Borrower, Horizon Pharma Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 99.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on March 30, 2017).

10.57	Amendment No. 3, dated October 23, 2017, to Credit Agreement, dated May 7, 2015, by and among Horizon Pharma, Inc., as Borrower, Horizon Pharma USA, Inc., as an Additional Borrower, Horizon Pharma Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 99.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on October 23, 2017).
10.58*	Global Supply Agreement, dated June 30, 2017, by and between Horizon Pharma Ireland Limited and Boehringer Ingelheim Biopharmaceuticals GmbH (incorporated by reference to Exhibit 10.3 to Horizon Pharma Public Limited Company's Amendment No. 1 to Quarterly Report on Form 10-Q, filed on September 28, 2017).
10.59*	Amended and Restated License Agreement, dated May 31, 2017, by and between Horizon Orphan LLC and The Regents of the University of California (incorporated by reference to Exhibit 10.4 to Horizon Pharma Public Limited Company's Amendment No. 1 to Quarterly Report on Form 10-Q, filed on September 28, 2017).
10.60+	Executive Employment Agreement, effective as of February 1, 2017, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Vikram Karnani (incorporated by reference to Exhibit 10.5 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2017).
10.61+	Second Amendment to Amended and Restated Executive Employment Agreement, dated May 4, 2017, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Jeffrey W. Sherman, M.D. (incorporated by reference to Exhibit 10.6 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2017).
10.62+	First Amendment to Executive Employment Agreement, dated May 4, 2017, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Paul W. Hoelscher (incorporated by reference to Exhibit 10.7 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2017).
10.63+	First Amendment to Executive Employment Agreement, dated May 4, 2017, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Barry Moze (incorporated by reference to Exhibit 10.8 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2017).
10.64+	First Amendment to Executive Employment Agreement, dated May 4, 2017, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Brian Beeler (incorporated by reference to Exhibit 10.9 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2017).
10.65+	First Amendment to Executive Employment Agreement, dated May 4, 2017, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and George P. Hampton (incorporated by reference to Exhibit 10.11 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2017).
10.66+	First Amendment to Executive Employment Agreement, dated May 4, 2017, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Robert F. Carey (incorporated by reference to Exhibit 10.12 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2017).
10.67+	Second Amendment to Amended and Restated Executive Employment Agreement, dated May 4, 2017, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Timothy P. Walbert (incorporated by reference to Exhibit 10.13 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2017).
10.68+	Executive Employment Agreement, effective as of February 16, 2017, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Michael DesJardin.
10.69+	First Amendment to Executive Employment Agreement, dated May 4, 2017, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Michael DesJardin.
10.70+	Consulting Agreement, effective as of February 1, 2018, by and between Horizon Pharma USA, Inc. and David Happel.
10.71***	Second Amendment to Supply Agreement, dated January 1, 2017, by and between Horizon Pharma Ireland Limited and Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.).
10.72***	Third Amendment to Supply Agreement, dated February 16, 2018, by and between Horizon Pharma Ireland Limited and Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.).

21.1	Subsidiaries of Horizon Pharma Public Limited Company.
23.1	Consent of PricewaterhouseCoopers LLP, independent registered public accounting firm.
24.1	Power of Attorney. Reference is made to the signature page hereto.
31.1	Certification of Principal Executive Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Exchange Act.
31.2	Certification of Principal Financial Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Exchange Act.
32.1	Certification of Principal Executive Officer pursuant to Rule 13a-14(b) or 15d-14(b) of the Exchange Act and 18 U.S.C. Section 1350.
32.2	Certification of Principal Financial Officer pursuant to Rule 13a-14(b) or 15d-14(b) of the Exchange Act and 18 U.S.C. Section 1350.
101.INS	XBRL Instance Document
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	XBRL Taxonomy Extension Label Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document

+ Indicates management contract or compensatory plan.

† Schedules have been omitted pursuant to Item 601(b)(2) of Regulation S-K. Horizon Pharma Public Limited Company undertakes to furnish supplemental copies of any of the omitted schedules upon request by the Securities and Exchange Commission.

†† Schedules have been omitted pursuant to Item 601(b)(2) of Regulation S-K. Horizon Pharma Public Limited Company undertakes to furnish supplemental copies of any of the omitted schedules upon request by the Securities and Exchange Commission; provided, however, that Horizon Pharma Public Limited Company may request confidential treatment pursuant to Rule 24b-2 of the Securities Exchange Act of 1934, as amended, for any schedule so furnished.

* Confidential treatment has been granted with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.

** Indicates an instrument, agreement or compensatory arrangement or plan assumed by Horizon Pharma Public Limited Company in the merger and no longer binding on Horizon Pharma, Inc.

*** Confidential treatment has been requested with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.

Item 16. Form 10-K Summary

None.

HORIZON PHARMA PLC

Index to Consolidated Financial Statements

Report of Independent Registered Public Accounting Firm

To the Board of Directors and Shareholders of Horizon Pharma plc

Opinions on the Financial Statements and Internal Control over Financial Reporting

We have audited the accompanying consolidated balance sheets of Horizon Pharma plc and its subsidiaries (the "Company") as of December 31, 2017 and 2016, and the related consolidated statements of comprehensive (loss) income, shareholders' equity, and cash flows for each of the three years in the period ended December 31, 2017, including the related notes and financial statement schedule listed in the index appearing under Item 15(a)(2) (collectively referred to as the "consolidated financial statements"). We also have audited the Company's internal control over financial reporting as of December 31, 2017, based on criteria established in *Internal Control - Integrated Framework* (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO).

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of the Company as of December 31, 2017 and 2016**,** and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2017 in conformity with accounting principles generally accepted in the United States of America. Also in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2017, based on criteria established in *Internal Control - Integrated Framework* (2013) issued by the COSO.

Basis for Opinions

The Company's management is responsible for these consolidated financial statements, for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting, included in Management's Report on Internal Control over Financial Reporting appearing under Item 9A. Our responsibility is to express opinions on the Company's consolidated financial statements and on the Company's internal control over financial reporting based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) ("PCAOB") and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud, and whether effective internal control over financial reporting was maintained in all material respects.

Our audits of the consolidated financial statements included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audits also included performing such other procedures as we considered necessary in the circumstances. We believe that our audits provide a reasonable basis for our opinions.

Definition and Limitations of Internal Control over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the

company; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ PricewaterhouseCoopers LLP
Chicago, Illinois
February 28, 2018

We have served as the Company's auditor since 2009.

HORIZON PHARMA PLC

CONSOLIDATED BALANCE SHEETS
(In thousands, except share data)

	As of December 31, 2017	As of December 31, 2016
ASSETS		
CURRENT ASSETS:		
Cash and cash equivalents	$ 751,368	$ 509,055
Restricted cash	6,529	7,095
Accounts receivable, net	367,351	305,725
Inventories, net	61,655	174,788
Prepaid expenses and other current assets	43,402	49,619
Total current assets	**1,230,305**	**1,046,282**
Property and equipment, net	20,405	23,484
Developed technology, net	2,443,949	2,767,184
Other intangible assets, net	5,441	6,251
Goodwill	426,441	445,579
Deferred tax assets, net	3,470	911
Other assets	36,081	2,368
Total assets	**$ 4,166,092**	**$ 4,292,059**
LIABILITIES AND SHAREHOLDERS' EQUITY		
CURRENT LIABILITIES:		
Long-term debt—current portion	$ 10,625	$ 7,750
Accounts payable	34,681	52,479
Accrued expenses	137,834	182,765
Accrued trade discounts and rebates	501,753	297,556
Accrued royalties—current portion	65,328	61,981
Deferred revenues—current portion	6,885	3,321
Total current liabilities	**757,106**	**605,852**
LONG-TERM LIABILITIES:		
Exchangeable notes, net	314,384	298,002
Long-term debt, net, net of current	1,576,646	1,501,741
Accrued royalties, net of current	291,185	272,293
Deferred revenues, net of current	9,713	7,763
Deferred tax liabilities, net	157,945	296,568
Other long-term liabilities	68,015	46,061
Total long-term liabilities	**2,417,888**	**2,422,428**
COMMITMENTS AND CONTINGENCIES		
SHAREHOLDERS' EQUITY:		
Ordinary shares, $0.0001 nominal value; 300,000,000 shares authorized; 164,785,083 and 162,004,956 shares issued at December 31, 2017 and December 31, 2016, respectively, and 164,400,717 and 161,620,590 shares outstanding at December 31, 2017 and December 31, 2016, respectively	16	16
Treasury stock, 384,366 ordinary shares at December 31, 2017 and December 31, 2016	(4,585)	(4,585)
Additional paid-in capital	2,248,979	2,119,455
Accumulated other comprehensive loss	(983)	(3,086)
Accumulated deficit	(1,252,329)	(848,021)
Total shareholders' equity	**991,098**	**1,263,779**
Total liabilities and shareholders' equity	**$ 4,166,092**	**$ 4,292,059**

The accompanying notes are an integral part of these consolidated financial statements.

HORIZON PHARMA PLC

CONSOLIDATED STATEMENTS OF COMPREHENSIVE (LOSS) INCOME
(In thousands, except share and per share data)

	For the Years Ended December 31,		
	2017	**2016**	**2015**
Net sales	$ 1,056,231	$ 981,120	$ 757,044
Cost of goods sold	546,275	393,272	219,502
Gross profit	509,956	587,848	537,542
OPERATING EXPENSES:			
Research and development	224,962	60,707	41,865
Selling, general and administrative	677,363	608,308	440,305
Impairment of in-process research and development	—	66,000	—
Total operating expenses	**902,325**	**735,015**	**482,170**
Operating (loss) income	**(392,369)**	**(147,167)**	**55,372**
OTHER EXPENSE, NET:			
Interest expense, net	(126,523)	(86,610)	(69,900)
Foreign exchange loss	(260)	(1,005)	(1,237)
Gain on divestiture	6,267	—	—
Loss on induced conversion of debt and debt extinguishment	(978)	—	(77,624)
Loss on sale of long-term investments	—	—	(29,032)
Other income (expense), net	588	6,697	(10,291)
Total other expense, net	**(120,906)**	**(80,918)**	**(188,084)**
Loss before benefit for income taxes	**(513,275)**	**(228,085)**	**(132,712)**
Benefit for income taxes	(102,749)	(61,251)	(172,244)
Net (loss) income	**$ (410,526)**	**$ (166,834)**	**$ 39,532**
Net (loss) income per ordinary share—basic	$ (2.52)	$ (1.04)	$ 0.27
Weighted average ordinary shares outstanding—basic	163,122,663	160,699,543	148,788,020
Net (loss) income per ordinary share —diluted	(2.52)	(1.04)	0.25
Weighted average ordinary shares outstanding—diluted	163,122,663	160,699,543	155,923,251
OTHER COMPREHENSIVE INCOME (LOSS), NET OF TAX			
Foreign currency translation adjustments	2,067	(302)	1,712
Pension remeasurements	36	(133)	—
Other comprehensive income (loss)	2,103	(435)	1,712
Comprehensive (loss) income	**$ (408,423)**	**$ (167,269)**	**$ 41,244**

The accompanying notes are an integral part of these consolidated financial statements.

HORIZON PHARMA PLC

CONSOLIDATED STATEMENTS OF SHAREHOLDERS' EQUITY
(In thousands, except share data)

	Ordinary Shares		Treasury Stock		Additional Paid-in	Accumulated Other Comprehensive	Accumulated	Total Shareholders'
	Shares	Amount	Shares	Amount	Capital	Loss	Deficit	Equity
Balances at December 31, 2014	124,425,853	$ 13	384,366	$ (4,585)	$ 1,269,858	$ (4,363)	$ (720,719)	$ 540,204
Issuance of ordinary shares	17,652,500	2	—	—	475,683	—	—	475,685
Issuance of ordinary shares in conjunction with vesting of restricted stock units and stock option exercises	1,157,807	—	—	—	5,217	—	—	5,217
Ordinary shares withheld for payment of employees' withholding tax liability	—	—	—	—	(3,024)	—	—	(3,024)
Issuance of ordinary shares in conjunction with inducement of convertible notes (net of the reacquisition of the equity component of $243,984)	11,368,921	1	—	—	57,543	—	—	57,544
Issuance of ordinary shares in conjunction with ESPP purchases	591,277	—	—	—	4,452	—	—	4,452
Share-based compensation	—	—	—	—	83,553	—	—	83,553
Issuance of ordinary shares in conjunction with warrant exercises	4,872,709	—	—	—	18,124	—	—	18,124
Issuance of Exchangeable Senior Notes	—	—	—	—	119,080	—	—	119,080
Deferred tax on Exchangeable Senior Notes	—	—	—	—	(29,770)	—	—	(29,770)
Deferred tax on capped call transactions	—	—	—	—	836	—	—	836
Currency translation adjustment	—	—	—	—	—	1,712	—	1,712
Net income	—	—	—	—	—	—	39,532	39,532
Balances at December 31, 2015	**160,069,067**	**$ 16**	**384,366**	**$ (4,585)**	**$ 2,001,552**	**$ (2,651)**	**$ (681,187)**	**$ 1,313,145**
Issuance of ordinary shares in conjunction with vesting of restricted stock units and stock option exercises	1,245,637	—	—	—	3,875	—	—	3,875
Ordinary shares withheld for payment of employees' withholding tax liability	—	—	—	—	(5,539)	—	—	(5,539)
Issuance of ordinary shares in conjunction with ESPP purchases	513,659	—	—	—	6,540	—	—	6,540
Issuance of ordinary shares in conjunction with PSU vesting	13,584	—	—	—	—	—	—	—
Share-based compensation	—	—	—	—	113,019	—	—	113,019
Issuance of ordinary shares in conjunction with warrant exercises	163,009	—	—	—	8	—	—	8
Currency translation adjustment	—	—	—	—	—	(302)	—	(302)
Pension remeasurements	—	—	—	—	—	(133)	—	(133)
Net loss	—	—	—	—	—	—	(166,834)	(166,834)
Balances at December 31, 2016	**162,004,956**	**$ 16**	**384,366**	**$ (4,585)**	**$ 2,119,455**	**$ (3,086)**	**$ (848,021)**	**$ 1,263,779**
Cumulative effect adjustment from adoption of ASU 2016-09	—	—	—	—	—	—	7,210	7,210
Issuance of ordinary shares in conjunction with vesting of restricted stock units and stock option exercises	1,117,876	—	—	—	2,167	—	—	2,167
Ordinary shares withheld for payment of employees' withholding tax liability	—	—	—	—	(6,533)	—	—	(6,533)
Issuance of ordinary shares in conjunction with ESPP purchases	822,231	—	—	—	7,082	—	—	7,082
Issuance of ordinary shares in conjunction with PSU vesting	25,000	—	—	—	—	—	—	—
Share-based compensation	—	—	—	—	125,019	—	—	125,019
Issuance of ordinary shares in conjunction with warrant exercises	915,020	—	—	—	1,789	—	—	1,789
Shares repurchased	(100,000)	—	—	—	—	—	(992)	(992)
Currency translation adjustment	—	—	—	—	—	2,067	—	2,067
Pension remeasurements	—	—	—	—	—	36	—	36
Net loss	—	—	—	—	—	—	(410,526)	(410,526)
Balances at December 31, 2017	**164,785,083**	**$ 16**	**384,366**	**$ (4,585)**	**$ 2,248,979**	**$ (983)**	**$ (1,252,329)**	**$ 991,098**

The accompanying notes are an integral part of these consolidated financial statements.

HORIZON PHARMA PLC

CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	For the Years Ended December 31,		
	2017	**2016**	**2015**
CASH FLOWS FROM OPERATING ACTIVITIES:			
Net (loss) income	$ (410,526)	$ (166,834)	$ 39,532
Adjustments to reconcile net (loss) income to net cash provided by operating activities:			
Depreciation and amortization expense	283,415	221,837	138,343
Equity-settled share-based compensation	125,019	113,019	83,553
Royalty accretion	51,263	40,616	20,088
Royalty liability remeasurement	21,774	386	21,151
Acquired in-process research and development expense	159,171	—	—
Gain on divestiture	(2,934)	—	—
Deferred income taxes	(132,231)	(65,561)	(180,549)
Loss on induced conversions of debt and debt extinguishment	834	—	21,581
Payments related to term loan refinancing	(3,988)	—	(3,000)
Amortization of debt discount and deferred financing costs	21,619	18,546	18,810
Impairment of non-current asset	22,270	5,260	—
Impairment of in-process research and development	—	66,000	—
Loss on sale of long-term investments	—	—	29,032
Foreign exchange and other adjustments	(1,466)	420	1,495
Changes in operating assets and liabilities:			
Accounts receivable	(61,828)	(67,496)	(124,766)
Inventories	108,371	67,633	12,216
Prepaid expenses and other current assets	5,110	(28,239)	1,014
Accounts payable	(16,521)	32,065	(8,362)
Accrued trade discounts and rebates	205,487	112,381	94,046
Accrued expenses and accrued royalties	(104,819)	13,854	20,169
Deferred revenues	4,468	1,114	1,693
Other non-current assets and liabilities	5,720	4,455	8,120
Net cash provided by operating activities	**280,208**	**369,456**	**194,166**
CASH FLOWS FROM INVESTING ACTIVITIES:			
Payments for acquisitions, net of cash acquired	(167,220)	(1,356,271)	(1,022,361)
Proceeds from divestiture, net of cash divested	69,371	—	—
Purchases of property and equipment	(4,334)	(15,731)	(7,156)
Change in restricted cash	564	(3,879)	(1,122)
Proceeds from liquidation of available-for-sale investments	—	—	64,623
Purchases of long-term investments	—	—	(71,813)
Proceeds from sale of long-term investments	—	—	42,781
Net cash used in investing activities	**(101,619)**	**(1,375,881)**	**(995,048)**
CASH FLOWS FROM FINANCING ACTIVITIES:			
Net proceeds from term loans	1,693,512	364,297	391,506
Repayment of term loans	(1,618,617)	(4,000)	(299,000)
Payment of contingent consideration	(20,000)	—	—
Repurchase of ordinary shares	(992)	—	—
Proceeds from the issuance of ordinary shares in connection with warrant exercises	1,789	8	18,124
Proceeds from the issuance of ordinary shares through an employee stock purchase plan	7,082	6,540	4,452
Proceeds from the issuance of ordinary shares in connection with stock option exercises	2,167	3,875	5,217
Payment of employee withholding taxes relating to share-based awards	(6,533)	(5,539)	(3,024)
Net proceeds from issuance of ordinary shares	—	—	475,685
Net proceeds from issuance of 2024 Senior Notes	—	291,893	—
Net proceeds from issuance of Exchangeable Senior Notes	—	—	387,181
Net proceeds from issuance of 2023 Senior Notes	—	—	462,340
Net cash provided by financing activities	**58,408**	**657,074**	**1,442,481**
Effect of foreign exchange rate changes on cash and cash equivalents	5,316	(1,210)	(790)
Net increase (decrease) in cash and cash equivalents	242,313	(350,561)	640,809
Cash and cash equivalents, beginning of the year	509,055	859,616	218,807
Cash and cash equivalents, end of the year	**$ 751,368**	**$ 509,055**	**$ 859,616**

HORIZON PHARMA PLC

CONSOLIDATED STATEMENTS OF CASH FLOWS (CONTINUED)
(In thousands)

	For the Years Ended December 31,		
	2017	**2016**	**2015**
Supplemental cash flow information:			
Cash paid for interest	$ 113,790	$ 60,817	$ 42,021
Cash paid for income taxes	2,548	22,339	1,880
Cash paid for debt extinguishment	145	—	45,367
Fees paid for debt commitments	—	—	9,000
Cash paid for induced conversions	—	—	10,005
Supplemental non-cash flow information:			
Purchases of acquired in-process research and development included in accounts payable and accrued expenses	12,000	—	—
Purchases of property and equipment included in accounts payable and accrued expenses	—	700	4,940
Conversion of Convertible Senior Notes to ordinary shares	—	—	60,985

The accompanying notes are an integral part of these consolidated financial statements.

NOTE 1 – BASIS OF PRESENTATION

Unless otherwise indicated or the context otherwise requires, references to the "Company", "we", "us" and "our" refer to Horizon Pharma plc and its consolidated subsidiaries, including its predecessor, Horizon Pharma, Inc. ("HPI").

During the years ended December 31, 2017, 2016 and 2015, the Company completed the following acquisitions and divestitures:

- On June 30, 2017, the Company completed its acquisition of certain rights to interferon gamma-1b from Boehringer Ingelheim International GmbH ("Boehringer Ingelheim International") in all territories outside of the United States, Canada and Japan.
- On June 23, 2017, the Company completed the sale of its European subsidiary that owned the marketing rights to PROCYSBI® (cysteamine bitartrate) delayed-release capsules and QUINSAIR™ (levofloxacin inhalation solution) in Europe, the Middle East and Africa ("EMEA") regions (the "Chiesi divestiture") to Chiesi Farmaceutici S.p.A. ("Chiesi").
- On May 8, 2017, the Company completed its acquisition of River Vision Development Corp. ("River Vision"), which added the late development-stage rare disease biologic medicine candidate teprotumumab to the Company's research and development pipeline.
- On October 25, 2016, the Company completed its acquisition of Raptor Pharmaceutical Corp. ("Raptor"), which added the rare disease medicines PROCYSBI and QUINSAIR to the Company's medicine portfolio.
- On January 13, 2016, the Company completed its acquisition of Crealta Holdings LLC ("Crealta"), which added the rare disease medicine KRYSTEXXA® and the primary care medicine MIGERGOT® to the Company's medicine portfolio.
- On May 7, 2015, the Company completed its acquisition of Hyperion Therapeutics, Inc. ("Hyperion"), which added the rare disease medicines RAVICTI® and BUPHENYL® to the Company's medicine portfolio.

The consolidated financial statements presented herein include the results of operations of the acquired Hyperion, Crealta and Raptor businesses from the applicable dates of acquisition. See Note 4 for further details of business acquisitions and divestitures.

Overview

The Company is a biopharmaceutical company focused on researching, developing and commercializing innovative medicines that address unmet treatment needs for rare and rheumatic diseases. By fostering a growing pipeline of medicines in development and exploring all potential uses for currently marketed medicines, the Company strives to make a powerful difference for patients, their caregivers and physicians. The Company markets eleven medicines through its orphan, rheumatology and primary care business units. The Company's marketed medicines are:

Orphan Business Unit
RAVICTI (glycerol phenylbutyrate) Oral Liquid
PROCYSBI (cysteamine bitartrate) delayed-release capsules
ACTIMMUNE® (interferon gamma-1b); marketed as IMUKIN® outside the United States, Canada and Japan
BUPHENYL (sodium phenylbutyrate) Tablets and Powder; marketed as AMMONAPS® in certain European countries and Japan
QUINSAIR (levofloxacin inhalation solution)
Rheumatology Business Unit
KRYSTEXXA (pegloticase)
RAYOS® (prednisone) delayed-release tablets; marketed as LODOTRA® outside the United States
Primary Care Business Unit
PENNSAID® (diclofenac sodium topical solution) 2% w/w ("PENNSAID 2%")
DUEXIS® (ibuprofen/famotidine)
VIMOVO® (naproxen/esomeprazole magnesium)
MIGERGOT (ergotamine tartrate & caffeine suppositories)

The Company is a public limited company formed under the laws of Ireland. The Company operates through a number of international and U.S. subsidiaries with principal business purposes to either perform research and development or manufacturing operations, serve as distributors of the Company's medicines, hold intellectual property assets or provide services and financial support to the Company.

NOTE 2 – SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Basis of Presentation

The accompanying consolidated financial statements have been prepared in accordance with the accounting principles generally accepted in the United States of America ("GAAP").

Certain reclassifications have been made to prior-period financial statements to conform to the 2017 presentation. Beginning in the first quarter of 2017, the Company modified its presentation of certain operating expenses. Previously, the Company presented "general and administrative" expenses as one line item in its consolidated statement of comprehensive income (loss), and "selling and marketing" expenses as another. For the year ended December 31, 2017 and prior-period comparisons, the Company now combines these two line items into one line item, titled "selling, general and administrative" expenses.

Principles of Consolidation

The consolidated financial statements include the Company's accounts and those of its wholly owned subsidiaries. All intercompany accounts and transactions have been eliminated.

Segment Information

The Company has determined that it operates in one operating segment, which focuses on researching, developing and commercializing innovative medicines that address unmet treatment needs. The Company's operating segment is reported in a manner consistent with the internal reporting provided to the chief operating decision maker ("CODM"). The Company's CODM has been identified as its chief executive officer.

U*se of Estimates*

The preparation of the accompanying consolidated financial statements in conformity with GAAP requires management to make certain estimates and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent liabilities at the date of the financial statements and reported amounts of revenues and expenses during the reporting period. Actual results could differ from those estimates.

Foreign Currency Translation and Transactions

The reporting currency of the Company and its subsidiaries is the U.S. dollar.

The U.S. dollar is the functional currency for the Company's Ireland and U.S.-based businesses and the majority of its subsidiaries. The Company has foreign subsidiaries that have the Euro and the Canadian Dollar as their functional currency. Foreign currency-denominated assets and liabilities of these subsidiaries are translated into U.S. dollars based on exchange rates prevailing at the end of the period, revenues and expenses are translated at average exchange rates prevailing during the corresponding period, and shareholders' equity accounts are translated at historical exchange rates as of the date of any equity transaction. The effects of foreign exchange gains and losses arising from the translation of assets and liabilities of those entities where the functional currency is not the U.S. dollar are included as a component of accumulated other comprehensive (loss) income.

Gains and losses resulting from foreign currency transactions are reflected within the Company's results of operations.

Revenue Recognition

Revenue is recognized when all of the following criteria are met: persuasive evidence of an arrangement exists; delivery has occurred or services have been rendered; the price is fixed or determinable; and collectability is reasonably assured. Some of the Company's agreements contain multiple elements and in accordance with these agreements, the Company may be eligible for upfront license fees, marketing or commercial milestones and payment for medicine deliveries.

Revenue From Medicine Deliveries

Revenue from medicine deliveries comprises substantially all of the Company's gross sales. The Company recognizes revenue from the sale of its medicines when delivery has occurred, title has transferred, the selling price is fixed or determinable, collectability is reasonably assured and the Company has no further performance obligations. In addition, revenue is only recognized when the right of return no longer exists (which is the earlier of the medicine being dispensed through patient prescriptions or the expiration of the right of return) or when medicine returns can be reasonably estimated. Due to the Company's ability to reasonably estimate and determine allowances for co-pay and other patient assistance, medicine returns, rebates and discounts based on its own internal data for DUEXIS and RAYOS or data relating to prior sales of its acquired medicines which was received in connection with the acquisition of those medicines, the Company recognizes revenue at the point of sale to wholesale pharmaceutical distributors and pharmacies for all currently distributed medicines.

Revenue From Upfront License Fees

The Company recognizes revenues from the receipt of non-refundable, upfront license fees. In situations where the licensee is able to obtain stand-alone value from the license and no further performance obligations exist on the Company's part, revenues are recognized on the earlier of when payments are received or collection is reasonably assured. Where continuing involvement by the Company is required in the form of technology transfer, medicine manufacturing or technical support, revenues are deferred and recognized over the term of the agreement.

Revenue From Milestone Receipts

Milestone payments are recognized as revenue based on achievement of the associated milestones, as defined in the relevant agreements. Revenue from a milestone achievement is recognized when earned, as evidenced by acknowledgment from the Company's partner, provided that (1) the milestone event is substantive and its achievability was not reasonably assured at the inception of the agreement, (2) the milestone represents the culmination of an earnings process and (3) the milestone payment is non-refundable. If any of these criteria are not met, revenue from the milestone achievement is recognized over the remaining minimum period of the Company's performance obligations under the agreement.

Medicine Sales Discounts and Allowances

The Company records allowances for medicine returns, rebates and discounts at the time of sale to wholesale pharmaceutical distributors and pharmacies. The Company is required to make significant judgments and estimates in determining some of these allowances. If actual results differ from its estimates, the Company will be required to make adjustments to these allowances in the future. Medicine returns and discounts are included in "accounts receivable" on the consolidated balance sheet. Accrued rebates are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Commercial Rebates

The Company participates in certain commercial rebate programs. Under these rebate programs, the Company pays a rebate to the commercial entity or third-party administrator of the program. The Company accrues estimated rebates based on contract prices, estimated percentages of medicine sold to qualified patients and estimated levels of inventory in the distribution channel and records the rebate as a reduction of revenue. Accrued commercial rebates are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Distribution Service Fees

The Company includes distribution service fees paid to its wholesalers for distribution and inventory management services as a reduction to revenue. The Company accrues estimated distribution fees based on contractually determined amounts, typically as a percentage of revenue. Accrued distribution service fees are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Patient Access Programs

The Company offers discount card and other programs such as its HorizonCares program to patients under which the patient receives a discount on his or her prescription. In certain circumstances when a patient's prescription is rejected by a managed care vendor, the Company will pay for the full cost of the prescription. The Company reimburses pharmacies for this discount through third-party vendors. The Company reduces gross sales by the amount of actual co-pay and other patient assistance in the period based on the invoices received. The Company also records an accrual to reduce gross sales for estimated co-pay and other patient assistance on units sold to distributors that have not yet been prescribed/dispensed to a patient. The estimate is based on contract prices, estimated percentages of medicine that will be prescribed to qualified patients, average assistance paid based on reporting from the third-party vendors and estimated levels of inventory in the distribution channel. Accrued co-pay and other patient assistance fees are included in "accrued trade discounts and rebates" on the consolidated balance sheet. Patient assistance programs include both co-pay assistance and fully bought down prescriptions.

Sales Returns

Consistent with industry practice, the Company maintains a return policy that allows customers to return medicine within a specified period prior to and subsequent to the medicine expiration date. Generally, medicine may be returned for a period beginning six months prior to its expiration date and up to one year after its expiration date. The right of return expires on the earlier of one year after the medicine expiration date or the time that the medicine is dispensed to the patient. The majority of medicine returns result from medicine dating, which falls within the range set by the Company's policy, and are settled through the issuance of a credit to the customer. The estimate of the provision for returns is based upon the Company's historical experience with actual returns, which is applied to the level of sales for the period that corresponds to the period during which the customer may return medicines. This period is known to the Company based on the shelf life of medicines at the time of shipment. The Company records sales returns as an allowance against accounts receivable and a reduction of revenue.

Prompt Pay Discounts

As an incentive for prompt payment, the Company offers a 2% cash discount to customers. The Company expects that all customers will comply with the contractual terms to earn the discount. The Company records the discount as an allowance against accounts receivable and a reduction of revenue.

Government Rebates

The Company participates in certain federal government rebate programs, such as Medicare and Medicaid. The Company accrues estimated rebates based on percentages of medicine sold to qualified patients, estimated rebate percentages and estimated levels of inventory in the distribution channel that will be sold to qualified patients and records the rebates as a reduction of revenue. Accrued government rebates are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Government Chargebacks

The Company provides discounts to federal government qualified entities with whom the Company has contracted. These federal entities purchase medicines from the wholesale pharmaceutical distributors at a discounted price, and the wholesale pharmaceutical distributors then charge back to the Company the difference between the current retail price and the contracted price that the federal entities paid for the medicines. The Company accrues estimated chargebacks based on contract prices and sell-through sales data obtained from third-party information and records the chargeback as a reduction of revenue. Accrued government chargebacks are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Bad Debt Expense

The Company's medicines are sold to wholesale pharmaceutical distributors and pharmacies. The Company monitors its accounts receivable balances to determine the impact, if any, of such factors as changes in customer concentration, credit risk and the realizability of its accounts receivable, and records a bad debt reserve when applicable.

Inventories

Inventories are stated at the lower of cost or market value, using the first-in, first-out convention. Inventories consist of raw materials, work-in-process and finished goods. The Company has entered into manufacturing and supply agreements for the manufacture or purchase of raw materials and production supplies. The Company's inventories include the direct purchase cost of materials and supplies and manufacturing overhead costs. The Company reviews its inventory balance and purchase obligations to assess if it has obsolete or excess inventory and records a charge to "cost of goods sold" when applicable.

Inventories acquired in business combinations are recorded at their estimated fair values. "Step-up" represents the write-up of inventory from the lower of cost or market value (the historical book value as previously recorded on the acquired company's balance sheet) to fair market value at the acquisition date. Inventory step-up expense is recorded in the consolidated statement of comprehensive (loss) income based on actual sales, or usage, using the first-in, first-out convention.

Inventories exclude medicine sample inventory, which is included in other current assets and is expensed as a component of "selling, general and administrative" expense when shipped to sales representatives.

Cost of Goods Sold

The Company recognizes cost of goods sold in connection with its sales of each of its distributed medicines. Cost of goods sold includes all costs directly related to the acquisition of the Company's medicines from its third-party manufacturers, including freight charges and other direct expenses such as insurance and supply chain costs. Cost of goods sold also includes amortization of intellectual property as described in the intangible assets accounting policy below, inventory step-up expense, drug substance harmonization costs, share-based compensation, charges relating to discontinuation of clinical trials, royalty payments to third parties, royalty accretion expense, changes in estimates associated with the contingent royalty liability as described in the accrued contingent royalty accounting policy below and loss on inventory purchase commitments.

Pre-clinical Studies and Clinical Trial Accruals

The Company's pre-clinical studies and clinical trials have historically been conducted by third-party contract research organizations and other vendors. Pre-clinical study and clinical trial expenses are based on the services received from these contract research organizations and vendors. Payments depend on factors such as the milestones accomplished, successful enrollment of certain numbers of patients and site initiation. In accruing service fees, the Company estimates the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from the estimate, the Company adjusts the accrual accordingly.

Net (Loss) Income Per Share

Basic net (loss) income per share is computed by dividing net (loss) income by the weighted-average number of ordinary shares outstanding during the period. Diluted earnings per share ("EPS") reflects the potential dilution beyond shares for basic EPS that could occur if securities or other contracts to issue ordinary shares were exercised, converted into ordinary shares, or resulted in the issuance of ordinary shares that would have shared in the Company's earnings.

Cash and Cash Equivalents

The Company considers all highly liquid investments, readily convertible to cash, that mature within three months or less from date of purchase to be cash equivalents. Cash and cash equivalents primarily consist of cash balances and money market funds. The Company generally invests excess cash in money market funds and other financial instruments with short-term durations, based upon operating requirements.

Restricted Cash

Restricted cash consists primarily of balances in interest-bearing money market accounts required by a vendor for the Company's sponsored employee business credit card program and collateral for a letter of credit.

Fair Value of Financial Instruments

The carrying amounts of the Company's financial instruments, including cash and cash equivalents, restricted cash, accounts receivable, accounts payable and accrued expenses, approximate their fair values due to their short maturities.

Business Combinations

The Company accounts for business combinations in accordance with the guidance in Accounting Standards Codification Topic 805, *Business Combinations* ("ASC 805") in which acquired assets and liabilities are measured at their respective estimated fair values as of the acquisition date. The Company may be required, as in the case of intangible assets, contingent royalties or derivatives, to determine the fair value associated with these amounts by estimating the fair value using an income approach under the discounted cash flow method, which may include revenue projections and other assumptions made by the Company to determine the fair value.

Provision for Income Taxes

The Company accounts for income taxes based upon an asset and liability approach. Deferred tax assets and liabilities represent the future tax consequences of the differences between the financial statement carrying amounts of assets and liabilities versus the tax basis of assets and liabilities. Under this method, deferred tax assets are recognized for deductible temporary differences, and operating loss and tax credit carryforwards. Deferred tax liabilities are recognized for taxable temporary differences. Deferred tax assets are reduced by a valuation allowance when, in the opinion of management, it is more likely than not that some portion or all of the deferred tax assets will not be realized. The impact of tax rate changes on deferred tax assets and liabilities is recognized in the year that the change is enacted. The Company also accounts for the uncertainty in income taxes by utilizing a comprehensive model for the recognition, measurement, presentation and disclosure in financial statements of any uncertain tax positions that have been taken or are expected to be taken on an income tax return. Deferred tax assets and deferred tax liabilities are netted by jurisdiction on the Company's consolidated balance sheets.

On December 22, 2017, the SEC staff issued Staff Accounting Bulletin No. 118 ("SAB 118") which provides guidance on accounting for the tax effects of the U.S. H.R. 1, "An Act to provide for reconciliation pursuant to titles II and V of the concurrent resolution on the budget for fiscal year 2018", informally titled the Tax Cuts and Jobs Act ("the Tax Act"). SAB 118 provides a measurement period that should not extend beyond one year from the date of enactment for companies to complete the accounting under ASC Topic 740, *Income Taxes*. In accordance with SAB 118, the Company reflects the income tax effects of those aspects of the Tax Act for which the accounting under ASC 740 is complete. To the extent that the Company's accounting for certain income tax effects of the Tax Act is incomplete but it is able to determine a reasonable estimate, the Company records a provisional estimate in the consolidated financial statements. As of December 31, 2017, the Company has not completed its accounting for the effects of the Tax Act. However, the Company has made reasonable estimates of the effects on its income tax provision with respect to certain items, primarily the revaluation of its existing U.S. deferred tax balances and the write-off of its U.S. deferred tax assets resulting from interest expense carryforwards under Section 163(j) of the Internal Revenue Code. In other cases, the Company has not been able to make reasonable estimates and continues to account for those items based on its existing accounting under the provisions of the tax laws that were in effect prior to enactment of the Tax Act. As described in Note 22, the Company recognized a net income tax benefit of $74.9 million for the year ended December 31, 2017, associated with the items the Company could reasonably estimate. This benefit reflects the revaluation of its U.S. net deferred tax liability based on the new U.S. federal tax rate of 21 percent, partially offset by the write-off of the deferred tax asset related to its U.S. interest expense carryforwards. The Company is still analyzing the Tax Act and refining its calculations and the results of this analysis could potentially impact the measurement of its income tax balances and income tax expense for the year ended December 31, 2017.

Property and Equipment, Net

Property and equipment are stated at cost less accumulated depreciation. Depreciation is recognized using the straight-line method over the estimated useful lives of the related assets for financial reporting purposes and an accelerated method for income tax reporting purposes. Upon retirement or sale of an asset, the cost and related accumulated depreciation and amortization are removed from the balance sheet and the resulting gain or loss is reflected in operations. Repair and maintenance costs are charged to expenses as incurred and improvements are capitalized.

Leasehold improvements are amortized on a straight-line basis over the term of the applicable lease, or the useful life of the assets, whichever is shorter.

Depreciation and amortization periods for the Company's property and equipment are as follows:

Machinery and equipment	5 to 7 years
Furniture and fixtures	3 to 5 years
Computer equipment	3 years
Software	3 years
Trade show equipment	3 years

The Company capitalizes software development costs associated with internal use software, including external direct costs of materials and services and payroll costs for employees devoting time to a software project. Costs incurred during the preliminary project stage, as well as costs for maintenance and training, are expensed as incurred.

Software includes internal-use software acquired and modified to meet the Company's internal requirements. Amortization commences when the software is ready for its intended use.

Intangible Assets

Definite-lived intangible assets are amortized over their estimated useful lives. The Company reviews its intangible assets when events or circumstances may indicate that the carrying value of these assets exceeds their fair value. The Company measures fair value based on the estimated future discounted cash flows associated with these assets in addition to other assumptions and projections that the Company deems to be reasonable and supportable. The estimated useful lives, from the date of acquisition, for all identified intangible assets that are subject to amortization are between five and thirteen years.

The Company determined that no impairment of its definite-lived intangible assets existed as of December 31, 2017.

Indefinite-lived intangible assets consist of capitalized in-process research and development ("IPR&D"). IPR&D assets represent capitalized incomplete research projects that the Company acquired through business combinations. Such assets are initially measured at their acquisition date fair values and are tested for impairment, until completion or abandonment of research and development efforts associated with the projects. An IPR&D asset is considered abandoned when research and development efforts associated with the asset have ceased, and there are no plans to sell or license the asset or derive value from the asset. At that point, the asset is considered to be impaired and is written off. Upon successful completion of each project, the Company will make a determination about the then remaining useful life of the intangible asset and begin amortization. The Company tests its indefinite-lived intangible assets, including IPR&D assets, for impairment annually during the fourth quarter and more frequently if events or changes in circumstances indicate that it is more likely than not that the asset is impaired.

Following an impairment charge recorded in the fourth quarter of 2016, the Company had no indefinite-lived intangible assets as of December 31, 2017 and 2016. See Note 8 for further details of the impairment charge.

Goodwill

Goodwill represents the excess of the purchase price of acquired businesses over the estimated fair value of the identifiable net assets acquired. Goodwill is not amortized but is tested for impairment at least annually at the reporting unit level or more frequently if events or changes in circumstances indicate that the asset might be impaired. Impairment loss, if any, is recognized based on a comparison of the fair value of the asset to its carrying value, without consideration of any recoverability. The Company tests goodwill for impairment annually during the fourth quarter and whenever indicators of impairment exist by first assessing qualitative factors to determine whether it is more likely than not that the fair value is less than its carrying amount. If the Company concludes it is more likely than not that the fair value of a reporting unit is less than its carrying amount, a quantitative impairment test is performed. If the Company concludes that goodwill is impaired, it will record an impairment charge in its consolidated statement of comprehensive (loss) income. Based upon the Company's most recent annual impairment test performed in the fourth quarter of 2017, the Company concluded goodwill was not impaired.

Research and Development Expenses

Research and development expenses include, but are not limited to, payroll and other personnel expenses, consultant expenses, expenses incurred under agreements with contract research organizations to conduct clinical trials, expenses incurred to manufacture clinical trial materials and acquired in-process research and development assets recorded to research and development expense. Research and development expenses were $225.0 million, $60.7 million and $41.9 million for the years ended December 31, 2017, 2016 and 2015, respectively.

Advertising Expenses

We expense the costs of advertising as incurred. Advertising expenses were $19.2 million, $14.4 million and $6.1 million for the years ended December 31, 2017, 2016 and 2015, respectively.

Deferred Financing Costs

Costs incurred in connection with debt financings have been capitalized to "Long-term debt, net, net of current" and "Exchangeable notes, net" in the Company's consolidated balance sheets as deferred financing costs, and are charged to interest expense using the effective interest method over the terms of the related debt agreements. These costs include document preparation costs, commissions, fees and expenses of investment bankers and underwriters, and accounting and legal fees.

Concentration of Credit Risk and Other Risks and Uncertainties

Financial instruments that may potentially subject the Company to significant concentrations of credit risk consist of cash and cash equivalents. The Company's cash and cash equivalents are invested primarily in money market funds and bank deposits in the United States, Bermuda, Ireland, Switzerland, Luxembourg, Germany, the United Kingdom and Canada that management believes are creditworthy. At times, deposits in these banks may exceed the amount of insurance provided on such deposits. To date, the Company has not experienced any losses on its investments of cash and cash equivalents.

The purchase cost of ACTIMMUNE under a contract with Boehringer Ingelheim RCV GmbH & Co. KG ("Boehringer Ingelheim") as well as sales contracts relating to LODOTRA and QUINSAIR, and sales of RAVICTI and PROCYSBI outside the United States, are principally denominated in Euros or the Canadian dollar and are subject to foreign currency risk. The Company also incurs certain operating expenses in currencies other than the U.S. dollar in relation to its operations and foreign subsidiaries in Ireland, Switzerland, Germany and Canada. The Company does not currently utilize and has not in the past utilized any foreign currency hedging strategies to mitigate the effect of its foreign currency exchange rate risk.

Historically, the Company's accounts receivable balances have been highly concentrated with a select number of customers, consisting primarily of large wholesale pharmaceutical distributors who, in turn, sell the medicines to pharmacies, hospitals and other customers. As of December 31, 2017 and 2016, the Company's top three customers accounted for approximately 79% and 78%, respectively, of the Company's total outstanding accounts receivable balances.

The Company depends on single-source suppliers and manufacturers for certain of its medicines, medicine candidates and their active pharmaceutical ingredients.

Comprehensive (Loss) Income

Comprehensive (loss) income is composed of net (loss) income and other comprehensive (loss) income ("OCI"). OCI includes certain changes in shareholders' equity that are excluded from net (loss) income, which consist of foreign currency translation adjustments and pension remeasurements. The Company reports the effect of significant reclassifications out of accumulated OCI on the respective line items in net income if the amount being reclassified is required under GAAP to be reclassified in its entirety to net income. For other amounts that are not required under GAAP to be reclassified in their entirety to net income in the same reporting period, the Company cross-references other disclosures required under GAAP that provide additional detail about those amounts.

Share-Based Compensation

The Company accounts for employee share-based compensation by measuring and recognizing compensation expense for all share-based payments based on estimated grant date fair values. The Company uses the straight-line method to allocate compensation cost to reporting periods over each awardee's requisite service period, which is generally the vesting period. The Company adopted ASU No. 2016-09, *Improvements to Employee Share-Based Payment Accounting* ("ASU No. 2016-09") on January 1, 2017 and has elected to retain a forfeiture rate after adoption.

Accrued Contingent Royalties

The Company's accrued contingent royalties consist of the contingent royalty obligations assumed by the Company related to the Company's acquisitions of rights to certain of its medicines. At the time of each acquisition, the Company assigned an estimated fair value to its contingent liability for royalties. The estimated royalty liability is based on anticipated revenue streams utilizing the income approach under the discounted cash flow method. The estimated liability for royalties is increased or decreased over time to reflect the change in its present value and accretion expense is recorded as part of cost of goods sold. The Company evaluates the adequacy of the estimated contingent royalty liability at least annually in the fourth quarter, or whenever events or changes in circumstances indicate that an evaluation of the estimate is necessary. As part of its evaluation, the Company adjusts the carrying value of the liability to the present value of the revised estimated cash flows using the original discount rate. Any adjustment to the liability is recorded as an increase or reduction in cost of goods sold. The royalty liability is included in current and long-term accrued royalties on the consolidated balance sheets.

Contingencies

From time to time, the Company may become involved in claims and other legal matters arising in the ordinary course of business. The Company records accruals for loss contingencies to the extent that it concludes that it is probable that a liability has been incurred and the amount of the related loss can be reasonably estimated. Legal fees and other expenses related to litigation are expensed as incurred and included in "selling, general and administrative" expenses.

Recent Accounting Pronouncements

From time to time, the Company adopts new accounting pronouncements issued by the Financial Accounting Standards Board ("FASB") or other standard-setting bodies.

Effective January 1, 2017, the Company elected to early adopt ASU No. 2017-01, *Business Combinations (Topic 805): Clarifying the Definition of a Business* ("ASU No. 2017-01"). The amendments in ASU No. 2017-01 clarify the definition of a business with the objective of adding guidance to assist entities with evaluating whether transactions should be accounted for as acquisitions (or disposals) of assets or businesses. The definition of a business affects many areas of accounting including acquisitions, disposals, goodwill and consolidation. The impact of the adoption of ASU No. 2017-01 is further described in Note 4.

Effective January 1, 2017, the Company adopted ASU No. 2016-09. The update requires excess tax benefits and tax deficiencies, which arise due to differences between the measure of compensation expense and the amount deductible for tax purposes, to be recorded directly through earnings as a component of income tax expense. Previously, these differences were generally recorded in additional paid-in capital and thus had no impact on net income. The change in treatment of excess tax benefits and tax deficiencies also impacts the computation of diluted earnings per share, and the cash flows associated with those items are classified as operating activities on the consolidated statements of cash flows. Additionally, ASU No. 2016-09 permits entities to make an accounting policy election for the impact of forfeitures on the recognition of expense for share-based payment awards. Forfeitures can be estimated, as allowed under previous standards, or recognized when they occur. As a result of the adoption, $7.2 million of excess tax benefits that had not previously been recognized, as the related tax deduction had not reduced current taxes payable, were recorded on a modified retrospective basis through a cumulative effect adjustment to its accumulated deficit as of January 1, 2017. During the year ended December 31, 2017, the Company recognized an excess tax deficiency in earnings of $2.8 million. The Company elected not to change its policy on accounting for forfeitures and continues to estimate a requisite forfeiture rate. Additional amendments to the accounting for income taxes and minimum statutory withholding requirements had no impact on the Company's results of operations and related disclosures.

In May 2014, the FASB issued ASU No. 2014-09, *Revenue from Contracts with Customers* ("ASU No. 2014-09"). The new standard aims to achieve a consistent application of revenue recognition within the United States, resulting in a single revenue model to be applied by reporting companies under GAAP. Under the new model, recognition of revenue occurs when a customer obtains control of promised goods or services in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. In addition, the new standard requires that reporting companies disclose the nature, amount, timing and uncertainty of revenue and cash flows arising from contracts with customers. The new standard is required to be applied retrospectively to each prior reporting period presented or modified retrospectively with the cumulative effect of initially applying it recognized at the date of initial application. The new standard is effective for the Company as of January 1, 2018, and the Company expects to elect to utilize the modified retrospective method. The performance obligations identified by the Company under ASC Topic 606*, Revenue From Contracts With Customers,* are similar to the unit of account and performance obligation determination under ASC Topic 605*, Revenue Recognition.* Based on its review of current customer contracts, the Company's assessment was that the implementation of this guidance did not have a material impact on its consolidated financial statements as the timing of revenue recognition for its primary revenue stream, product sales, is not expected to significantly change. Certain of the Company's contracts for sales outside the United States include contingent amounts of variable consideration that the Company was precluded from recognizing because of the requirement for amounts to be "fixed or determinable". As such, the Company assessed that the new standard required a cumulative-effect adjustment of certain deferred revenues that were originally expected to be recognized in the future. Upon adoption, the Company expects to reclassify approximately $11.0 million of deferred revenue directly to retained earnings.

In October 2016, the FASB issued ASU No. 2016-16, *Income Taxes (Topic 740): Intra-Entity Transfers of Assets Other Than Inventory* ("ASU No. 2016-16"). ASU No. 2016-16 was issued to improve the accounting for the income tax consequences of intra-entity transfers of assets other than inventory. Current GAAP prohibits the recognition of current and deferred income taxes for an intra-entity asset transfer until the asset has been sold to an outside party which has resulted in diversity in practice and increased complexity within financial reporting. ASU No. 2016-16 requires an entity to recognize the income tax consequences of an intra-entity transfer of an asset other than inventory when the transfer occurs and does not require new disclosures. ASU No. 2016-16 is effective for annual reporting periods beginning after December 15, 2017, and interim periods within those annual periods. The new standard is effective for the Company as of January 1, 2018, and the adoption of ASU No. 2016-16 is expected to be applied on a modified retrospective basis through a cumulative-effect adjustment directly to retained earnings as of the beginning of the period of adoption. Upon adoption, the Company expects to reclassify approximately $9.0 million of deferred tax assets directly to retained earnings.

In May 2017, the FASB issued ASU No. 2017-09, *Compensation-Stock Compensation (Topic 718): Scope of Modification Accounting* ("ASU No. 2017-09"). The amendment amends the scope of modification accounting for share-based payment arrangements, provides guidance on the types of changes to the terms or conditions of share-based payment awards to which an entity would be required to apply modification accounting under ASC Topic 718, *Compensation- Stock Compensation*. The ASU is effective for annual reporting periods, including interim periods within those annual reporting periods, beginning after December 15, 2017. The Company will account for future modification under this guidance.

In February 2017, the FASB issued ASU No. 2017-05, ("*Subtopic 610-20*"), *Other Income - Gains and Losses from the Derecognition of Nonfinancial Assets* ("ASU No. 2017-05") which provides clarification regarding the scope of the asset derecognition guidance and accounting for partial sales of nonfinancial assets. The update defines an in-substance nonfinancial asset and clarifies that an entity should identify each distinct nonfinancial asset or in-substance nonfinancial asset promised to a counterparty and derecognize each asset when a counterparty obtains control of it. All businesses and nonprofit activities within the scope of Subtopic 610-20 are excluded from the amendments in this update. This guidance will be effective for annual and interim periods beginning after December 15, 2017 and is required to be applied at the same time as ASU No. 2014-09 (described below) is applied. The guidance can be applied using one of two methods: retrospectively to each prior reporting period presented or modified retrospectively with the cumulative effect of initially applying the guidance recognized against retained earnings as of the beginning of the fiscal year of adoption. The Company does not expect the adoption of ASU No. 2017-05 to have a material impact on the Company's consolidated financial statements and related disclosures.

In February 2018, the FASB issued ASU No. 2018-02, *Reclassification of Certain Tax Effects from Accumulated Other Comprehensive Income (Topic 220),* ("ASU No. 2018-02"), which permits a company to reclassify the income tax effects of the Tax Act on items within other comprehensive income ("OCI") to retained earnings. ASU No. 2018-02 requires certain new disclosures, some of which are applicable for all companies and is effective for fiscal years beginning after December 15, 2018, and interim periods during those fiscal years. The guidance can be applied using one of two transition methods, retrospectively to each period or periods in which the income tax effects of the Tax Act related to items remaining in OCI are recognized, or at the beginning of the period of adoption. The Company is currently evaluating the impact of adoption of ASU No. 2018-02 on its consolidated financial statements and related disclosures.

In November 2016, the FASB issued ASU No. 2016-18, *Statement of Cash Flows (Topic 230): Restricted Cash* ("ASU No. 2016-18"), which addresses diversity in practice related to the classification and presentation of changes in restricted cash on the statement of cash flows. ASU No. 2016-18 requires that a statement of cash flows explain the change during the period in the total of cash, cash equivalents and amounts generally described as restricted cash or restricted cash equivalents. Therefore, amounts generally described as restricted cash and restricted cash equivalents should be included with cash and cash equivalents when reconciling the beginning-of-period and end-of-period total amounts shown on the statement of cash flows. ASU No. 2016-18 is effective for fiscal years, and interim periods within those years, beginning after December 15, 2017. The Company does not expect the adoption of ASU No. 2016-18 to have a material impact on the Company's consolidated financial statements and related disclosures.

In August 2016, the FASB issued ASU No. 2016-15, *Statement of Cash Flows (Topic 230): Classification of Certain Cash Receipts and Cash Payments* ("ASU No. 2016-15"). The amendments in this ASU provide guidance on the following eight specific cash flow classification issues: (1) debt prepayment or debt extinguishment costs; (2) settlement of zero-coupon debt instruments or other debt instruments with coupon interest rates that are insignificant in relation to the effective interest rate of the borrowing; (3) contingent consideration payments made after a business combination; (4) proceeds from the settlement of insurance claims; (5) proceeds from the settlement of corporate-owned life insurance policies, including bank-owned life insurance policies; (6) distributions received from equity method investees; (7) beneficial interests in securitization transactions; and (8) separately identifiable cash flows and application of the predominance principle. Current GAAP does not include specific guidance on these eight cash flow classification issues. The amendments in ASU No. 2016-15 are effective for reporting periods beginning after December 15, 2017. The Company does not expect the adoption of ASU No. 2016-15 to have a material impact on the Company's consolidated financial statements and related disclosures.

In February 2016, the FASB issued ASU No. 2016-02, *Leases (Topic 842)* ("ASU No. 2016-02"). Under ASU No. 2016-02, an entity will be required to recognize right-of-use assets and lease liabilities on its balance sheet and disclose key information about leasing arrangements. ASU No. 2016-02 offers specific accounting guidance for a lessee, a lessor and sale and leaseback transactions. Lessees and lessors are required to disclose qualitative and quantitative information about leasing arrangements to enable a user of the financial statements to assess the amount, timing and uncertainty of cash flows arising from leases. ASU No. 2016-02 is effective for annual reporting periods beginning after December 15, 2018, including interim periods within that reporting period, with early adoption permitted. The Company is currently in the process of evaluating the impact of adoption of ASU No. 2016-02 on its consolidated financial statements and related disclosures.

In January 2017, the FASB issued ASU No. 2017-04, *Intangibles - Goodwill and Other (Topic 350): Simplifying the Test for Goodwill Impairment* ("ASU No. 2017-04"), to eliminate the second step of the goodwill impairment test. ASU No. 2017-04 requires an entity to measure a goodwill impairment loss as the amount by which the carrying value of a reporting unit exceeds its fair value. Additionally, an entity should include the income tax effects from any tax deductible goodwill on the carrying value of the reporting unit when measuring a goodwill impairment loss, if applicable. ASU No. 2017-04 is effective for fiscal years beginning after December 15, 2019 and interim periods within those years. Early adoption is permitted for interim or annual goodwill impairment tests performed on testing dates after January 1, 2017. The Company does not expect the adoption of ASU No. 2017-04 to have a material impact on the Company's consolidated financial statements and related disclosures.

Other recent authoritative guidance issued by the FASB (including technical corrections to the Accounting Standards Codification), the American Institute of Certified Public Accountants, and the Securities and Exchange Commission did not, or are not expected to, have a material impact on the Company's consolidated financial statements and related disclosures.

NOTE 3 – NET (LOSS) INCOME PER SHARE

The following table presents basic net (loss) income per share for the years ended December 31, 2017, 2016 and 2015 (in thousands, except share and per share data):

	For the Years Ended December 31,		
	2017	2016	2015
Basic earnings per share calculation:			
Net (loss) income	$ (410,526)	$ (166,834)	$ 39,532
Weighted average of ordinary shares outstanding	163,122,663	160,699,543	148,788,020
Basic net (loss) income per share	**$ (2.52)**	**$ (1.04)**	**$ 0.27**

The following table presents diluted net (loss) income per share for the years ended December 31, 2017, 2016 and 2015 (in thousands, except share and per share data):

	For the Years Ended December 31,		
	2017	2016	2015
Diluted earnings per share calculation:			
Net (loss) income	$ (410,526)	$ (166,834)	$ 39,532
Weighted average of ordinary shares outstanding	163,122,663	160,699,543	155,923,251
Diluted net (loss) income per share	**$ (2.52)**	**$ (1.04)**	**$ 0.25**

Basic net (loss) income per share is computed by dividing net (loss) income by the weighted-average number of ordinary shares outstanding during the period. Diluted net (loss) income per share reflects the potential dilution beyond shares for basic net (loss) income per share that could occur if securities or other contracts to issue ordinary shares were exercised, converted into ordinary shares, or resulted in the issuance of ordinary shares that would have shared in the Company's earnings.

The outstanding securities listed in the table below were excluded from the computation of diluted (loss) income per ordinary share for the years ended December 31, 2017, 2016 and 2015 due to being anti-dilutive:

	For the Years Ended December 31,		
	2017	2016	2015
Stock options	12,887,595	7,515,297	2,853,821
Restricted stock units	1,095,768	492,030	817,168
Performance stock units	2,742,301	5,247,987	1,074
Employee stock purchase plan	63,445	56,805	1,046,275
Warrants	388,841	1,123,737	2,416,894
	17,177,950	**14,435,856**	**7,135,232**

The potentially dilutive impact of the March 2015 private placement of $400.0 million aggregate principal amount of 2.50% Exchangeable Senior Notes due 2022 (the "Exchangeable Senior Notes") by Horizon Pharma Investment Limited ("Horizon Investment"), a wholly owned subsidiary of the Company, is determined using a method similar to the treasury stock method. Under this method, no numerator or denominator adjustments arise from the principal and interest components of the Exchangeable Senior Notes because the Company has the intent and ability to settle the Exchangeable Senior Notes' principal and interest in cash. Instead, the Company is required to increase the diluted net (loss) income per share denominator by the variable number of shares that would be issued upon conversion if it settled the conversion spread obligation with shares. For diluted net (loss) income per share purposes, the conversion spread obligation is calculated based on whether the average market price of the Company's ordinary shares over the reporting period is in excess of the exchange price of the Exchangeable Senior Notes. There was no calculated spread added to the denominator for the years ended December 31, 2017, 2016 and 2015.

NOTE 4 –ACQUISITIONS, DIVESTITURES AND OTHER ARRANGEMENTS

Acquisitions

Acquisition of River Vision

On May 8, 2017, the Company acquired 100% of the equity interests in River Vision for upfront cash payments totaling approximately $150.3 million, including cash acquired of $6.3 million, with additional potential future milestone and royalty payments contingent on the satisfaction of certain regulatory milestones and sales thresholds. Pursuant to ASC 805 (as amended by ASU No. 2017-01), the Company accounted for the River Vision acquisition as the purchase of an in-process research and development ("IPR&D") asset and, pursuant to ASC Topic 730, *Research and Development,* recorded the purchase price as research and development expense during the year ended December 31, 2017. Further, the Company recognized approximately $13.1 million of federal net operating losses, $2.8 million of state net operating losses and $5.8 million of federal tax credits. The acquired tax attributes were set up as deferred tax assets which were further netted within the net deferred tax liabilities of the U.S. group, offset by a deferred credit recorded in long-term liabilities.

Acquisition of Additional Rights to Interferon Gamma-1b

On June 30, 2017, the Company completed its acquisition of certain rights to interferon gamma-1b from Boehringer Ingelheim International in all territories outside of the United States, Canada and Japan, as the Company previously held marketing rights to interferon gamma-1b in these territories. Boehringer Ingelheim International commercialized interferon gamma-1b as IMUKIN in an estimated thirty countries, primarily in Europe and the Middle East. In May 2016, the Company paid Boehringer Ingelheim International €5.0 million ($5.6 million when converted using a Euro-to-Dollar exchange rate at date of payment of 1.1132) for such rights and upon closing in June 2017, the Company paid Boehringer Ingelheim International an additional €19.5 million ($22.3 million when converted using a Euro-to-Dollar exchange rate at date of payment of 1.1406). The Company currently markets interferon gamma-1b as ACTIMMUNE in the United States. The €5.0 million upfront amount paid in May 2016 had initially been included in "other assets" in the Company's consolidated balance sheet. Following the discontinuation of the Friedreich's ataxia ("FA") program in December 2016, the Company recorded an impairment charge of €5.0 million ($5.3 million when converted using a Euro-to-Dollar exchange rate at date of impairment of 1.052) to fully write off the asset in its consolidated statements of comprehensive loss during the year ended December 31, 2016 as projections for future net sales of IMUKIN in these territories did not exceed the related costs. Upon closing, during the year ended December 31, 2017, the Company accounted for the additional €19.5 million payment ($22.3 million when converted using a Euro-to-Dollar exchange rate at date of payment of 1.1406) as the acquisition of an asset which was immediately impaired, and recorded the payment as a "selling, general and administrative" expense in its consolidated statement of comprehensive loss.

Acquisition of Raptor

On October 25, 2016, the Company completed its acquisition of Raptor in which the Company acquired all of the issued and outstanding shares of Raptor's common stock for $9.00 per share. The acquisition added two medicines, PROCYSBI and QUINSAIR, to the Company's medicine portfolio. Following completion of the acquisition, Raptor became a wholly owned subsidiary of the Company and converted to a limited liability company, changing its name to Horizon Pharmaceutical LLC. The Company financed the transaction through $300.0 million of aggregate principal amount of 8.75% Senior Notes due 2024 (the "2024 Senior Notes"), $375.0 million aggregate principal amount of loans pursuant to an amendment to the Company's existing credit agreement, as described in Note 16, and cash on hand. The total consideration for the acquisition was approximately $860.8 million, including cash acquired of $24.9 million and $56.0 million paid to settle Raptor's outstanding debt, and was composed of the following (in thousands):

Cash	$	841,494
Net settlements on the exercise of stock options and restricted stock units		19,268
Total consideration	**$**	**860,762**

During the year ended December 31, 2016, the Company incurred $15.7 million, in Raptor acquisition-related transaction costs including advisory, legal and other professional and consulting fees, which were recorded for as "selling, general and administrative" expenses in the consolidated statement of comprehensive loss.

Pursuant to ASC 805, the Company accounted for the Raptor acquisition as a business combination using the acquisition method of accounting. Identifiable assets and liabilities of Raptor, including identifiable intangible assets, were recorded based on their estimated fair values as of the date of the closing of the acquisition. The excess of the purchase price over the fair value of the net assets acquired was recorded as goodwill. Significant judgment was required in determining the estimated fair values of developed technology intangible assets, inventories and certain other assets and liabilities. Such valuation required estimates and assumptions including, but not limited to, estimating future cash flows and direct costs in addition to developing the appropriate discount rates and current market profit margins. The Company's management believes the fair values recognized for the assets acquired and the liabilities assumed were based on reasonable estimates and assumptions.

During the year ended December 31, 2017, the Company recorded measurement period adjustments related to accrued expenses, accrued trade discounts and rebates and deferred tax liabilities as a result of new information regarding facts existing at the acquisition date, resulting in a net decrease to goodwill of $2.9 million.

The following table summarizes the preliminary fair values assigned to the assets acquired and the liabilities assumed by the Company, along with the resulting goodwill before and after the measurement period adjustments (in thousands):

(Liabilities assumed) and assets acquired:	**Preliminary**	**Adjustment**	**Final**
Accounts payable and accrued expenses	$ (28,345)	$ (240)	$ (28,585)
Accrued trade discounts and rebates	(6,377)	1,350	(5,027)
Deferred tax liabilities	(237,166)	1,743	(235,423)
Contingent and accrued royalties	(104,705)		(104,705)
Other non-current liability	(25,500)		(25,500)
Cash and cash equivalents	24,897		24,897
Restricted cash	1,350		1,350
Accounts receivable, net	17,767		17,767
Inventories	74,463		74,463
Prepaid expenses and other current assets	4,194		4,194
Property and equipment	3,373		3,373
Developed technology	946,000		946,000
Other non-current assets	1,765		1,765
Goodwill	189,046	(2,853)	186,193
Fair value of consideration paid	**$ 860,762**	**$ —**	**$ 860,762**

Inventories acquired included raw materials, work-in-process and finished goods for PROCYSBI and QUINSAIR. Inventories were recorded at their estimated fair values. The fair value of finished goods was determined based on the

estimated selling price, net of selling costs and a margin on the selling costs. The fair value of work-in-process was determined based on estimated selling price, net of selling costs and costs to complete the manufacturing, and a margin on the selling and manufacturing costs. The fair value of raw materials was estimated to equal the replacement cost. A step-up in the value of inventory of $67.0 million was recorded in connection with the acquisition. During the year ended December 31, 2017, the Company recorded inventory step-up expense of $44.0 million, related to PROCYSBI and QUINSAIR, of which $3.2 million was recorded to "gain on divestiture" in the consolidated statement of comprehensive loss during the year ended December 31, 2017. During the year ended December 31, 2016, the Company recorded inventory step-up expense of $22.4 million related to PROCYSBI and QUINSAIR. As at December 31, 2017 inventory step-up relating to PROCYSBI has been fully expensed.

Other tangible assets and liabilities were valued at their respective carrying amounts as management believes that these amounts approximated their acquisition date fair values.

Other non-current liability of $25.5 million represents the fair value of an assumed contingent liability arising from contingent payments associated with development, regulatory and commercial milestones following Raptor's acquisition of QUINSAIR. During the year ended December 31, 2017, the Company paid $20.0 million relating to milestones in connection with this assumed contingent consideration liability.

Identifiable intangible assets and liabilities acquired include developed technology and contingent royalties. The estimated fair values of the developed technology and contingent royalties represent valuations performed with the assistance of an independent appraisal firm based on management's estimates, forecasted financial information and reasonable and supportable assumptions.

Developed technology intangible assets reflect the estimated fair value of Raptor's rights to PROCYSBI. The fair value of developed technology was determined using an income approach. The income approach explicitly recognizes that the fair value of an asset is premised upon the expected receipt of future economic benefits such as earnings and cash inflows based on current sales projections and estimated direct costs for Raptor's medicines. Indications of value were developed by discounting these benefits to their acquisition-date worth at a discount rate of 12.5%. The fair value of the PROCYSBI developed technology was capitalized as of the Raptor acquisition date and is subsequently being amortized over approximately thirteen years and nine years for the U.S. rights and ex-U.S. rights, respectively, which are the periods in which over 90% of the estimated cash flows are expected to be realized. The Company assigned no fair value to QUINSAIR developed technology as projections of future net sales do not exceed the related costs. See Note 8 for details of developed technology sold in the Chiesi divestiture.

The Company assigned a fair value of $102.0 million to a contingent liability for royalties potentially payable under previously existing agreements related to PROCYSBI. The royalties for PROCYSBI are payable under the terms of an amended and restated license agreement with The Regents of the University of California, San Diego ("UCSD"). See Note 18 for details of the percentages of royalties payable under this agreement. The initial fair value of this liability was determined using a discounted cash flow analysis incorporating the estimated future cash flows of royalty payments resulting from future sales. The discount rate used was the same as for the fair value of the developed technology.

Deferred tax assets and liabilities arise from acquisition accounting adjustments where book values of certain assets and liabilities differ from their tax bases. Deferred tax assets and liabilities are recorded at the currently enacted rates which will be in effect at the time when the temporary differences are expected to reverse in the country where the underlying assets and liabilities are located. Raptor's developed technology as of the acquisition date was located primarily in the United States where a U.S. tax rate of 36.6% was used and a significant deferred tax liability was recorded. Goodwill represents the excess of the acquisition consideration over the estimated fair value of net assets acquired and was recorded in the consolidated balance sheet as of the acquisition date. The Company does not expect any portion of this goodwill to be deductible for tax purposes.

Acquisition of Crealta

On January 13, 2016, the Company completed its acquisition of all the membership interests of Crealta. The acquisition added two medicines, KRYSTEXXA and MIGERGOT, to the Company's medicine portfolio. The total consideration for the acquisition was approximately $539.7 million, including cash acquired of $24.9 million and $70.9 million paid to settle Crealta's outstanding debt, and was composed of the following (in thousands):

	Before	Adjustments	After
Cash	$ 536,181	$ 25	$ 536,206
Net settlements on the exercise of stock options and restricted units	3,526	—	3,526
Total consideration	**$ 539,707**	**$ 25**	**$ 539,732**

During the years ended December 31, 2016 and 2015, the Company incurred $3.5 million and $1.9 million, respectively, in Crealta acquisition-related transaction costs including investment advisory costs, legal and other professional and consulting fees, which were accounted for as "selling, general and administrative" expenses in the consolidated statements of comprehensive (loss) income.

Pursuant to ASC 805, the Company accounted for the Crealta acquisition as a business combination using the acquisition method of accounting. Identifiable assets and liabilities of Crealta, including identifiable intangible assets, were recorded based on their estimated fair values as of the date of the closing of the acquisition. The excess of the purchase price over the fair value of the net assets acquired was recorded as goodwill. Significant judgment was required in determining the estimated fair values of developed technology intangible assets, inventories and certain other assets and liabilities. Such valuation required estimates and assumptions including, but not limited to, estimating future cash flows and direct costs in addition to developing the appropriate discount rates and current market profit margins. The Company's management believes the fair values recognized for the assets acquired and the liabilities assumed were based on reasonable estimates and assumptions.

During the year ended December 31, 2016, the Company recorded measurement period adjustments related to developed technology, inventory and deferred tax liabilities, which adjustments resulted in a net increase in goodwill of $8.1 million. The measurement period adjustments were the result of an adjustment for inventory that was subsequently discovered to have been damaged and defective as of the acquisition date, a net working capital true-up adjustment and the alignment of Crealta's inventory and obsolescence reserve policy to the Company's policy.

The following table summarizes the preliminary fair values assigned to the assets acquired and the liabilities assumed by the Company along with the resulting goodwill before and after the measurement period adjustments (in thousands):

(Liabilities assumed) and assets acquired:	Preliminary	Adjustment	Final
Accounts payable and accrued expenses	$ (4,543)	$ —	$ (4,543)
Accrued trade discounts and rebates	(1,424)	—	(1,424)
Deferred tax liabilities	(20,835)	694	(20,141)
Other non-current liabilities	(6,900)	—	(6,900)
Contingent royalty liabilities	(51,300)	—	(51,300)
Cash and cash equivalents	24,893	—	24,893
Accounts receivable	10,014	—	10,014
Inventories	169,054	(19,691)	149,363
Prepaid expenses and other current assets	1,382	—	1,382
Developed technology	417,300	10,900	428,200
Other non-current assets	275	—	275
Goodwill	1,791	8,122	9,913
Fair value of consideration paid	**$ 539,707**	**$ 25**	**$ 539,732**

Inventories acquired included raw materials, work-in-process and finished goods for KRYSTEXXA and MIGERGOT. Inventories were recorded at their preliminary estimated fair values. The fair value of finished goods was determined based on the estimated selling price, net of selling costs and a margin on the selling costs. The fair value of work-in-process was determined based on estimated selling price, net of selling costs and costs to complete the manufacturing, and a margin on the selling and manufacturing costs. The fair value of raw materials was estimated to equal the replacement cost. A step-up in the value of inventory of $144.3 million was recorded in connection with the acquisition. During the year ended December 31, 2017, the Company recorded inventory step-up expense of $78.3 million related to KRYSTEXXA.

Other tangible assets and liabilities were valued at their respective carrying amounts as management believes that these amounts approximated their acquisition date fair values.

Other non-current liabilities represented an assumed $6.9 million probable contingent liability which was released to "other income (expense)" in the consolidated statement of comprehensive loss during the year ended December 31, 2016.

Identifiable intangible assets and liabilities acquired include developed technology and contingent royalties. The estimated fair values of the developed technology and contingent royalties represent valuations performed with the assistance of an independent appraisal firm based on management's estimates, forecasted financial information and reasonable and supportable assumptions.

Developed technology intangible assets reflect the estimated fair value of Crealta's rights to its currently marketed medicines, KRYSTEXXA and MIGERGOT. The fair value of developed technology was determined using an income approach. The income approach explicitly recognizes that the fair value of an asset is premised upon the expected receipt of future economic benefits such as earnings and cash inflows based on current sales projections and estimated direct costs for Crealta's medicines. Indications of value were developed by discounting these benefits to their acquisition-date worth at a discount rate of 27% for KRYSTEXXA and 23% for MIGERGOT. The fair value of the KRYSTEXXA and MIGERGOT developed technologies were capitalized as of the Crealta acquisition date and are subsequently being amortized over approximately twelve and ten years, respectively, which are the periods in which over 90% of the estimated cash flows are expected to be realized.

The Company has assigned a fair value of $51.3 million to a contingent liability for royalties potentially payable under previously existing agreements related to KRYSTEXXA and MIGERGOT. The royalties for KRYSTEXXA are payable under the terms of a license agreement with Duke University ("Duke") and Mountain View Pharmaceuticals ("MVP"). See Note 18 for details of the percentages of royalties payable under such agreements. The initial fair value of this liability was determined using a discounted cash flow analysis incorporating the estimated future cash flows of royalty payments resulting from future sales. The discount rate used was the same as for the fair value of the developed technology.

The deferred tax liability recorded represents deferred tax liabilities assumed as part of the acquisition, net of deferred tax assets, related to net operating tax loss carryforwards of Crealta.

Goodwill represents the excess of the acquisition consideration over the estimated fair value of net assets acquired and was recorded in the consolidated balance sheet as of the acquisition date. The Company does not expect any portion of this goodwill to be deductible for tax purposes.

Divestiture of PROCYSBI and QUINSAIR rights in EMEA Regions

On June 23, 2017, the Company completed the Chiesi divestiture for an upfront payment of $72.5 million, which reflects $3.1 million of cash divested, with additional potential milestone payments based on sales thresholds.

Pursuant to ASU No. 2017-01, the Company accounted for the Chiesi divestiture as a sale of a business. The Company determined that the sale of the business and its assets in connection with the Chiesi divestiture did not constitute a strategic shift and that it did not and will not have a major effect on its operations and financial results. Accordingly, the operations associated with the Chiesi divestiture are not reported in discontinued operations.

The gain on divestiture was determined as follows (in thousands):

	For the Year Ended December 31, 2017
Cash proceeds	$ 72,462
Add reimbursement of royalties	27,101
Less net assets sold:	
Developed technology	(47,261)
Goodwill	(16,285)
Other	(24,482)
Transaction and other costs	(5,268)
Gain on divestiture	**$ 6,267**

Under the terms of its agreement with Chiesi, the Company will continue to pay third parties for the royalties on sales of PROCYSBI and QUINSAIR in EMEA, and Chiesi will reimburse the Company for those royalties. At the date of divestiture, the Company recorded an asset of $27.1 million to "other assets", which represented the estimated amounts that

are expected to be reimbursed from Chiesi for the PROCYSBI and QUINSAIR royalties. These estimated royalties are accrued in "accrued expenses" and "other long-term liabilities".

Transaction and other costs primarily relate to professional and license fees attributable to the divestiture.

Other Arrangements

Collaboration and option agreement

On November 8, 2016, the Company entered into a collaboration and option agreement with a privately held life-science entity. Under the terms of the agreement, the privately held life-science entity will conduct certain research and pre-clinical and clinical development activities. Upon execution of the agreement, the Company paid $0.1 million for the option to acquire certain assets of the privately held life-science entity for $25.0 million, which is exercisable on specified key dates. Under the collaboration and option agreement, the Company is required to pay up to $9.8 million upon the attainment of various milestones, primarily to fund clinical development costs for the medicine candidate. The initial upfront amount paid of $0.1 million has been included in "other assets" in the Company's consolidated balance sheet as of December 31, 2017 and 2016. During the years ended December 31, 2017 and 2016, $1.5 million and $1.1 million, respectively, was recorded as "research and development" expenses in the consolidated statement of comprehensive loss related to milestones. The Company has determined that the privately held life-science entity is a variable interest entity ("VIE") as it does not have enough equity to finance its activities without additional financial support. As the Company does not have the power to direct the activities of the VIE that most significantly affect its economic performance, it is not the primary beneficiary of, and does not consolidate the financial results of the VIE. The Company will reassess the appropriate accounting treatment for this arrangement throughout the life of the agreement and modify these accounting conclusions accordingly.

Licensing agreement

On December 12, 2017, the Company entered into an agreement to license HZN-003 (formerly MEDI4945), a potential next-generation biologic for uncontrolled gout, from MedImmune LLC ("MedImmune"), the global biologics research and development arm of the AstraZeneca Group. HZN-003 is a pre-clinical, genetically engineered uricase derivative with optimized uricase and optimized PEGylation technology that has the potential to improve the response rate to the biologic as well as the potential for subcutaneous dosing. Under the terms of the agreement, the Company agreed to pay MedImmune an upfront cash payment of $12.0 million with additional potential future milestone payments of up to $153.5 million contingent on the satisfaction of certain development and sales thresholds. The $12.0 million upfront payment was accounted for as the acquisition of an asset and was recorded as "research and development" expenses in the consolidated statement of comprehensive loss during the year ended December 31, 2017 and included in "accrued expenses" as of December 31, 2017. The upfront payment was subsequently paid in January 2018.

Pro Forma Information (Unaudited)

The following table represents consolidated financial information for the Company on a pro forma basis. The pro forma adjustments assume that the Crealta and Raptor acquisitions occurred as of January 1, 2015 and the Hyperion acquisition occurred as of January 1, 2014.

The results of Raptor from October 25, 2016 to December 31, 2016 and the results of Crealta from January 13, 2016 to December 31, 2016 are included in the 2016 as reported figures and the results of Hyperion from May 7, 2015 to December 31, 2016 are included in the 2015 and 2016 as reported figures.

The historical financial information has been adjusted to give effect to pro forma items that are directly attributable to the Hyperion, Crealta and Raptor acquisitions, and are expected to have a continuing impact on the consolidated results. These items include, among others, adjustments to record the amortization of definite-lived intangible assets, interest expense, debt discount and deferred financing costs associated with the debt in connection with the acquisitions.

Additionally, the following table sets forth unaudited financial information and has been compiled from historical financial statements and other information, but is not necessarily indicative of the results that actually would have been achieved had the transactions occurred on the dates indicated or that may be achieved in the future (in thousands, except per share data):

	For the Year Ended December 31,					
	2016			2015		
	As reported	Pro forma adjustments	Pro forma	As reported	Pro forma adjustments	Pro forma
Net sales	$ 981,120	$ 109,298	$ 1,090,418	$ 757,044	$ 200,611	$ 957,655
Net (loss) income	(166,834)	(201,765)	(368,599)	39,532	(127,801)	(88,269)
Basic net (loss) income per share	$ (1.04)	$ (1.26)	$ (2.30)	$ 0.27	$ (0.86)	$ (0.59)
Diluted net (loss) income per share	(1.04)	(1.26)	(2.30)	0.25	(0.86)	(0.59)

The Company's consolidated statement of comprehensive loss for the year ended December 31, 2016 includes KRYSTEXXA and MIGERGOT net sales as a result of the acquisition of Crealta in January 2016 of $91.1 million and $4.7 million, respectively, and PROCYSBI and QUINSAIR net sales as a result of the acquisition of Raptor in October 2016 of $25.3 million and $1.0 million, respectively. The Company's consolidated statement of comprehensive income for the year ended December 31, 2015 includes RAVICTI and BUPHENYL net sales as a result of the acquisition of Hyperion in May 2015 of $86.9 million and $13.5 million, respectively.

Hyperion, Crealta and Raptor have been integrated into the Company's business and as a result of these integration efforts, the Company cannot distinguish between these operations and those of the Company's legacy business.

NOTE 5 – INVENTORIES

Inventories are stated at the lower of cost or market value. Inventories consist of raw materials, work-in-process and finished goods. The Company has entered into manufacturing and supply agreements for the manufacture of finished goods or the purchase of raw materials and production supplies. The Company's inventories include the direct purchase cost of materials and supplies and manufacturing overhead costs.

The components of inventories as of December 31, 2017 and 2016 consisted of the following (in thousands):

	As of December 31,	
	2017	2016
Raw materials	$ 4,553	$ 10,233
Work-in-process	27,589	85,022
Finished goods	29,513	79,533
Inventories, net	**$ 61,655**	**$ 174,788**

Finished goods at December 31, 2017 included $17.0 million of stepped-up KRYSTEXXA inventory. The Company recorded $78.3 million of KRYSTEXXA inventory step-up expense during the year ended December 31, 2017. Finished goods at December 31, 2016 included $27.7 million of stepped-up KRYSTEXXA inventory. Work-in-process at December 31, 2016 included $67.6 million of stepped-up KRYSTEXXA inventory.

The Company expects that the KRYSTEXXA inventory step-up will be fully expensed by the end of the first quarter of 2018. Following that period, the Company expects the costs of goods sold related to KRYSTEXXA to decrease significantly to levels consistent with the historical cost of goods sold of Crealta.

During the year ended December 31, 2017, the Company recorded $40.8 million of PROCYSBI and QUINSAIR inventory step-up expense. In addition, during the year ended December 31, 2017, the Company recorded $3.2 million of inventory step-up expense to "gain on divestiture" relating to PROCYSBI and QUINSAIR in connection with the Chiesi divestiture in June 2017. Finished goods at December 31, 2016 included $38.1 million of stepped-up PROCYSBI and QUINSAIR inventory. Work-in-process at December 31, 2016 included $5.9 million of stepped-up PROCYSBI and QUINSAIR inventory.

Because inventory step-up expense is acquisition-related, will not continue indefinitely and has a significant effect on the Company's gross profit, gross margin percentage and net income (loss) for all affected periods, the Company discloses balance sheet and income statement amounts related to inventory step-up.

NOTE 6 – PREPAID EXPENSES AND OTHER CURRENT ASSETS

Prepaid expenses and other current assets as of December 31, 2017 and 2016 consisted of the following (in thousands):

	As of December 31,	
	2017	2016
Medicine samples inventory	$ 11,415	$ 10,192
Rabbi trust assets	6,490	3,073
Other prepaid expenses and other current assets	25,497	36,354
Prepaid expenses and other current assets	**$ 43,402**	**$ 49,619**

NOTE 7 – PROPERTY AND EQUIPMENT

Property and equipment as of December 31, 2017 and 2016 consisted of the following (in thousands):

	As of December 31,	
	2017	2016
Software	$ 14,956	$ 10,876
Leasehold improvements	9,415	9,184
Machinery and equipment	4,819	4,566
Computer equipment	2,235	3,069
Other	2,508	2,664
	33,933	**30,359**
Less accumulated depreciation	(13,672)	(8,319)
Construction in process	144	1,444
Property and equipment, net	**$ 20,405**	**$ 23,484**

The Company capitalizes development costs associated with internal use software, including external direct costs of materials and services and payroll costs for employees devoting time to a software project. Costs incurred during the preliminary project stage, as well as costs for maintenance and training, are expensed as incurred.

Depreciation expense for the years ended December 31, 2017, 2016 and 2015 was $6.6 million, $5.0 million and $5.4 million, respectively.

NOTE 8 – GOODWILL AND INTANGIBLE ASSETS

Goodwill

The gross carrying amount of goodwill as of December 31, 2017 was as follows (in thousands):

Balance at December 31, 2015	$	253,811
Goodwill recognized on acquisition of Crealta		9,913
Goodwill recognized on acquisition of Raptor		189,046
Adjustment relating to the acquisition of Hyperion in the prior year		(7,191)
Balance at December 31, 2016		**445,579**
Goodwill derecognized on Chiesi divestiture		(16,285)
Adjustment relating to the acquisition of Raptor in the prior year		(2,853)
Balance at December 31, 2017	**$**	**426,441**

During the year ended December 31, 2017, in connection with the Chiesi divestiture, the Company recorded a reduction to goodwill of $16.3 million.

During the year ended December 31, 2016, the Company recognized goodwill with a preliminary value of $189.1 million in connection with the Raptor acquisition, which represented the excess of the purchase price over the fair value of the net assets acquired. During the year ended December 31, 2017, the Company recorded measurement period adjustments related to deferred tax liabilities, accrued trade discounts and rebates and accrued expenses, which resulted in a net decrease in goodwill of $2.9 million, to $186.2 million.

During the year ended December 31, 2016, the Company recognized goodwill with a value of $9.9 million in connection with the Crealta acquisition, which represented the excess of the purchase price over the fair value of the net assets acquired.

During the year ended December 31, 2016, the Company recorded an adjustment related to deferred tax liabilities which resulted in a decrease to goodwill of $7.2 million. The adjustment was the result of a correction of an error in the Hyperion pre-acquisition deferred tax calculation. The Company concluded that this misstatement was not material, individually or in the aggregate, to any of the reporting periods impacted. As such, the correction for this error was made during the year ended December 31, 2016.

As of December 31, 2017, there were no accumulated goodwill impairment losses. See Note 4 for further details of goodwill acquired and disposed of in business acquisitions and divestitures.

Intangible Assets

As of December 31, 2017, the Company's intangible assets consisted of developed technology related to ACTIMMUNE, BUPHENYL, KRYSTEXXA, MIGERGOT, PENNSAID 2%, PROCYSBI, RAVICTI, RAYOS and VIMOVO in the United States, and AMMONAPS, BUPHENYL, LODOTRA and PROCYSBI outside the United States, as well as customer relationships for ACTIMMUNE.

During the year ended December 31, 2017, in connection with the Chiesi divestiture, the Company recorded a reduction in the net book value of developed technology related to PROCYSBI of $47.3 million.

During the year ended December 31, 2016, in connection with the acquisition of Raptor, the Company capitalized $946.0 million of developed technology related to PROCYSBI.

During the year ended December 31, 2016, in connection with the acquisition of Crealta, the Company capitalized $402.2 million of developed technology related to KRYSTEXXA and $26.0 million of developed technology related to MIGERGOT.

See Note 4 for further details of intangible assets acquired and disposed of in business acquisitions and divestitures.

Prior to the fourth quarter of 2016, the Company had IPR&D of $66.0 million related to one research and development project to evaluate ACTIMMUNE in the treatment of FA. During December 2016, the Company discontinued this project and recorded an impairment charge of $66.0 million to "impairment of in-process research and development" in its consolidated statements of comprehensive loss during the year ended December 31, 2016, to fully write off the value of the asset on its consolidated balance sheet.

The Company tests its intangible assets for impairment when events or circumstances may indicate that the carrying value of these assets exceeds their fair value. The Company does not believe there have been any circumstances or events that would indicate that the carrying value of any of its intangible assets, except for IPR&D as described above, was impaired at December 31, 2017 or 2016.

As of December 31, 2017 and 2016, amortizable intangible assets consisted of the following (in thousands):

	As of December 31,					
	2017			2016		
	Cost Basis	Accumulated Amortization	Net Book Value	Cost Basis	Accumulated Amortization	Net Book Value
Developed technology	$ 3,115,695	$ (671,746)	$ 2,443,949	$ 3,166,695	$ (399,511)	$ 2,767,184
Customer relationships	8,100	(2,659)	5,441	8,100	(1,849)	6,251
Amortizable intangible assets	**$ 3,123,795**	**$ (674,405)**	**$ 2,449,390**	**$ 3,174,795**	**$ (401,360)**	**$ 2,773,435**

Amortization expense for the years ended December 31, 2017, 2016 and 2015 was $276.8 million, $216.9 million and $132.9 million, respectively. As of December 31, 2017, estimated future amortization expense was as follows (in thousands):

2018	$ 274,084
2019	261,092
2020	261,068
2021	253,373
2022	251,551
Thereafter	1,148,222
Total	**$ 2,449,390**

NOTE 9 - OTHER ASSETS

Included in other assets at December 31, 2017, is $24.6 million which represents the long-term portion of the estimated amounts that are expected to be reimbursed from Chiesi for PROCYSBI and QUINSAIR royalties.

NOTE 10 – ACCRUED EXPENSES

Accrued expenses as of December 31, 2017 and 2016 consisted of the following (in thousands):

	As of December 31,	
	2017	2016
Payroll-related expenses	$ 56,338	$ 66,417
Consulting and professional services	27,542	33,614
Accrued interest	14,127	18,938
Accrued upfront payment related to license agreement	12,000	—
Litigation settlement	—	32,500
Accrued other	27,827	31,296
Accrued expenses	**$ 137,834**	**$ 182,765**

Accrued litigation settlement at December 31, 2016 included $32.5 million in relation to a litigation settlement with Express Scripts, Inc., which was paid in two equal installments in January 2017 and April 2017.

During the year ended December 31, 2017, the Company entered into an agreement to license HZN-003 from MedImmune. Under the terms of the agreement, the Company agreed to pay MedImmune an upfront cash payment of $12.0 million, which was recorded as "research and development" expenses in the consolidated statement of comprehensive loss during the year ended December 31, 2017 and was included in "accrued expenses" as of December 31, 2017.

Accrued other as of December 31, 2017 and 2016 included $2.1 million and $9.5 million, respectively, related to a loss on inventory purchase commitments. During the year ended December 31, 2016, the Company committed to purchase additional units of ACTIMMUNE from Boehringer Ingelheim RCV GmbH & Co KG ("Boehringer Ingelheim"). These additional units of ACTIMMUNE were intended to cover anticipated demand if the Phase 3 trial, Safety, Tolerability and Efficacy of ACTIMMUNE Dose Escalation in Friedreich's Ataxia study (the "FA program") had been successful. Following the discontinuation of the FA program during the year ended December 31, 2016, the Company recorded a loss of $14.3 million in "cost of goods sold" in the consolidated statement of comprehensive loss for firm, non-cancellable and unconditional purchase commitments for quantities in excess of the Company's current forecasts for future demand. During the year ended December 31, 2017, the Company renegotiated its purchase commitments with Boehringer Ingelheim and reassessed its excess commitments based on updated forecasts for future demand and recorded additional expense of $1.7 million to "cost of goods sold". "Other long-term liabilities" as of December 31, 2017 and 2016 included $7.8 million and $4.8 million, respectively, related to this loss on inventory purchase commitments. During the year ended December 31, 2016, the Company recorded $4.0 million related to costs to be incurred to discontinue the clinical trial. Accrued other as of December 31, 2016 included $4.0 million related to these costs. During the year ended December 31, 2017, the Company recorded a reduction of $1.5 million to "research and development" expenses reflecting lower costs to discontinue the clinical trial than previously estimated.

NOTE 11 – ACCRUED TRADE DISCOUNTS AND REBATES

Accrued trade discounts and rebates as of December 31, 2017 and 2016 consisted of the following (in thousands):

	As of December 31,	
	2017	2016
Accrued wholesaler fees and commercial rebates	$ 190,215	$ 47,460
Accrued co-pay and other patient assistance	230,533	188,504
Accrued government rebates and chargebacks	81,005	61,592
Accrued trade discounts and rebates	**$ 501,753**	**$ 297,556**
Invoiced wholesaler fees and commercial rebates, co-pay and other patient assistance, and government rebates and chargebacks in accounts payable	15,042	16,830
Total customer-related accruals and allowances	**$ 516,795**	**$ 314,386**

The following table summarizes changes in the Company's customer-related accruals and allowances during the years ended December 31, 2017 and 2016 (in thousands):

	Wholesaler Fees and Commercial Rebates	Co-Pay and Other Patient Assistance	Government Rebates and Chargebacks	Total
Balance at December 31, 2015	$ 21,112	$ 114,201	$ 48,456	**$ 183,769**
Current provisions relating to sales during the year ended December 31, 2016	133,012	1,701,287	278,877	**2,113,176**
Adjustments relating to prior-year sales	671	—	(6,875)	**(6,204)**
Payments relating to sales during the year ended December 31, 2016	(87,147)	(1,496,240)	(224,343)	**(1,807,730)**
Payments relating to prior-year sales	(20,644)	(114,201)	(41,581)	**(176,426)**
Crealta acquisition on January 13, 2016	492	—	932	**1,424**
Raptor acquisition on October 25, 2016	155	96	6,126	**6,377**
Balance at December 31, 2016	**$ 47,651**	**$ 205,143**	**$ 61,592**	**$ 314,386**
Measurement period adjustment	—	—	(1,350)	**(1,350)**
Current provisions relating to sales during the year ended December 31, 2017	635,919	1,907,669	331,559	**2,875,147**
Adjustments relating to prior-year sales	5,580	(59)	(4,905)	**616**
Payments relating to sales during the year ended December 31, 2017	(445,621)	(1,675,344)	(237,574)	**(2,358,539)**
Payments relating to prior-year sales	(53,044)	(205,084)	(55,337)	**(313,465)**
Balance at December 31, 2017	**$ 190,485**	**$ 232,325**	**$ 93,985**	**$ 516,795**

NOTE 12 – ACCRUED ROYALTIES

Changes to the liability for royalties for medicines acquired through business combinations during the years ended December 31, 2017 and 2016 consisted of the following (in thousands):

Balance as of December 31, 2015	$ 175,219
Accrued royalties - current portion as of December 31, 2015	51,700
Accrued royalties, net of current as of December 31, 2015	123,519
Assumed KRYSTEXXA and MIGERGOT contingent royalty liabilities	51,300
Assumed KRYSTEXXA and MIGERGOT accrued royalties	1,401
Assumed PROCYSBI contingent royalty liabilities	102,000
Assumed PROCYSBI and QUINSAIR accrued royalties	2,705
Remeasurement of royalty liabilities	386
Royalty payments	(39,448)
Accretion expense	40,616
Other royalty expense	95
Balance as of December 31, 2016	**334,274**
Accrued royalties - current portion as of December 31, 2016	61,981
Accrued royalties, net of current as of December 31, 2016	272,293
Reclassification to other long-term liabilities	(5,233)
Remeasurement of royalty liabilities	21,774
Royalty payments	(45,739)
Accretion expense	51,127
Other royalty expense	310
Balance as of December 31, 2017	**356,513**
Accrued royalties - current portion as of December 31, 2017	65,328
Accrued royalties, net of current as of December 31, 2017	**$ 291,185**

The reclassification to other long-term liabilities in the table above relates to the reclassification of a contingent royalty liability for PROCYSBI to other long-term liabilities as a result of the Chiesi divestiture.

During the year ended December 31, 2017, based on higher sales of certain of the Company's medicines versus its previous expectations and estimates for future sales of these medicines, the Company recorded total charges of $64.7 million and $0.6 million to "cost of goods sold" and "selling, general and administrative" expenses, respectively, (primarily composed of $40.5 million and $24.2 million related to KRYSTEXXA and RAVICTI, respectively). The Company also recorded a reduction of $43.5 million to cost of goods sold related to certain of its other medicines as a result of updated estimates of future sales of these medicines (primarily composed of $23.2 million, $11.7 million and $7.0 million related to PROCYSBI, VIMOVO and ACTIMMUNE, respectively).

NOTE 13 – LONG-TERM INVESTMENTS

During the third quarter of 2015, the Company purchased 2,250,000 shares of common stock of Depomed, Inc. ("Depomed"), representing 3.75% of Depomed's then outstanding common stock. The shares were acquired at a cost of $71.8 million. During the fourth quarter of 2015, following the Company's decision to withdraw its offer to acquire Depomed, the Company sold all of its shares in Depomed, receiving sales proceeds of $42.8 million and the Company recognized a realized loss of $29.0 million in the consolidated statement of comprehensive income.

There were no gains or losses on long-term investments during the years ended December 31, 2017 or 2016.

NOTE 14 – SEGMENT AND OTHER INFORMATION

The Company has determined that it operates in one operating segment, which focuses on researching, developing and commercializing innovative medicines that address unmet treatment needs. The Company's operating segment is reported in a manner consistent with the internal reporting provided to the CODM. The Company's CODM has been identified as its chief executive officer.

The following table presents a summary of total net sales by medicine (in thousands):

	Year Ended December 31,		
	2017	2016	2015
RAVICTI	$ 193,918	$ 151,532	$ 86,875
PENNSAID 2%	191,050	304,433	147,010
KRYSTEXXA	156,483	91,102	—
PROCYSBI	137,740	25,268	—
DUEXIS	121,161	173,728	190,357
ACTIMMUNE	110,993	104,624	107,444
VIMOVO	57,666	121,315	166,672
RAYOS	52,125	47,356	40,329
BUPHENYL	20,792	16,879	13,458
MIGERGOT	5,468	4,651	—
LODOTRA	5,393	4,193	4,899
QUINSAIR	3,442	1,039	—
Litigation settlement	—	(65,000)	—
Total net sales	**$ 1,056,231**	**$ 981,120**	**$ 757,044**

The following table presents a summary of total net sales by geography (in thousands, except for percentages):

	Year Ended December 31, 2017		Year Ended December 31, 2016		Year Ended December 31, 2015	
	Amount	% of Total Net Sales	Amount	% of Total Net Sales	Amount	% of Total Net Sales
United States	$ 1,026,527	97%	$ 964,041	98%	$ 744,036	98%
Rest of world	29,704	3%	17,079	2%	13,008	2%
Total net sales	**$ 1,056,231**		**$ 981,120**		**$ 757,044**	

The following table presents the amount and percentage of gross sales from customers that represented more than 10% of the Company's gross sales included in its single operating segment, and all other customers as a group (in thousands, except percentages):

	Year ended December 31,					
	2017		2016		2015	
	Amount	% of Gross Sales	Amount	% of Gross Sales	Amount	% of Gross Sales
Customer A	$ 1,205,268	30%	$ 1,413,774	44%	$ 607,771	30%
Customer B	1,165,591	29%	667,031	21%	166,661	8%
Customer C	567,583	14%	355,920	11%	207,009	10%
Other Customers	1,119,397	27%	797,463	24%	1,075,853	52%
Gross Sales	**$ 4,057,839**	**100%**	**$ 3,234,188**	**100%**	**$ 2,057,294**	**100%**

The following table presents total tangible long-lived assets by location (in thousands):

	As of December 31,	
	2017	2016
United States	$ 17,089	$ 19,542
Other	3,316	3,942
Total long-lived assets (1)	**$ 20,405**	**$ 23,484**

(1) Long-lived assets consist of property and equipment.

NOTE 15 – FAIR VALUE MEASUREMENTS

The following tables and paragraphs set forth the Company's financial instruments that are measured at fair value on a recurring basis within the fair value hierarchy. Assets and liabilities measured at fair value are classified in their entirety based on the lowest level of input that is significant to the fair value measurement. The Company's assessment of the significance of a particular input to the fair value measurement in its entirety requires management to make judgments and consider factors specific to the asset or liability. The following describes three levels of inputs that may be used to measure fair value:

Level 1—Observable inputs such as quoted prices in active markets for identical assets or liabilities.

Level 2—Observable inputs other than Level 1 prices such as quoted prices for similar assets or liabilities, quoted prices in markets that are not active, or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.

Level 3—Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

The Company utilizes the market approach to measure fair value for its money market funds. The market approach uses prices and other relevant information generated by market transactions involving identical or comparable assets or liabilities.

As of December 31, 2017, the Company's restricted cash included bank time deposits which were measured at fair value using Level 2 inputs and their carrying values were approximately equal to their fair values. Level 2 inputs, obtained from various third-party data providers, represent quoted prices for similar assets in active markets, or these inputs were derived from observable market data, or if not directly observable, were derived from or corroborated by other observable market data.

Other current assets and other long-term liabilities recorded at fair value on a recurring basis are composed of investments held in a rabbi trust and the related deferred liability for deferred compensation arrangements. Quoted prices for this investment, primarily in mutual funds, are available in active markets. Thus, the Company's investments related to deferred compensation arrangements and the related long-term liability are classified as Level 1 measurements in the fair value hierarchy.

The Company transfers its financial assets and liabilities between fair value hierarchies at the end of each reporting period. There were no transfers between the different levels of the fair value hierarchy in 2017 or in 2016.

Assets and liabilities measured at fair value on a recurring basis

The following table sets forth the Company's financial assets and liabilities at fair value on a recurring basis as of December 31, 2017 and 2016 (in thousands):

	December 31, 2017			
	Level 1	Level 2	Level 3	Total
Assets:				
Bank time deposits	$ —	$ 3,000	$ —	$ 3,000
Money market funds	687,000	—	—	687,000
Other current assets	6,490	—	—	6,490
Total assets at fair value	**$ 693,490**	**$ 3,000**	**$ —**	**$ 696,490**
Liabilities:				
Other long-term liabilities	(6,490)	—	—	(6,490)
Total liabilities at fair value	**$ (6,490)**	**$ —**	**$ —**	**$ (6,490)**

	December 31, 2016			
	Level 1	Level 2	Level 3	Total
Assets:				
Bank time deposits	$ —	$ 3,000	$ —	$ 3,000
Money market funds	170,000	—	—	170,000
Other current assets	3,038	—	—	3,038
Total assets at fair value	**$ 173,038**	**$ 3,000**	**$ —**	**$ 176,038**
Liabilities:				
Other long-term liabilities	(3,038)	—	—	(3,038)
Total liabilities at fair value	**$ (3,038)**	**$ —**	**$ —**	**$ (3,038)**

NOTE 16 – DEBT AGREEMENTS

The Company's outstanding debt balances as of December 31, 2017 and 2016 consisted of the following (in thousands):

	As of December 31,	
	2017	2016
2017 Term Loan Facility	$ 845,750	$ —
2015 Term Loan Facility	—	394,000
2016 Incremental Loan Facility	—	375,000
2023 Senior Notes	475,000	475,000
2024 Senior Notes	300,000	300,000
Exchangeable Senior Notes	400,000	400,000
Total face value	**2,020,750**	**1,944,000**
Debt discount	(108,054)	(126,352)
Deferred financing fees	(11,041)	(10,155)
Total long-term debt	**1,901,655**	**1,807,493**
Less: current maturities	10,625	7,750
Long-term debt, net of current maturities	**$ 1,891,030**	**$ 1,799,743**

Scheduled maturities with respect to the Company's long-term debt are as follows (in thousands):

2018	$ 10,625
2019	8,500
2020	8,500
2021	8,500
2022	406,375
Thereafter	1,578,250
Total	**$ 2,020,750**

2017 Term Loan Facilities

On October 23, 2017, HPI and Horizon Pharma USA, Inc. ("HPUSA" and, together with HPI, in such capacity, the "Borrowers"), wholly owned subsidiaries of the Company, borrowed approximately $845.8 million aggregate principal amount of loans (the "October 2017 Refinancing Loans") pursuant to an amendment (the "October 2017 Refinancing Amendment") to the credit agreement, dated as of May 7, 2015, by and among the Borrowers, the Company and certain of its subsidiaries as guarantors, the lenders party thereto from time to time and Citibank, N.A., as administrative agent and collateral agent, as amended by Amendment No. 1, dated as of October 25, 2016 (the "2016 Credit Agreement"), and Amendment No. 2, dated March 29, 2017 (the "March 2017 Credit Agreement") (the "2017 Term Loan Facility"). As used herein, all references to the "Credit Agreement" are references to the March 2017 Credit Agreement, as amended by the October 2017 Refinancing Amendment.

The October 2017 Refinancing Loans were incurred as a separate new class of term loans under the Credit Agreement with substantially the same terms as the previously outstanding senior secured term loans incurred on March 29, 2017 under the March 2017 Credit Agreement (the "October 2017 Refinanced Loans") to effectuate a repricing of the October 2017 Refinanced Loans. The Borrowers used the proceeds of the October 2017 Refinancing Loans to repay the October 2017 Refinanced Loans, which totaled approximately $845.8 million. The October 2017 Refinancing Loans bear interest, at the Borrowers' option, at a rate equal to either the London Inter-Bank Offer Rate ("LIBOR"), plus an applicable margin of 3.25% per year (subject to a LIBOR floor of 1.00%), or the adjusted base rate plus 2.25%. The adjusted base rate is defined as the greater of (a) LIBOR (using one-month interest period) plus 1.00%, (b) prime rate, (c) fed funds plus 0.5%, and (d) 2.00%. The Credit Agreement provides for (i) the October 2017 Refinancing Loans, (ii) one or more uncommitted additional incremental loan facilities subject to the satisfaction of certain financial and other conditions, and (iii) one or more uncommitted refinancing loan facilities with respect to loans thereunder. The Credit Agreement allows for the Company and certain of its subsidiaries to become borrowers under incremental or refinancing facilities.

The Company elected to exercise its reinvestment rights under the mandatory prepayment provisions of the March 2017 Credit Agreement with respect to the net proceeds from the Chiesi divestiture. To the extent the Company does not apply such net proceeds to permitted acquisitions (including the acquisition of rights to products and products lines) and/or the acquisition of capital assets within 365 days of the receipt thereof (or commit to so apply and then apply within 180 days after the end of such 365-day period), the Borrowers under the March 2017 Credit Agreement would be required to make a mandatory prepayment under the March 2017 Credit Agreement in an amount equal to the unapplied net proceeds. Until such time, the net proceeds are not legally restricted for use. As of December 31, 2017, the Company had applied a portion of such net proceeds to the acquisition of additional rights to interferon gamma-1b and to the agreement to license HZN-003. See Note 4 for further details of this acquisition and license agreement.

The obligations under the Credit Agreement (including obligations in respect of the October 2017 Refinancing Loans) and any swap obligations and cash management obligations owing to a lender (or an affiliate of a lender) thereunder are guaranteed by the Company and each of the Company's existing and subsequently acquired or formed direct and indirect subsidiaries (other than certain immaterial subsidiaries, subsidiaries whose guarantee would result in material adverse tax consequences and subsidiaries whose guarantee is prohibited by applicable law). The obligations under the Credit Agreement (including obligations in respect of the October 2017 Refinancing Loans) and any such swap and cash management obligations are secured, subject to customary permitted liens and other agreed upon exceptions, by a perfected security interest in (i) all tangible and intangible assets of the Borrowers and the guarantors, except for certain customary excluded assets, and (ii) all of the capital stock owned by the Borrowers and guarantors thereunder (limited, in the case of the stock of certain non-U.S. subsidiaries of the Borrowers, to 65% of the capital stock of such subsidiaries). The Borrowers and the guarantors under the Credit Agreement are individually and collectively referred to herein as a "Loan Party" and the "Loan Parties," as applicable.

Borrowers under the Credit Agreement are permitted to make voluntary prepayments of the loans under the Credit Agreement at any time without payment of a premium, except that with respect to the October 2017 Refinancing Loans, a 1.00% premium will apply to a repayment of the October 2017 Refinancing Loans in connection with a repricing of, or any amendment to the Credit Agreement in a repricing of, such loans effected on or prior to the date that is six months following October 23, 2017. The Borrowers are required to make mandatory prepayments of loans under the Credit Agreement (without payment of a premium) with (a) net cash proceeds from certain non-ordinary course asset sales (subject to reinvestment rights and other exceptions), (b) casualty proceeds and condemnation awards (subject to reinvestment rights and other exceptions), (c) net cash proceeds from issuances of debt (other than certain permitted debt), and (d) 50% of the Company's excess cash flow (subject to decrease to 25% or 0% if the Company's first lien leverage ratio is less than 2.25:1 or 1.75:1, respectively). The October 2017 Refinancing Loans will amortize in equal quarterly installments beginning on December 31, 2017, in an aggregate annual amount equal to 1.00% of the original principal amount of the October 2017 Refinanced Loans (i.e. $850.0 million), with any remaining balance payable on March 29, 2024, the final maturity date of the October 2017 Refinancing Loans.

The Credit Agreement contains customary representations and warranties and customary affirmative and negative covenants, including, among other things, restrictions on indebtedness, liens, investments, mergers, dispositions, prepayment of other indebtedness and dividends and other distributions.

Events of default under the Credit Agreement include: (i) the failure by any Borrower to timely make payments due under the Credit Agreement; (ii) material misrepresentations or misstatements in any representation or warranty by any Loan Party when made; (iii) failure by any Loan Party to comply with the covenants under the Credit Agreement and other related agreements; (iv) certain defaults under a specified amount of other indebtedness of the Company or its subsidiaries; (v) insolvency or bankruptcy-related events with respect to the Company or any of its material subsidiaries; (vi) certain undischarged judgments against the Company or any of its restricted subsidiaries; (vii) certain ERISA-related events reasonably expected to have a material adverse effect on the Company and its restricted subsidiaries taken as a whole; (viii) certain security interests or liens under the loan documents ceasing to be, or being asserted by the Company or its restricted subsidiaries not to be, in full force and effect; (ix) any loan document or material provision thereof ceasing to be, or any challenge or assertion by any Loan Party that such loan document or material provision is not, in full force and effect; and (x) the occurrence of a change of control. If one or more events of default occurs and continues beyond any applicable cure period, the administrative agent may, with the consent of the lenders holding a majority of the loans and commitments under the facilities, or will, at the request of such lenders, terminate the commitments of the lenders to make further loans and declare all of the obligations of the Loan Parties under the March 2017 Credit Agreement to be immediately due and payable.

The interest on the Company's 2017 Term Loan Facility is variable and as of December 31, 2017, the interest rate on the 2017 Term Loan Facility was 4.75% and the effective interest rate was 5.16%.

As of December 31, 2017, the fair value of the amounts outstanding under the 2017 Term Loan Facility was approximately $848.9 million, categorized as a Level 2 instrument, as defined in Note 15.

2016 Incremental Loan Facility and 2015 Term Loan Facility

On May 7, 2015, HPI, as borrower, and the Company and certain of its subsidiaries, as guarantors, entered into a credit agreement (the "2015 Credit Agreement") with Citibank, N.A., as administrative and collateral agent, and the lenders from time to time party thereto providing for (i) a six-year $400.0 million term loan facility (the "2015 Term Loan Facility"); (ii) an uncommitted accordion facility subject to the satisfaction of certain financial and other conditions; and (iii) one or more uncommitted refinancing loan facilities with respect to loans thereunder. The senior secured term loans (the "2015 Loans") under the 2015 Term Loan Facility bore interest, at each borrower's option, at a rate equal to either the LIBOR, plus an applicable margin of 3.50% per year (subject to a 1.00% LIBOR floor), or the adjusted base rate plus 2.50%. The adjusted base rate was defined as the greater of (a) LIBOR (using one-month interest period) plus 1.00%, (b) prime rate, (c) fed funds plus 0.5%, and (d) 2.00%. HPI borrowed the full $400.0 million available on the 2015 Term Loan Facility on May 7, 2015 as a LIBOR-based borrowing.

On October 25, 2016 and in connection with the financing for the acquisition of Raptor, HPI and HPUSA (together, in such capacity, the "Incremental Borrowers") entered into an amendment to the 2015 Credit Agreement (the "2016 Amendment") with Citibank, N.A., as administrative and collateral agent, and Bank of America, N.A., as the incremental B-1 lender thereunder, pursuant to which the Incremental Borrowers borrowed $375.0 million aggregate principal amount of loans (the "2016 Incremental Loan Facility"). The 2016 Incremental Loan Facility was incurred as a separate class of term loans under the 2015 Credit Agreement with the same terms as the loans under the 2015 Term Loan Facility, except as described below.

The senior secured term loans (the "2016 Loans") under the 2016 Incremental Loan Facility bore interest, at the Incremental Borrowers' option, at a rate equal to either LIBOR plus an applicable margin of 4.50% per year (subject to a LIBOR floor of 1.00%), or the adjusted base rate plus 3.50%. The terms of the 2015 Loans provided for an amendment such that the effective yield of the 2015 Loans would not be less than the effective yield of the 2016 Loans minus 0.50%. Consequently, the issuance of the 2016 Loans resulted in an increase of the interest rate applicable to the 2015 Loans, as of October 25, 2016, to LIBOR plus 4.00%, subject to a LIBOR floor of 1.00% (an initial interest rate of 5.00%).

On March 29, 2017, the Borrowers used the proceeds of the October 2017 Refinanced Loans under the 2017 Term Loan Facility to repay the 2015 Loans and 2016 Loans, which collectively totaled $769.0 million.

The 2015 Loans and the 2016 Loans were repaid, and a portion of the repayment was accounted for as a debt modification and a portion was accounted for as a debt extinguishment. Under debt extinguishment accounting, the Company recorded a charge of $0.5 million to "loss on debt extinguishment" in the consolidated statements of comprehensive loss, which reflected the write-off of the unamortized portion of debt discount and deferred financing costs previously incurred and a one percent prepayment penalty fee. Under debt modification accounting, the Company capitalized an incremental $5.8 million of debt discount and deferred financing fees.

2023 Senior Notes

On April 29, 2015, Horizon Pharma Financing Inc. ("Horizon Financing"), a wholly owned subsidiary of the Company, completed a private placement of $475.0 million aggregate principal amount of 6.625% Senior Notes due 2023 (the "2023 Senior Notes") to certain investment banks acting as initial purchasers who subsequently resold the 2023 Senior Notes to qualified institutional buyers as defined in Rule 144A under the Securities Act, and in offshore transactions to non-U.S. persons in reliance on Regulation S under the Securities Act. The net proceeds from the offering of the 2023 Senior Notes were approximately $462.3 million, after deducting the initial purchasers' discount and offering expenses payable by Horizon Financing.

In connection with the closing of the Hyperion acquisition on May 7, 2015, Horizon Financing merged with and into HPI and, as a result, the 2023 Senior Notes became HPI's general unsecured senior obligations. The obligations under the 2023 Senior Notes are fully and unconditionally guaranteed on a senior unsecured basis by the Company and all of the Company's direct and indirect subsidiaries that are guarantors from time to time under the Credit Agreement.

The 2023 Senior Notes accrue interest at an annual rate of 6.625% payable semiannually in arrears on May 1 and November 1 of each year, beginning on November 1, 2015. The 2023 Senior Notes will mature on May 1, 2023, unless earlier repurchased or redeemed.

Except as described below, the 2023 Senior Notes may not be redeemed before May 1, 2018. Thereafter, some or all of the 2023 Senior Notes may be redeemed at any time at specified redemption prices, plus accrued and unpaid interest to the redemption date. At any time prior to May 1, 2018, some or all of the 2023 Senior Notes may be redeemed at a price equal to 100% of the aggregate principal amount thereof, plus a make-whole premium and accrued and unpaid interest to the redemption date. Also prior to May 1, 2018, up to 35% of the aggregate principal amount of the 2023 Senior Notes may be redeemed at a redemption price of 106.625% of the aggregate principal amount thereof, plus accrued and unpaid interest, with the net proceeds of certain equity offerings. In addition, the 2023 Senior Notes may be redeemed in whole but not in part at a redemption price equal to 100% of the principal amount plus accrued and unpaid interest and additional amounts, if any, to, but excluding, the redemption date, if on the next date on which any amount would be payable in respect of the 2023 Senior Notes, HPI or any guarantor is or would be required to pay additional amounts as a result of certain tax-related events.

If the Company undergoes a change of control, HPI will be required to make an offer to purchase all of the 2023 Senior Notes at a price in cash equal to 101% of the aggregate principal amount thereof plus accrued and unpaid interest to, but not including, the repurchase date. If the Company or certain of its subsidiaries engages in certain asset sales, HPI will be required under certain circumstances to make an offer to purchase the 2023 Senior Notes at 100% of the principal amount thereof, plus accrued and unpaid interest to the repurchase date.

The indenture governing the 2023 Senior Notes contains covenants that limit the ability of the Company and its restricted subsidiaries to, among other things, pay dividends or distributions, repurchase equity, prepay junior debt and make certain investments, incur additional debt and issue certain preferred stock, incur liens on assets, engage in certain asset sales, merge, consolidate with or merge or sell all or substantially all of their assets, enter into transactions with affiliates, designate subsidiaries as unrestricted subsidiaries, and allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to the Company. Certain of the covenants will be suspended during any period in which the notes receive investment grade ratings. The indenture governing the 2023 Senior Notes also includes customary events of default.

As of December 31, 2017, the interest rate on the 2023 Senior Notes was 6.63% and the effective interest rate 6.68%.

As of December 31, 2017, the fair value of the 2023 Senior Notes was approximately $473.8 million, categorized as a Level 2 instrument, as defined in Note 15.

2024 Senior Notes

On October 25, 2016, HPI and HPUSA (together, in such capacity, the "2024 Issuers"), completed a private placement of $300.0 million aggregate principal amount of the 2024 Senior Notes to certain investment banks acting as initial purchasers who subsequently resold the 2024 Senior Notes to qualified institutional buyers as defined in Rule 144A under the Securities Act. The net proceeds from the offering of the 2024 Senior Notes were approximately $291.9 million, after deducting the initial purchasers' discount and offering expenses payable by the 2024 Issuers.

The obligations under the 2024 Senior Notes are the 2024 Issuers' general unsecured senior obligations and are fully and unconditionally guaranteed on a senior unsecured basis by the Company and all of the Company's direct and indirect subsidiaries that are guarantors from time to time under the Credit Agreement.

The Company used the net proceeds from the offering of the 2024 Senior Notes as well as $375.0 million principal amount of 2016 Loans under the 2016 Incremental Loan Facility to fund a portion of the acquisition of Raptor, repay Raptor's outstanding debt, and pay any prepayment premiums, fees and expenses in connection with the foregoing.

The 2024 Senior Notes accrue interest at an annual rate of 8.750% payable semiannually in arrears on May 1 and November 1 of each year, beginning on May 1, 2017. The 2024 Senior Notes will mature on November 1, 2024, unless earlier repurchased or redeemed.

Except as described below, the 2024 Senior Notes may not be redeemed before November 1, 2019. Thereafter, some or all of the 2024 Senior Notes may be redeemed at any time at specified redemption prices, plus accrued and unpaid interest to the redemption date. At any time prior to November 1, 2019, some or all of the 2024 Senior Notes may be redeemed at a price equal to 100% of the aggregate principal amount thereof, plus a make-whole premium and accrued and unpaid interest to the redemption date. Also prior to November 1, 2019, up to 35% of the aggregate principal amount of the 2024 Senior Notes may be redeemed at a redemption price of 108.75% of the aggregate principal amount thereof, plus accrued and unpaid interest, with the net proceeds of certain equity offerings. In addition, the 2024 Senior Notes may be redeemed in whole but not in part at a redemption price equal to 100% of the principal amount plus accrued and unpaid interest and additional amounts, if any, to, but excluding, the redemption date, if on the next date on which any amount would be payable in respect of the 2024 Senior Notes, the 2024 Issuers or any guarantor is or would be required to pay additional amounts as a result of certain tax-related events.

If the Company undergoes a change of control, the 2024 Issuers will be required to make an offer to purchase all of the 2024 Senior Notes at a price in cash equal to 101% of the aggregate principal amount thereof plus accrued and unpaid interest to, but not including, the repurchase date. If the Company or certain of its subsidiaries engages in certain asset sales, the 2024 Issuers will be required under certain circumstances to make an offer to purchase the 2024 Senior Notes at 100% of the principal amount thereof, plus accrued and unpaid interest to the repurchase date.

The indenture governing the 2024 Senior Notes contains covenants that limit the ability of the Company and its restricted subsidiaries to, among other things, pay dividends or distributions, repurchase equity, prepay junior debt and make certain investments, incur additional debt and issue certain preferred stock, incur liens on assets, engage in certain asset sales, merge, consolidate with or merge or sell all or substantially all of their assets, enter into transactions with affiliates, designate subsidiaries as unrestricted subsidiaries, and allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to the Company. Certain of the covenants will be suspended during any period in which the notes receive investment grade ratings. The indenture also includes customary events of default.

As of December 31, 2017, the interest rate on the 2024 Senior Notes was 8.75% and the effective interest rate 9.20%.

As of December 31, 2017, the fair value of the 2024 Senior Notes was approximately $316.5 million, categorized as a Level 2 instrument, as defined in Note 15.

Exchangeable Senior Notes

On March 13, 2015, Horizon Investment completed a private placement of $400.0 million aggregate principal amount of Exchangeable Senior Notes to certain investment banks acting as initial purchasers who subsequently resold the Exchangeable Senior Notes to qualified institutional buyers as defined in Rule 144A under the Securities Act. The net proceeds from the offering of the Exchangeable Senior Notes were approximately $387.2 million, after deducting the initial purchasers' discount and offering expenses payable by Horizon Investment.

The Exchangeable Senior Notes are fully and unconditionally guaranteed, on a senior unsecured basis, by the Company (the "Guarantee"). The Exchangeable Senior Notes and the Guarantee are Horizon Investment's and the Company's senior unsecured obligations. The Exchangeable Senior Notes accrue interest at an annual rate of 2.50% payable semiannually in arrears on March 15 and September 15 of each year, beginning on September 15, 2015. The Exchangeable Senior Notes will mature on March 15, 2022, unless earlier exchanged, repurchased or redeemed. The initial exchange rate is 34.8979 ordinary shares of the Company per $1,000 principal amount of the Exchangeable Senior Notes (equivalent to an initial exchange price of approximately $28.66 per ordinary share). The exchange rate will be subject to adjustment in some events but will not be adjusted for any accrued and unpaid interest. In addition, following certain corporate events that occur prior to the maturity date or upon a tax redemption, Horizon Investment will increase the exchange rate for a holder who elects to exchange its Exchangeable Senior Notes in connection with such a corporate event or a tax redemption in certain circumstances.

Other than as described below, the Exchangeable Senior Notes may not be redeemed by the Company.

Issuer Redemptions:

Optional Redemption for Changes in the Tax Laws of a Relevant Taxing Jurisdiction: Horizon Investment may redeem the Exchangeable Senior Notes at its option, prior to March 15, 2022, in whole but not in part, in connection with certain tax-related events.

Provisional Redemption on or After March 20, 2019: On or after March 20, 2019, Horizon Investment may redeem for cash all or a portion of the Exchangeable Senior Notes if the last reported sale price of ordinary shares of the Company has been at least 130% of the exchange price then in effect for at least twenty trading days whether or not consecutive) during any thirty consecutive trading day period ending on, and including, the trading day immediately preceding the date on which Horizon Investment provide written notice of redemption. The redemption price will be equal to 100% of the principal amount of the Exchangeable Senior Notes to be redeemed, plus accrued and unpaid interest to, but not including, the redemption date; provided that if the redemption date occurs after a regular record date and on or prior to the corresponding interest payment date, Horizon Investment will pay the full amount of accrued and unpaid interest due on such interest payment date to the record holder of the Exchangeable Senior Notes on the regular record date corresponding to such interest payment date, and the redemption price payable to the holder who presents an Exchangeable Senior Note for redemption will be equal to 100% of the principal amount of such Exchangeable Senior Note.

Holder Exchange Rights:

Holders may exchange all or any portion of their Exchangeable Senior Notes at their option at any time prior to the close of business on the business day immediately preceding December 15, 2021 only upon satisfaction of one or more of the following conditions:

1. Exchange upon Satisfaction of Sale Price Condition – During any calendar quarter commencing after the calendar quarter ended June 30, 2015 (and only during such calendar quarter), if the last reported sale price of ordinary shares of the Company for at least twenty trading days (whether or not consecutive) during the period of thirty consecutive trading days ending on the last trading day of the immediately preceding calendar quarter is greater than or equal to 130% of the applicable exchange price on each applicable trading day.

2. Exchange upon Satisfaction of Trading Price Condition – During the five business day period after any ten consecutive trading day period in which the trading price per $1,000 principal amount of Exchangeable Senior Notes for each trading day of such period was less than 98% of the product of the last reported sale price of ordinary shares of the Company and the applicable exchange rate on such trading day.

3. Exchange upon Notice of Redemption – Prior to the close of business on the business day immediately preceding December 15, 2021, if Horizon Investment provides a notice of redemption, at any time prior to the close of business on the second scheduled trading day immediately preceding the redemption date.

As of December 31, 2017, none of the above conditions had been satisfied and no exchange of Exchangeable Senior Notes had been triggered.

On or after December 15, 2021, a holder may exchange all or any portion of its Exchangeable Senior Notes at any time prior to the close of business on the second scheduled trading day immediately preceding the maturity date regardless of the foregoing conditions.

Upon exchange, Horizon Investment will settle exchanges of the Exchangeable Senior Notes by paying or causing to be delivered, as the case may be, cash, ordinary shares or a combination of cash and ordinary shares, at its election.

The Company recorded the Exchangeable Senior Notes under the guidance in ASC Topic 470-20, *Debt with Conversion and Other Options,* and separated them into a liability component and equity component. The carrying amount of the liability component of $268.9 million was determined by measuring the fair value of a similar liability that does not have an associated equity component. The carrying amount of the equity component of $119.1 million represented by the embedded conversion option was determined by deducting the fair value of the liability component of $268.9 million from the initial proceeds of $387.2 million ascribed to the convertible debt instrument as a whole. The initial debt discount of $131.1 million is being charged to interest expense over the life of the Exchangeable Senior Notes using the effective interest rate method.

As of December 31, 2017, the interest rate on the Exchangeable Senior Notes was 2.50% and the effective interest rate was 8.88%.

As of December 31, 2017, the fair value of the Exchangeable Senior Notes was approximately $372.0 million, categorized as a Level 2 instrument, as defined in Note 15.

NOTE 17 – OTHER LONG-TERM LIABILITIES

Included in other long-term liabilities at December 31, 2017 and 2016, is $26.4 million and $25.5 million, respectively, representing the fair value of the long-term portion of the contingent liability for royalties potentially payable under agreements related to PROCYSBI and QUINSAIR.

See Note 10 for details of amounts included in other long-term liabilities at December 31, 2017 and 2016, related to a loss on inventory purchase commitments.

NOTE 18 – COMMITMENTS AND CONTINGENCIES

Lease Obligations

The Company has the following office space lease agreements in place for real properties:

Location	Approximate Square Footage	Lease Expiry Date
Dublin, Ireland	18,900	November 3, 2029
Lake Forest, Illinois (1)	160,000	March 31, 2024
Novato, California (2)	61,000	August 31, 2021
Deerfield, Illinois (3)	32,300	June 30, 2018
Brisbane, California	20,100	November 30, 2019
Mannheim, Germany	14,300	December 31, 2018
Chicago, Illinois	6,500	December 31, 2018
Other	13,300	March 31, 2018 to May 31, 2020

(1) In connection with the Lake Forest lease, the Company has provided a $2.0 million letter of credit to the landlord, through a commercial bank.

(2) During March 2017, the Company vacated an area of the office space in Novato, California. During March and April 2017, the Company entered into sublease arrangements for this space with third parties.

(3) During January 2016, the Company vacated the premises in Deerfield, Illinois and began occupying the premises in Lake Forest, Illinois. During April 2017, the Company entered into a sublease arrangement for a portion of this space with a third party. During June 2017, the Company terminated a portion of the lease, resulting in 32,300 square feet remaining.

The Company recognizes rent expense on a monthly basis over the lease term based on a straight-line method. Rent expense was $6.4 million, $5.1 million and $2.5 million for the years ended December 31, 2017, 2016 and 2015, respectively.

As of December 31, 2017, minimum future cash payments due under lease obligations were as follows (in thousands):

2018	$	7,356
2019		6,659
2020		5,951
2021		5,350
2022		4,092
Thereafter		11,994
Total	**$**	**41,402**

Purchase Commitments

In November 2010, Raptor and Patheon entered into a manufacturing services agreement, which the Company assumed as a result of its acquisition of Raptor. Under the agreement, which was amended in April 2012 and June 2013, Patheon is obligated to manufacture PROCYSBI for the Company through December 31, 2019. The Company must provide Patheon with rolling, non-binding forecasts of PROCYSBI, with a portion of the forecast being a firm written order. In November 2010, Raptor and Cambrex Profarmaco Milano ("Cambrex") entered into an active pharmaceutical ingredient ("API") supply agreement, which the Company assumed as a result of its acquisition of Raptor. Under the agreement, which was amended in April 2013 and August 2016, Cambrex is obligated to manufacture PROCYSBI API for the Company through November 30, 2020. The Company must provide Cambrex with rolling, non-binding forecasts, with a portion of the forecast being the minimum floor of the firm order that must be placed. At December 31, 2017, the Company had a binding purchase commitment with Patheon for PROCYSBI of $1.8 million, which is to be delivered through April 2018 and with Cambrex for PROCYSBI API of $2.4 million, which is to be delivered through December 2020.

In July 2013, Vidara Therapeutics International Public Limited Company ("Vidara") and Boehringer Ingelheim entered into an exclusive supply agreement, which the Company assumed in September 2014 and amended effective as of September 5, 2014, and June 1, 2015. That supply agreement was replaced with an exclusive global supply agreement between the Company and Boehringer Ingelheim Biopharmaceuticals GmbH ("Boehringer Ingelheim Biopharmaceuticals") effective June 30, 2017. Under the agreement, Boehringer Ingelheim Biopharmaceuticals is required to manufacture and supply ACTIMMUNE and IMUKIN to the Company. The Company is required to purchase minimum quantities of finished medicine during the term of the agreement, which term extends to at least June 30, 2024. During the year ended December 31, 2016, the Company committed to purchase additional amounts of ACTIMMUNE from Boehringer Ingelheim. These additional amounts were intended to cover anticipated demand if the results of the FA program of ACTIMMUNE for the treatment of FA had been successful. As of December 31, 2017, the minimum binding purchase commitment to Boehringer Ingelheim Biopharmaceuticals was $24.3 million (converted using a Dollar-to-Euro exchange rate of 1.2003) through July 2024. Following the discontinuation of the FA program, the Company recorded a loss of $14.3 million in "cost of goods sold" in the consolidated statement of comprehensive loss during the year ended December 31, 2016 for firm, non-cancellable and unconditional purchase commitments for quantities in excess of the Company's current forecasts for future demand. During the year ended December 31, 2017, the Company renegotiated the purchase commitments with Boehringer Ingelheim and reassessed its excess commitments based on updated forecasts for future demand and recorded an additional net expense of $1.7 million to "cost of goods sold". During the year ended December 31, 2016, the Company also committed to incur an additional $14.9 million for the harmonization of the drug substance manufacturing process with Boehringer Ingelheim. These additional costs were incurred and will be incurred during the years 2017 through 2021. During the year ended December 31, 2017, the Company recorded $12.1 million, in its consolidated statement of comprehensive loss related to the harmonization of the drug substance manufacturing process.

In March 2007, Savient Pharmaceuticals, Inc. (as predecessor in interest to Crealta), entered into a commercial supply agreement with Bio-Technology General (Israel) Ltd ("BTG Israel") for the production of the bulk KRYSTEXXA medicine ("bulk product"). The Company assumed this agreement as part of the Crealta acquisition and amended the agreement in September 2016. Under this agreement, the Company has agreed to purchase certain minimum annual order quantities and is obligated to purchase at least eighty percent of its annual world-wide bulk product requirements from BTG Israel. The term of the agreement runs until December 31, 2030, and will automatically renew for successive three year periods unless earlier terminated by either party upon three years' prior written notice. The agreement may be terminated earlier by either party in the event of a force majeure, liquidation, dissolution, bankruptcy or insolvency of the other party, uncured material breach by the other party or after January 1, 2024, upon three years' prior written notice. Under the agreement if the manufacture of the bulk product is moved out of Israel, the Company may be required to obtain the approval of the Israeli Office of the Chief Scientist ("OCS") because certain KRYSTEXXA intellectual property was initially developed with a grant funded by the OCS. The Company issues eighteen-month forecasts of the volume of KRYSTEXXA that the Company expects to order. The first six months of the forecast are considered binding firm orders. At December 31, 2017, the Company had a binding purchase commitment with BTG Israel for KRYSTEXXA of $48.0 million, which is to be delivered through December 31, 2026. Additionally, other binding commitments relating to the manufacture of KRYSTEXXA of $2.8 million were in place at December 31, 2017.

In August 2007, the Company entered into a manufacturing and supply agreement with Jagotec AG ("Jagotec"), which was amended in March 2011 and in January 2017. Under the agreement, Jagotec or its affiliates are required to manufacture and supply RAYOS/LODOTRA exclusively to the Company in bulk. The earliest the agreement can expire is December 31, 2023, and the minimum purchase commitment is in force until December 2023. At December 31, 2017, the minimum purchase commitment based on tablet pricing in effect under the agreement was $6.7 million through December 2023. Additionally, purchase orders relating to the manufacture of RAYOS/LODOTRA of $0.5 million were outstanding at December 31, 2017.

In October 2014, in connection with the acquisition of the U.S. rights to PENNSAID 2% from Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.) ("Nuvo"), the Company and Nuvo entered into an exclusive supply agreement. Under the supply agreement, which was amended in February 2016, January 2017 and February 2018, Nuvo is obligated to manufacture and supply PENNSAID 2% to the Company. The term of the supply agreement is through December 31, 2029, but the agreement may be terminated earlier by either party for any uncured material breach by the other party of its obligations under the supply agreement or upon the bankruptcy or similar proceeding of the other party. At least ninety days prior to the first day of each calendar month during the term of the supply agreement, the Company submits a binding written purchase order to Nuvo for PENNSAID 2% in minimum batch quantities. At December 31, 2017, the Company had a binding purchase commitment with Nuvo for PENNSAID 2% of $2.7 million, which was delivered through February 2018.

In May 2011, the Company entered into a manufacturing and supply agreement with Sanofi-Aventis U.S. LLC ("Sanofi-Aventis U.S."), and amended the agreement effective as of September 25, 2013. Pursuant to the agreement, as amended, Sanofi-Aventis U.S. is obligated to manufacture and supply DUEXIS to the Company in final, packaged form, and the Company is obligated to purchase DUEXIS exclusively from Sanofi-Aventis U.S. for the commercial requirements of DUEXIS in North America, South America and certain countries and territories in Europe, including the European Union ("EU") member states and Scandinavia. The agreement term extends until May 2019, and automatically renews for successive two-year terms unless terminated by either party upon two years' prior written notice. At December 31, 2017, the Company had a binding purchase commitment to Sanofi-Aventis U.S. for DUEXIS of $7.1 million, which is to be delivered through June 2018.

Excluding the above, additional purchase orders and other commitments relating to the manufacture of RAVICTI, BUPHENYL, QUINSAIR, VIMOVO and MIGERGOT of $12.4 million were outstanding at December 31, 2017. Additionally, at December 31, 2017, the Company had a binding purchase commitment related to process validation activities for teprotumumab of $2.8 million.

Royalty and Milestone Agreements

RAVICTI

Under the terms of an asset purchase agreement with Ucyclyd Pharma, Inc. ("Ucyclyd"), the Company is obligated to pay to Ucyclyd tiered mid to high single-digit royalties on its global net sales of RAVICTI. Under the terms of a license agreement with Saul W. Brusilow, M.D. and Brusilow Enterprises, Inc. ("Brusilow"), the Company is obligated to pay low single-digit royalties to Brusilow on net sales of RAVICTI that are covered by a valid claim of a licensed patent.

PROCYSBI

Under the terms of an amended and restated license agreement with UCSD, the Company is obligated to pay to UCSD tiered low to mid-single-digit royalties on its net sales of PROCYSBI, including a minimum annual royalty in an amount less than $0.1 million. The Company must also pay UCSD a percentage in the mid-teens of any fees it receives from its sublicensees under the agreement that are not earned royalties. The Company may also be obligated to pay UCSD aggregate developmental milestone payments of $0.3 million and aggregate regulatory milestone payments of $1.8 million for each orphan indication, and aggregate developmental milestone payments of $0.8 million and aggregate regulatory milestone payments of $3.5 million for each non-orphan indication.

ACTIMMUNE

Under a license agreement, as amended, with Genentech Inc. ("Genentech"), who was the original developer of ACTIMMUNE, the Company is, or was, obligated to pay royalties to Genentech on its net sales of ACTIMMUNE as follows:

- For the period from November 26, 2014 through May 5, 2018, a royalty in the 20% to 30% range for the first $3.7 million in net sales achieved in any calendar year and in the 1% to 9% range for all additional net sales in any year; and
- From May 6, 2018 and for so long as the Company continues to commercially sell ACTIMMUNE, an annual royalty in the low single digits as a percentage of annual net sales.

Under the terms of an assignment and option agreement with Connetics Corporation (which was the predecessor parent company to InterMune Pharmaceuticals Inc. and is now part of GlaxoSmithKline), ("Connetics"), the Company is obligated to pay low single-digit royalties to Connetics on the Company's net sales of ACTIMMUNE in the United States.

BUPHENYL

Under the terms of an amended and restated collaboration agreement with Ucyclyd, the Company is obligated to pay to Ucyclyd tiered mid to high single-digit royalties on its net sales in the United States of BUPHENYL to urea cycle disorder patients outside of the U.S. Food and Drug Administration ("FDA") approved labeled age range for RAVICTI.

KRYSTEXXA

Under the terms of a license agreement with Duke and MVP, the Company is obligated to pay Duke a mid-single-digit royalty on its global net sales of KRYSTEXXA and a royalty of between 5% and 15% on any global sublicense revenue. The Company is also obligated to pay MVP a mid-single-digit royalty on its net sales of KRYSTEXXA outside of the United States and a royalty of between 5% and 15% on any sublicense revenue outside of the United States.

RAYOS/LODOTRA

Jagotec is entitled to receive a mid-single digit percentage royalty on adjusted gross sales of RAYOS/LODOTRA and on any sub-licensing income, which includes any payments not calculated based on the adjusted gross sales of RAYOS/LODOTRA, such as license fees, lump sums and milestone payments.

VIMOVO

The Company is required to pay Aralez Pharmaceuticals Inc. ("Aralez") a ten percent royalty on net sales of VIMOVO and other medicines sold by the Company, its affiliates or sublicensees during the royalty term that contain gastroprotective agents in a single fixed combination oral solid dosage form with nonsteroidal anti-inflammatory drugs, subject to minimum annual royalty obligations of $7.5 million. These minimum royalty obligations will continue for each year during which one of Aralez's patents covers such medicines in the United States and there are no competing medicines in the United States. The royalty rate may be reduced to a mid-single digit royalty rate as a result of loss of market share to competing medicines. The Company's obligation to pay royalties to Aralez will expire upon the later of (a) expiration of the last-to-expire of certain patents covering such medicines in the United States, and (b) ten years after the first commercial sale of such medicines in the United States.

The royalty obligations described above are included in accrued royalties on the Company's consolidated balance sheets.

For all of the royalty agreements entered into by the Company, a total expense of $82.3 million was recorded during the year ended December 31, 2017, of which $81.6 million was recorded in "cost of goods sold" and $0.7 million was recorded in "selling, general and administrative" expenses in the consolidated statements of comprehensive loss. During the year ended December 31, 2016 and 2015, a total expense of $46.5 million and $45.5 million, respectively, was recorded in cost of goods sold in the consolidated statements of comprehensive loss.

Other Agreements

On November 8, 2016, the Company entered into a collaboration and option agreement with a privately held life-science entity. Under the terms of the agreement, the privately held life-science entity will conduct certain research and pre-clinical and clinical development activities. Upon execution of the agreement, the Company paid $0.1 million for the option to acquire certain of the privately held life-science entity's assets for $25.0 million, which is exercisable on specified key dates. Under the collaboration and option agreement, the Company is required to pay up to $9.8 million upon the attainment of various milestones, primarily to fund clinical development costs for the medicine candidate. The Company paid an aggregate of $2.6 million in relation to these milestones during the years ended December 31, 2017 and 2016.

On May 8, 2017, the Company acquired River Vision for upfront cash payments totaling approximately $150.3 million, including cash acquired of $6.3 million, and potential future milestone and royalty payments contingent on the satisfaction of certain regulatory milestones and sales thresholds. Under the agreement, the Company is required to pay up to $325.0 million upon the attainment of various milestones related to FDA approval and net sales thresholds. The agreement also includes a royalty payment of three percent of the portion of annual worldwide net sales exceeding $300.0 million (if any). Under a separate agreement, the Company is also required to pay up to CHF103.0 million ($105.7 million when converted using a CHF-to-Dollar exchange rate at December 31, 2017 of 1.0263) upon the attainment of various milestones related to approval, filing and net sales thresholds. During the year ended December 31, 2017, CHF2.0 million ($2.0 million when converted using a CHF-to-Dollar exchange rate at the date of payment of 1.0169) was paid in relation to these milestones. The agreement also includes a royalty payment of between nine percent and twelve percent of the portion of annual worldwide net sales.

On December 12, 2017, the Company entered into an agreement to license HZN-003 (formerly MEDI4945), a rheumatology pipeline program with the objective of enhancing the Company's leadership position in the uncontrolled gout market, from MedImmune. Under the terms of the agreement, the Company paid MedImmune an upfront cash payment of $12.0 million. Under the license agreement, the Company is required to pay up to $153.5 million upon the attainment of various milestones linked to the initiation of clinical trials and the attainment of net sales thresholds, and royalties on net sales.

Contingencies

The Company is subject to claims and assessments from time to time in the ordinary course of business. The Company's management does not believe that any such matters, individually or in the aggregate, will have a material adverse effect on the Company's business, financial condition, results of operations or cash flows. In addition, the Company from time to time has billing disputes with vendors in which amounts invoiced are not in accordance with the terms of their contracts.

In November 2015, the Company received a subpoena from the U.S. Attorney's Office for the Southern District of New York requesting documents and information related to its patient access programs and other aspects of its marketing and commercialization activities. The Company is unable to predict how long this investigation will continue or its outcome, but it anticipates that it will continue to incur significant costs in connection with the investigation, regardless of the outcome. The Company may also become subject to similar investigations by other governmental agencies. The investigation by the U.S. Attorney's Office and any additional investigations of the Company's patient access programs and sales and marketing activities may result in damages, fines, penalties or other administrative sanctions against the Company.

Indemnification

In the normal course of business, the Company enters into contracts and agreements that contain a variety of representations and warranties and provide for general indemnifications. The Company's exposure under these agreements is unknown because it involves claims that may be made against the Company in the future, but have not yet been made. In connection with the federal securities class action litigation (described in Note 19 below), the Company has received notice from the Underwriter Defendants (as defined below) of their intention to seek indemnification and has received and paid several invoices from the Underwriter Defendants. On November 14, 2016, all defendants moved to dismiss the plaintiffs' amended complaint. Plaintiffs filed their opposition to the motion to dismiss on December 21, 2016. On January 18, 2018, the District Court dismissed all Plaintiffs' claims against all Defendants, and denied the Plaintiffs any further opportunity to amend their complaint. On February 16, 2018, plaintiffs filed a notice of appeal to the District Court's ruling. The Company may record charges in the future as a result of these indemnification obligations.

In accordance with its memorandum and articles of association, the Company has indemnification obligations to its officers and directors for certain events or occurrences, subject to certain limits, while they are serving at the Company's request in such capacity. Additionally, the Company has entered into, and intends to continue to enter into, separate indemnification agreements with its directors and executive officers. These agreements, among other things, require the Company to indemnify its directors and executive officers for certain expenses, including attorneys' fees, judgments, fines and settlement amounts incurred by a director or executive officer in any action or proceeding arising out of their services as one of the Company's directors or executive officers, or any of the Company's subsidiaries or any other company or enterprise to which the person provides services at the Company's request. In connection with the federal securities class action litigation (described in Note 19 below), the Company has paid legal fees and costs on behalf of itself and the current and former officers and directors of the Company who are named as defendants in that litigation. The Company also has a director and officer insurance policy that enables it to recover a portion of any amounts paid for current and future potential claims. All of the Company's officers and directors have also entered into separate indemnification agreements with HPI.

NOTE 19 - LEGAL PROCEEDINGS

RAVICTI

On March 17, 2014, Hyperion received notice from Par Pharmaceutical, Inc. ("Par Pharmaceutical") that it had filed an ANDA with the FDA seeking approval for a generic version of the Company's medicine RAVICTI. The ANDA contained a Paragraph IV Patent Certification alleging that two of the patents covering RAVICTI, U.S. Patent No. 8,404,215, titled "Methods of therapeutic monitoring of nitrogen scavenging drugs," which expires in March 2032 (the "'215 patent"), and U.S. Patent No. 8,642,012, titled "Methods of treatment using ammonia scavenging drugs," which expires in September 2030 (the "'012 patent"), are invalid and/or will not be infringed by Par Pharmaceutical's manufacture, use or sale of the medicine for which the ANDA was submitted. Par Pharmaceutical did not challenge the validity, enforceability, or infringement of the Company's primary composition of matter patent for RAVICTI, U.S. Patent No. 5,968,979 titled "Triglycerides and ethyl esters of phenylalkanoic acid and phenylalkanoic acid useful in treatment of various disorders," which would have expired on February 7, 2015, but as to which Hyperion was granted an interim term of extension until February 7, 2016 and to which the U.S. PTO has granted a final term extension of 1,267 days, which extends the expiration date to July 28, 2018. Hyperion filed suit in the United States District Court for the Eastern District of Texas, Marshall Division, against Par Pharmaceutical on April 23, 2014 seeking an injunction to prevent the approval of Par Pharmaceutical's ANDA and/or to prevent Par Pharmaceutical from selling a generic version of RAVICTI, and the Company has taken over and is responsible for this patent litigation. On September 15, 2015, the Company received notice from Par Pharmaceutical that it had filed a Paragraph IV Patent Certification alleging that U.S. Patent No. 9,095,559 (the "'559 patent") is invalid and/or will not be infringed by Par Pharmaceutical's manufacture, use or sale of the medicine for which the ANDA was submitted. On March 14, 2016, the Company received notice from Par Pharmaceutical that it had filed a Paragraph IV Patent Certification alleging that U.S. Patent No. 9,254,278 (the "'278 patent") is invalid and/or will not be infringed by Par Pharmaceutical's manufacture, use or sale of the medicine for which the ANDA was submitted. On June 3, 2016, the Company received notice from Par Pharmaceutical that it had filed a Paragraph IV Patent Certification alleging that U.S. Patent No. 9,326,966 (the "'966 patent") is invalid and/or will not be infringed by Par Pharmaceutical's manufacture, use or sale of the medicine for which the ANDA was submitted. The Company filed suit in the United States District Court for the District of New Jersey against Par Pharmaceutical on June 30, 2016 (the "Par New Jersey action"), seeking an injunction to prevent the approval of Par Pharmaceutical's ANDA and/or to prevent Par Pharmaceutical from selling a generic version of RAVICTI. The lawsuit alleges that Par Pharmaceutical has infringed the '559 patent, the '278 patent and the '966 patent by filing an ANDA seeking approval from the FDA to market generic versions of RAVICTI prior to the expiration of the patents. The subject patents are listed in the Orange Book. The Par New Jersey action has been stayed pending the resolution of the PTAB's IPR of the '559 patent.

On April 29, 2015, Par Pharmaceutical filed Petitions for IPR of U.S. Patent 8,404,215 and U.S. Patent 8,642,012, two of the patents involved in the above mentioned RAVICTI cases. On November 4, 2015, the PTAB issued decisions instituting such IPRs. On September 29, 2016, the PTAB found all of the claims in U.S. Patent 8,404,215 to be unpatentable. The Company did not appeal the PTAB's final written decision with respect to U.S. Patent 8,404,215. On November 3, 2016, the PTAB issued a final written decision holding all of the claims of U.S. Patent 8,642,012 patentable. On December 29, 2016, Par Pharmaceutical filed a notice of appeal with the Federal Circuit to appeal the final written decision of the PTAB concerning the patentability of U.S. Patent 8,642,012. On September 4, 2015, the Company received notice from Lupin of Lupin's Paragraph IV Patent Certification against the '215 patent and the '012 patent, advising that Lupin had filed an ANDA with the FDA for a generic version of RAVICTI. On November 6, 2015, the Company also received Notice of Lupin's Paragraph IV Patent Certification against the '559 patent. Lupin has not advised the Company as to the timing or status of the FDA's review of its filing. On October 19, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Lupin seeking an injunction to prevent the approval of the ANDA. The lawsuit alleges that Lupin has infringed the '215 patent, the '012 patent and the '559 patent by filing an ANDA seeking approval from the FDA to market generic versions of RAVICTI prior to the expiration of the patents. The subject patents are listed in the Orange Book. On April 6, 2016, the Company filed an amended complaint in the United States District Court for the District of New Jersey against Lupin alleging that Lupin has infringed the '559 patent by filing an ANDA seeking approval from the FDA to market generic versions of RAVICTI prior to expiration of the '559 patent. The commencement of the patent infringement lawsuit stays, or bars, FDA approval of Lupin's ANDA for 30 months or until an earlier district court decision that the subject patents are not infringed or are invalid. On April 18, 2016, the Company received notice from Lupin of Lupin's Paragraph IV Patent Certification against the '278 patent. On July 6, 2016, the Company received notice from Lupin of Lupin's Paragraph IV Patent Certification against the '966 patent. The Company filed suit in the United States District Court for the District of New Jersey against Lupin on July 21, 2016, seeking an injunction to prevent the approval of Lupin's ANDA and/or to prevent Lupin from selling a generic version of RAVICTI. The lawsuit alleges that Lupin has infringed the '278 patent and the '966 patent by filing an ANDA seeking approval from the FDA to market generic versions of RAVICTI prior to the expiration of the patents. The subject patents are listed in the Orange Book. The Lupin New Jersey actions have been stayed pending the resolution of the PTAB's IPR of the '559 patent.

On April 1, 2016, Lupin filed a Petition for IPR of U.S. Patent 9,095,559, a patent currently at issue in the Lupin RAVICTI case. On September 30, 2016, the PTAB issued a decision instituting the IPR. On September 26, 2017, the PTAB issued its final written decision, ruling that the challenged claims of the '559 patent are unpatentable. The Company filed a Notice of Appeal on November 22, 2017. On March 27, 2017, Lupin filed a Petition to request an IPR of the '278 patent and a Petition to request an IPR of the '966 patent. The Company filed its response on the '966 patent on July 6, 2017. The Company's preliminary patent owner response for the '278 patent was filed on July 24, 2017. On September 28, 2017, the PTAB issued its orders granting Lupin's petitions to institute an IPR of the '278 and the '966 patents. The PTAB must issue a final written decision on the IPRs no later than September 28, 2018.

On July 13, 2017, Par Pharmaceutical filed Petitions for IPR of the '559, '278, and '966 patents. The Company filed its Preliminary Patent Owner Responses on November 6, 2017. The IPR requests were granted on January 30, 2018.

On August 8, 2017, the Company filed suit against Lupin and Par Pharmaceutical, alleging infringement of U.S. Patent No. 9,561,197 ("the '197 Patent"), in the United States District Court for New Jersey, Case Nos. 1:17-cv-05900 and 1:17-cv-05901, respectively. Par Pharmaceutical and Lupin have answered and counterclaimed.

On January 12, 2018, Lupin filed a petition for IPR (IPR 2018-00459) of the '197 Patent. The Company's Preliminary Patent Owner Response is due by April 12, 2018.

RAYOS

On July 15, 2013, the Company received a Paragraph IV Patent Certification from Teva Pharmaceuticals Industries Limited (formerly known as Actavis Laboratories FL, Inc., which itself was formerly known as Watson Laboratories, Inc. – Florida) ("Teva"), advising that Teva had filed an Abbreviated New Drug Application ("ANDA") with the FDA for a generic version of RAYOS, containing up to 5 mg of prednisone. On August 26, 2013, the Company, together with Jagotec, filed suit in the United States District Court for the District of New Jersey against Teva, Actavis Pharma, Inc., Andrx Corp., and Actavis, Inc. seeking an injunction to prevent the approval of the ANDA.

On October 1, 2015, the Company's subsidiary Horizon Pharma Switzerland GmbH, as well as Jagotec, entered into a license and settlement agreement (the "Teva settlement agreement") with Teva relating to the Company's and Jagotec's patent infringement litigation against Teva. Under the Teva settlement agreement, the Company and Jagotec granted Teva a non-exclusive license to manufacture and commercialize Teva's generic version of RAYOS tablets in the United States after December 23, 2022 (the "Teva generic entry date"); however, Teva may be able to enter the market earlier under certain circumstances. Such events relate to the resolution of any other third-party RAYOS patent litigation, the entry of other generic versions of RAYOS tablets or certain substantial reductions in RAYOS prescriptions over specified periods of time. The Company and Jagotec also agreed that during the 180 days after the Teva generic entry date, the license granted to Teva would be exclusive with respect to any third-party generic version of RAYOS tablets. The court entered the stipulation of dismissal and closed the case on December 4, 2015.

PENNSAID 2%

On November 13, 2014, the Company received a Paragraph IV Patent Certification from Watson Laboratories, Inc., now known as Actavis Laboratories UT, Inc. ("Actavis UT"), advising that Actavis UT had filed an ANDA with the FDA for a generic version of PENNSAID 2%. On December 23, 2014, the Company filed suit in the United States District Court for the District of New Jersey against Actavis Laboratories UT, Inc., and Actavis plc (collectively "Actavis") seeking an injunction to prevent the approval of the ANDA. The lawsuit alleged that Actavis has infringed U.S. Patents 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164, and 8,871,809 by filing an ANDA seeking approval from the FDA to market a generic version of PENNSAID 2% prior to the expiration of certain of the Company's patents listed in the FDA's Orange Book ("Orange Book").

On June 30, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Actavis for patent infringement of U.S. Patent 9,066,913. On August 11, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Actavis for patent infringement of U.S. Patent 9,101,591. On September 17, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Actavis for patent infringement of U.S. Patent 9,132,110. These three cases were consolidated with the case filed against Actavis on December 23, 2014. On October 27, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Actavis for patent infringement of U.S. Patents 9,168,304 and 9,168,305. On February 5, 2016, the Company filed suit in the United States District Court for the District of New Jersey against Actavis for patent infringement of U.S. Patent No. 9,220,784.

On August 17, 2016, the district court issued a Markman opinion holding certain of the asserted claims of U.S. Patents 8,252,838, 8,563,613, 9,066,913, 9,101,591, 9,168,304, 9,168,305, and 9,220,784 invalid as indefinite. On March 16, 2017, the court granted Actavis' motion for summary judgment of non-infringement of the asserted claims of U.S. Patents 8,546,450, 8,217,078 and 9,132,110. In view of the *Markman* and summary judgment decisions, a bench trial was held on March 21-30, 2017, regarding claim 12 of U.S. Patent 9,066,913. On May 14, 2017, the court issued its opinion upholding the validity of claim 12 of the '913 patent, which Actavis had previously admitted its proposed generic diclofenac sodium topical solution product would infringe. Actavis filed its Notice of Appeal on June 16, 2017. The Company filed its Notice of Appeal of the district court's rulings on certain claims of the '450, '078, '838, '613, '591, '304, '784, '913, '110, '304, '305', and '784 patents on June 9, 2017. The Company's opening brief was filed on August 14, 2017. Actavis's opening brief, challenging the district court's judgment on the '913 patent, was filed on October 10, 2017. The Company's brief defending the judgment on the '913 patent was filed on November 20, 2017.

On August 18, 2016, the Company filed suit in the United States District Court for the District of New Jersey against Actavis for patent infringement of U.S. Patents 9,339,551, 9,339,552, 9,370,501 and 9,375,412. All four patents of such patents are listed in the Orange Book and have claims that cover PENNSAID 2%. This litigation is currently stayed by agreement of the parties.

The Company received from Actavis a Paragraph IV Patent Certification Notice Letter dated September 27, 2016, against Orange Book listed U.S. Patent No. 9,415,029, advising that Actavis had filed an ANDA with the FDA for a generic version of PENNSAID 2%.

On December 2, 2014, the Company received a Paragraph IV Patent Certification against Orange Book listed U.S. Patents. 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164 and 8,741,956 from Paddock Laboratories, LLC ("Paddock") advising that Paddock had filed an ANDA with the FDA for a generic version of PENNSAID 2%. On January 9, 2015, the Company received from Paddock another Paragraph IV Patent Certification against newly Orange Book listed U.S. Patent No. 8,871,809. On January 13, 2015 and January 14, 2015, the Company filed suits in the United States District Court for the District of New Jersey and the United States District Court for the District of Delaware, respectively, against Paddock seeking an injunction to prevent the approval of the ANDA.

On May 6, 2015, the Company entered into a settlement and license agreement (the "Perrigo settlement agreement") with Perrigo Company plc and its subsidiary Paddock (collectively, "Perrigo"). The Perrigo settlement agreement provides for a full settlement and release by both the Company and Perrigo of all claims that were or could have been asserted in the litigation and that arise out of the issues that were the subject of the litigation or Perrigo's generic version of PENNSAID 2%. A stipulation of dismissal was entered by the district court on May 13, 2015.

Under the Perrigo settlement agreement, the Company granted Perrigo a non-exclusive license to manufacture and commercialize Perrigo's generic version of PENNSAID 2% in the United States after January 10, 2029; however, Perrigo may be able to enter the market earlier under certain circumstances. Such events relate to the resolution of any other third-party PENNSAID 2% patent litigation, the entry of other third-party generic versions of PENNSAID 2% or certain substantial reductions in the Company's PENNSAID 2% shipments over specified periods of time.

In certain circumstances following the entry of other third-party generic versions of PENNSAID 2%, the Company may be required to supply Perrigo PENNSAID 2% as its authorized distributor of generic PENNSAID 2%, with the Company receiving specified percentages of any net sales by Perrigo.

On February 2, 2015, the Company received a Paragraph IV Patent Certification against Orange Book listed U.S. Patents 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164, 8,741,956 and 8,871,809 from Taro Pharmaceuticals USA, Inc. and Taro Pharmaceutical Industries, Ltd. (collectively, "Taro") advising that Taro had filed an ANDA with the FDA for a generic version of PENNSAID 2%. On March 13, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Taro seeking an injunction to prevent the approval of the ANDA.

On September 9, 2015, certain subsidiaries of the Company (the "Horizon Subsidiaries") entered into a settlement and license agreement with Taro (the "Taro settlement agreement") relating to the Horizon Subsidiaries' patent infringement litigation against Taro. The Taro settlement agreement provides for a full settlement and release by the Horizon Subsidiaries and Taro of all claims that were or could have been asserted in the litigation and that arise out of the issues that were subject of the litigation or Taro's generic version of PENNSAID 2%. A stipulation of dismissal was entered by the district court on November 3, 2015.

Under the Taro settlement agreement, the Horizon Subsidiaries granted Taro a non-exclusive license to manufacture and commercialize Taro's generic version of PENNSAID 2% in the United States after January 10, 2029; however, Taro may be able to enter the market earlier under certain circumstances. Such events relate to the resolution of any other third-party PENNSAID 2% patent litigation, the entry of other third-party generic versions of PENNSAID 2% or certain substantial reductions in the Company's PENNSAID 2% shipments over specified periods of time.

On March 18, 2015, the Company received a Paragraph IV Patent Certification against Orange Book listed U.S. Patents 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164, 8,741,956 and 8,871,809 from Lupin Limited advising that Lupin Limited had filed an ANDA with the FDA for generic version of PENNSAID 2%. On April 30, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Lupin Limited and Lupin Pharmaceuticals Inc. (collectively, "Lupin"), seeking an injunction to prevent the approval of the ANDA. The lawsuit alleges that Lupin has infringed U.S. Patents 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164 and 8,871,809 by filing an ANDA seeking approval from the FDA to market generic versions of PENNSAID 2% prior to the expiration of certain of the Company's patents listed in the Orange Book.

On June 30, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Lupin for patent infringement of U.S. Patent No. 9,066,913. On August 11, 2015, the Company filed an amended complaint in the United States District Court for the District of New Jersey against Lupin that added U.S. Patent No. 9,101,591 to the litigation concerning U.S. Patent 9,066,913. On September 17, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Lupin for patent infringement of U.S. Patent 9,132,110.

On October 27, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Lupin for patent infringement of U.S. Patents 9,168,304 and 9,168,305. On February 5, 2016, the Company filed suit in the United States District Court for the District of New Jersey against Lupin for patent infringement of U.S. Patent No. 9,220,784. On August 18, 2016, the Company filed suit in the United States District Court for the District of New Jersey against Lupin for patent infringement of U.S. Patents 9,339,551, 9,339,552, 9,370,501 and 9,375,412. All seven patents, U.S. Patents 9,168,304, 9,168,305, 9,220,784, 9,339,551, 9,339,552, 9,370,501 and 9,375,412, are listed in the Orange Book and have claims that cover PENNSAID 2%. All of the infringement actions brought against Lupin remain pending, with certain claims of the '809, '913, '450, '110, '551, '552, '412 and '501 patents being asserted. The decisions reached by the court in the related Actavis actions regarding the '809, '913, '450, '110, '551, '552, '412 and '501 patents as described above, are expected to apply to the same claims asserted against Lupin in these actions. The court has not yet set a trial date for the Lupin actions.

The Company received from Teligent, Inc., formerly known as IGI Laboratories, Inc. ("Teligent"), a Paragraph IV Patent Certification dated March 24, 2015 against Orange Book listed U.S. Patents 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164, 8,741,956 and 8,871,809 advising that Teligent had filed an ANDA with the FDA for a generic version of PENNSAID 2%. On May 21, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Teligent seeking an injunction to prevent the approval of the ANDA. The lawsuit alleged that Teligent has infringed U.S. Patents 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164 and 8,871,809 by filing an ANDA seeking approval from the FDA to market generic versions of PENNSAID 2% prior to the expiration of certain of the Company's patents listed in the Orange Book.

On June 30, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Teligent for patent infringement of U.S. Patent 9,066,913. On August 11, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Teligent for patent infringement of U.S. Patent 9,101,591. On September 17, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Teligent for patent infringement of U.S. Patent No. 9,132,110.

On October 27, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Teligent for patent infringement of U.S. Patents 9,168,304 and 9,168,305. On February 5, 2016, the Company filed suit in the United States District Court for the District of New Jersey against Teligent for patent infringement of U.S. Patent 9,220,784.

The Company entered into a settlement and license agreement with Teligent (the "Teligent settlement agreement"), effective May 9, 2016, relating to the patent infringement litigation against Teligent. The Teligent settlement agreement provides for a full settlement and release by both the Company and Teligent of all claims that were or could have been asserted in the litigation and that arise out of the issues that were subject of the litigation or Teligent's generic version of PENNSAID 2%. A stipulation of dismissal was entered by the district court on May 2, 2016.

Under the Teligent settlement agreement, the Company granted Teligent a non-exclusive license to manufacture and commercialize Teligent's generic version of PENNSAID 2% in the United States after January 10, 2029; however, Teligent may be able to enter the market earlier under certain circumstances. Such events relate to the resolution of any other third-party PENNSAID 2% patent litigation, the entry of other third-party generic versions of PENNSAID 2% or certain substantial reductions in the Company's PENNSAID 2% shipments over specified periods of time. In certain circumstances following the entry of other third-party generic versions of PENNSAID 2%, the Company may be required to supply Teligent PENNSAID 2% as an authorized distributor of generic PENNSAID 2%, with the Company receiving specified percentages of any net sales by Teligent.

The Company received from Amneal Pharmaceuticals LLC ("Amneal") a Paragraph IV Patent Certification dated April 2, 2015 against Orange Book listed U.S. Patents 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164, 8,741,956 and 8,871,809 advising that Amneal had filed an ANDA with the FDA for a generic version of PENNSAID 2%. On May 15, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Amneal seeking an injunction to prevent the approval of the ANDA. The lawsuit alleged that Amneal has infringed U.S. Patents 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164 and 8,871,809 by filing an ANDA seeking approval from the FDA to market generic versions of PENNSAID 2% prior to the expiration of certain of the Company's patents listed in the Orange Book.

On June 30, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Amneal for patent infringement of U.S. Patent 9,066,913. On August 11, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Amneal for patent infringement of U.S. Patent 9,101,591. On September 17, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Amneal for patent infringement of U.S. Patent 9,132,110. All three patents, U.S. Patents 9,066,913, 9,101,591 and 9,132,110, are listed in the Orange Book and have claims that cover PENNSAID 2%.

On October 27, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Amneal for patent infringement of U.S. Patents 9,168,304 and 9,168,305. On February 5, 2016, the Company filed suit in the United States District Court for the District of New Jersey against Amneal for patent infringement of U.S. Patent 9,220,784. All three patents, U.S. Patents 9,168,304, 9,168,305, and 9,220,784, are listed in the Orange Book and have claims that cover PENNSAID 2%.

On April 18, 2016, the Company entered into a settlement and license agreement (the "Amneal settlement agreement") with Amneal relating to the Company's patent infringement litigation against Amneal. The Amneal settlement agreement provides for a full settlement and release by both the Company and Amneal of all claims that were or could have been asserted in the litigation and that arise out of the issues that were the subject of the litigation or Amneal's generic version of PENNSAID 2%.

Under the Amneal settlement agreement, the Company granted Amneal a non-exclusive license to manufacture and commercialize Amneal's generic version of PENNSAID 2% in the United States after January 10, 2029; however, Amneal may be able to enter the market earlier under certain circumstances. Such events relate to the resolution of any other third-party PENNSAID 2% patent litigation or the entry of other third-party generic versions of PENNSAID 2% and to take steps necessary to develop inventory of, and prepare to commercialize, Amneal's generic version of PENNSAID 2% during certain limited periods prior to the license effective date.

In certain circumstances following the entry of other third-party generic versions of PENNSAID 2%, the Company may be required to supply Amneal with PENNSAID 2% as a non-exclusive, authorized distributor of generic PENNSAID 2%, with the Company receiving specified percentages of any net sales by Amneal.

The Company received from Apotex Inc. ("Apotex") a Paragraph IV Patent Certification Notice Letter dated April 1, 2016, against Orange Book listed U.S. Patents 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164, 8,741,956, 8,871,809, 9,066,913, 9,101,591, 9,132,110, 9,168,304, 9,168,305 and 9,220,784 advising that Apotex had filed an ANDA with the FDA for a generic version of PENNSAID 2%. The Company also received from Apotex a second Paragraph IV Patent Certification Notice Letter dated June 30, 2016, against Orange Book listed U.S. Patents 9,339,551 and 9,339,552, advising that Apotex had filed an ANDA with the FDA for a generic version of PENNSAID 2%. The Company also received from Apotex a third Paragraph IV Patent Certification Notice Letter dated September 21, 2016, against Orange Book listed U.S. Patent 9,415,029, advising that Apotex had filed an ANDA with the FDA for a generic version of PENNSAID 2%. The Company also received from Apotex additional Paragraph IV Patent Certification Notice Letters dated April 20, 2017 and April 27, 2017 against Orange Book listed U.S. Patent 9,539,335 and 9,370,501.

VIMOVO

Currently, patent litigation is pending in the United States District Court for the District of New Jersey and the Court of Appeals for the Federal Circuit against three generic companies intending to market VIMOVO prior to the expiration of certain of the Company's patents listed in the Orange Book. These cases are in the United States District Court for the District of New Jersey. They are collectively known as the VIMOVO cases, and involve the following sets of defendants: (i) Dr. Reddy's Laboratories Inc. and Dr. Reddy's Laboratories Ltd. (collectively, "Dr. Reddy's"); (ii) Lupin; and (iii) Mylan Pharmaceuticals Inc., Mylan Laboratories Limited, and Mylan Inc. (collectively, "Mylan"). Patent litigation in the United States District Court for the District of New Jersey against a fourth generic company, Actavis Laboratories FL., Inc. and Actavis Pharma, Inc. (collectively, "Actavis Pharma"), was dismissed on January 10, 2017 after the court granted Actavis' motion to compel enforcement of a settlement agreement. On February 3, 2017, the Company appealed this dismissal decision to the Court of Appeals for the Federal Circuit. Patent litigation in the United States District Court for the District of New Jersey against a fifth generic company, Anchen Pharmaceuticals Inc. ("Anchen"), was dismissed on June 9, 2014 after Anchen recertified under Paragraph III. The Company understands that Dr. Reddy's has entered into a settlement with AstraZeneca with respect to patent rights directed to Nexium® (esomeprazole) for the commercialization of VIMOVO. The settlement agreement, however, has no effect on the Aralez VIMOVO patents, which are still the subject of patent litigations. As part of the Company's acquisition of the U.S. rights to VIMOVO, the Company has taken over and is responsible for the patent litigation that includes the Aralez patents licensed to the Company under the amended and restated collaboration and license agreement for the United States with Aralez.

The VIMOVO cases were filed on April 21, 2011, July 25, 2011, October 28, 2011, January 4, 2013, May 10, 2013, June 28, 2013, October 23, 2013, May 13, 2015 and November 24, 2015 and collectively include allegations of infringement of U.S. Patent Nos. 6,926,907, 8,557,285, 8,852,636, and 8,858,996 (the "'996 patent"). On June 18, 2015, the Company amended the complaints to add a charge of infringement of U.S. Patent No. 8,865,190 (the "'190 patent"). On January 7, 2016, Actavis Pharma asserted a counterclaim for declaratory judgment of invalidity and non-infringement of U.S. Patent No. 8,945,621 (the "'621 patent"). On January 25, 2016, the Company filed a new case against Actavis Pharma including allegations of infringement of U.S. Patent Nos. 9,161,920 and 9,198,888. This case was subsequently consolidated with the Actavis Pharma case involving the '996 patent, the '190 patent and U.S. Patent No. 8,852,636. On February 10, 2016, the Company amended the complaints against Dr. Reddy's, Lupin, and Mylan to add charges of infringement of U.S. Patent Nos. 9,161,920 and 9,198,888. On February 19, 2016, Mylan asserted a counterclaim for declaratory judgment of invalidity and non-infringement of U.S. Patent No. 9,220,698. On August 11, 2016, the Company filed new complaints asserting the '621 patent and U.S. Patent Nos. 9,220,698, and 9,345,695 against the defendants. On December 6, 2016, the Company asserted U.S. Patent No. 9,393,208 (the "'208 patent") against Lupin, Mylan, and Actavis in amended complaints, and against Dr. Reddy's in a new complaint.

"Case I" consists of the cases asserting U.S. Patent Nos. 8,557,285 and 6,926,907. "Case II" consists of the cases asserting the '996 patent, the '190 patent and U.S. Patent Nos. 8,852,636, 9,161,920, and 9,198,888. "Case III" consists of the cases asserting U.S. Patent Nos. 8,945,621, 9,220,698, 9,345,695, and the '208 patent against Lupin and Mylan, and the case asserting U.S. Patent Nos. 8,945,621, 9,220,698, 9,345,695, and the '208 patent against Dr. Reddy's.

On December 19, 2016, defendant Actavis filed a motion to compel enforcement of settlement agreement related to Cases I, II, and III. On December 22, 2016, Magistrate Judge Arpert entered a report and recommendation that Actavis' motion to compel the enforcement of settlement be granted. On December 30, 2016, the Honorable Judge Mary Cooper ordered the adoption of the report and recommendation. On January 10, 2017, an order of dismissal was entered for all claims in Cases I, II and III. The Company appealed the district court's order enforcing the settlement with Actavis to the Court of Appeals for the Federal Circuit. Briefing before the Federal Circuit has been completed.

The Case I cases were consolidated for discovery. The court issued a claim construction order for Case I and conducted trial beginning on January 12, 2017. On May 12, 2016, the court granted Dr. Reddy's motion for summary judgment of non-infringement of U.S. Patent No. 6,926,907 with respect to one of Dr. Reddy's two ANDAs. On January 12, 2017, a six-day bench trial commenced against defendants Dr. Reddy's and Mylan before Honorable Judge Mary Cooper in the District of New Jersey for Case I. The patents at issue in this trial included two Orange Book listed patents: U.S. Patent Nos. 6,926,907 and 8,557,285. Defendant Lupin formerly entered into a stay pending the entry of judgment in Case I. On June 26, 2017, the court issued its opinion upholding the validity of the '285 and '907 patents and finding that Dr. Reddy's, Mylan's, and Lupin's proposed generic naproxen/esomeprazole magnesium products would all infringe at least one of the two patents. The court entered the final judgment on July 21, 2017. Dr. Reddy's, Mylan and Lupin appealed the District Court's judgment to the Court of Appeals for the Federal Circuit, and the Company appealed the District Court's entry of judgment of non-infringement on the '907 in favor of Dr. Reddy's.

The Case II and Case III cases have been consolidated for discovery. On January 19, 2017, the court entered a scheduling order for Case II and Case III, which was subsequently updated. The court's scheduling order requires, *inter alia*, filing and serving of the opening claim construction submissions by May 26, 2017. The court has not issued a claim construction order in Case II. A trial date for Cases II and III has not yet been set. On December 20, 2016, Mylan filed a motion to dismiss the Company's first amended complaint for patent infringement in Case III. On August 18, 2017, the District Court granted Dr. Reddy's and Mylan's motions to dismiss the Company's claims relating to the '621 patent.

On June 5, 2015, the Coalition for Affordable Drugs VII LLC ("Coalition for Affordable Drugs") filed a Petition for inter partes review ("IPR") of the '996 patent, one of the patents in litigation in the above referenced VIMOVO cases. On December 17, 2015, the United States Patent and Trademark Office (the "U.S. PTO") denied such Petition for IPR.

On August 7, 2015, the Coalition for Affordable Drugs filed another Petition for IPR of U.S. Patent No. 8,852,636, one of the patents in litigation in the above referenced VIMOVO cases. On February 11, 2016, the U.S. PTO denied such Petition for IPR.

On August 12, 2015, the Coalition for Affordable Drugs filed another Petition for IPR of the '621 patent, one of the patents in litigation in the above referenced VIMOVO cases. On February 22, 2016, the Patent Trial and Appeal Board (the "PTAB") issued a decision to institute the IPR. The PTAB hearing for the '621 patent was held on November 16, 2016. The PTAB issued a final written decision finding the '621 patent valid on February 21, 2017.

On August 19, 2015, Lupin filed Petitions for IPR of the '996 patent, the '190 patent and U.S. Patent No. 8,852,636, all patents in litigation in the above referenced VIMOVO cases. On March 1, 2016, the PTAB issued decisions to institute the IPRs for the '996 patent" and the '190 patent. On March 1, 2016, the PTAB denied the Petition for IPR for U.S. Patent No. 8,852,636. The PTAB hearings for the '996 patent and '190 patent were both held on November 29, 2016. On February 28, 2017, the PTAB issued final written decisions on the IPRs of the '996 and '190 patents, upholding the validity of both patents.

On August 24, 2017, Mylan filed a Petition for IPR of the '698 patent. The Company filed its Preliminary Patent Owner Response on December 12, 2017. The parties are awaiting the PTAB's decision on whether to institute an IPR proceeding.

On December 4, 2017, Mylan filed a Petition for IPR of the '208 patent. The Company's Preliminary Patent Owner Response is due on March 4, 2018.

Other

Beginning on March 8, 2016, two federal securities class action lawsuits (captioned Schaffer v. Horizon Pharma plc, et al., Case No. 16-cv-01763-JMF and Banie v. Horizon Pharma plc, et al., Case No. 16-cv-01789-JMF) were filed in the United States District Court for the Southern District of New York against the Company and certain of the Company's current and former officers (the "Officer Defendants"). On March 24, 2016, the court consolidated the two actions under Schaffer v. Horizon Pharma plc, et al. On June 3, 2016, the court appointed Locals 302 and 612 of the International Union of Operating Engineers-Employers Construction Industry Retirement Trust and the Carpenters Pension Trust Fund for Northern California as lead plaintiffs and Labaton Sucharow LLP as lead counsel. On July 25, 2016, lead plaintiffs and additional named plaintiff Automotive Industries Pension Trust Fund filed their consolidated complaint, which they subsequently amended on October 7, 2016, including additional current and former officers, the Company's Board of Directors (the "Director Defendants"), and underwriters involved with the Company's April 2015 public offering (the "Underwriter Defendants") as defendants. The plaintiffs allege that certain of the Company and the Officer Defendants violated sections 10(b) and 20(a) of the Securities Exchange Act of 1934, as amended, by making false and/or misleading statements about, among other things: (a) the Company's financial performance, (b) the Company's business prospects and drug-pricing practices, (c) the Company's sales and promotional practices, and (d) the Company's design, implementation, performance, and risks associated with the Company's Prescriptions-Made-Easy program. The plaintiffs allege that certain of the Company, the Director Defendants and the Underwriter Defendants violated sections 11, 12(a)(2) and 15 of the Securities Act of 1933, as amended (the "Securities Act"), in connection with the Company's April 2015 public offering. The plaintiffs seek, among other things, an award of damages allegedly sustained by plaintiffs and the putative class, including a reasonable allowance for costs and attorneys' fees. On November 14, 2016, all defendants moved to dismiss the plaintiffs' amended complaint. Plaintiffs filed their opposition to the motion to dismiss on December 21, 2016. On January 18, 2018, the District Court dismissed all plaintiffs' claims against all defendants, and denied the plaintiffs any further opportunity to amend their complaint. On February 16, 2018, plaintiffs filed a notice of appeal to the District Court's ruling.

NOTE 20 – SHAREHOLDERS' EQUITY

During the year ended December 31, 2017, the Company issued an aggregate of 2.0 million of ordinary shares in connection with stock option exercises, the vesting of restricted stock units, employee share purchase plan purchases and the vesting of performance stock units. The Company received a total of $9.2 million in net proceeds in connection with such issuances.

During the year ended December 31, 2017, the Company issued an aggregate of 391,500 ordinary shares upon the cash exercise of warrants and the Company received proceeds of $1.8 million representing the aggregate exercise price for such warrants. In addition, warrants to purchase an aggregate of 704,285 ordinary shares of the Company were exercised in cashless exercises, resulting in the issuance of 523,520 ordinary shares. As of December 31, 2017, there were no outstanding warrants to purchase ordinary shares of the Company.

During the year ended December 31, 2017, the Company made payments of $6.5 million for employee withholding taxes relating to share-based awards.

On January 1, 2017, the Company adopted ASU No. 2016-09. As a result of the adoption, $7.2 million of excess tax benefits that had not previously been recognized, as the related tax deduction had not reduced current taxes payable, were recorded on a modified retrospective basis through a cumulative effect adjustment to its accumulated deficit as of January 1, 2017.

In May 2016, the Company's board of directors authorized a share repurchase program pursuant to which the Company may repurchase up to 5,000,000 of its ordinary shares. In May 2017, the Company's board of directors reauthorized a share repurchase program pursuant to which the Company may repurchase up to 16,000,000 of its ordinary shares. As of December 31, 2017, the Company had repurchased 100,000 of its ordinary shares under this repurchase program, for total consideration of $1.0 million. The timing and amount of future repurchases, if any, will depend on a variety of factors, including the price of the Company's ordinary shares, alternative investment opportunities, the Company's cash resources, restrictions under the Credit Agreement and market conditions.

NOTE 21 – EQUITY INCENTIVE PLANS

Employee Stock Purchase Plan

2014 Employee Stock Purchase Plan. On May 17, 2014, HPI's board of directors adopted the 2014 Employee Stock Purchase Plan (the "2014 ESPP"). On September 18, 2014, at a special meeting of the stockholders of HPI (the "Special Meeting"), HPI's stockholders approved the 2014 ESPP. Upon consummation of the Company's merger transaction with Vidara (the "Vidara Merger"), the Company assumed the 2014 ESPP.

As of December 31, 2017, an aggregate of 3,002,169 ordinary shares were authorized and available for future issuance under the 2014 ESPP.

Share-Based Compensation Plans

2005 Stock Plan. In October 2005, HPI adopted the 2005 Stock Plan (the "2005 Plan"). Upon the signing of the underwriting agreement related to HPI's initial public offering, on July 28, 2011, no further option grants were made under the 2005 Plan. All stock awards granted under the 2005 Plan prior to July 28, 2011 continue to be governed by the terms of the 2005 Plan. Upon consummation of the Vidara Merger, the Company assumed the 2005 Plan.

2011 Equity Incentive Plan. In July 2010, HPI's board of directors adopted the 2011 Equity Incentive Plan (the "2011 EIP"). In June 2011, HPI's stockholders approved the 2011 EIP, and it became effective upon the signing of the underwriting agreement related to HPI's initial public offering on July 28, 2011. Upon consummation of the Vidara Merger, the Company assumed the 2011 EIP, and upon the effectiveness of the Horizon Pharma Public Limited Company 2014 Equity Incentive Plan (the "2014 EIP"), no additional stock awards were or will be made under the 2011 Plan, although all outstanding stock awards granted under the 2011 Plan continue to be governed by the terms of the 2011 Plan.

2014 Equity Incentive Plan and 2014 Non-Employee Equity Plan. On May 17, 2014, HPI's board of directors adopted the 2014 EIP and the Horizon Pharma Public Limited Company 2014 Non-Employee Equity Plan (the "2014 Non-Employee Equity Plan"). At the Special Meeting, HPI's stockholders approved the 2014 EIP and 2014 Non-Employee Equity Plan. Upon consummation of the Vidara Merger, the Company assumed the 2014 EIP and 2014 Non-Employee Equity Plan, which serve as successors to the 2011 EIP.

The 2014 EIP provides for the grant of incentive and nonstatutory stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards, performance awards and other stock awards that may be settled in cash, shares or other property to the employees of the Company (or a subsidiary company). During the year ended December 31, 2017, the compensation committee of the Company's board of directors (the "Committee") approved an amendment to the 2014 EIP to reserve additional shares to be used exclusively for grants of awards to individuals who were not previously employees or non-employee directors of the Company (or following a bona fide period of non-employment with the Company) (the "2017 Inducement Pool"), as an inducement material to the individual's entry into employment with the Company within the meaning of Rule 5635(c)(4) of the NASDAQ Listing Rules, ("Rule 5635(c)(4)"). The 2014 EIP was amended by the Committee without shareholder approval pursuant to Rule 5635(c)(4).

The 2014 Non-Employee Equity Plan provides for the grant of nonstatutory stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards and other forms of stock awards that may be settled in cash, shares or other property to the non-employee directors and consultants of the Company (or a subsidiary company). The Company's board of directors has authority to suspend or terminate the 2014 Non-Employee Equity Plan at any time.

As of December 31, 2017, an aggregate of 3,885,178 ordinary shares were authorized and available for future grants under the 2014 EIP, of which 356,636 shares relate to the 2017 Inducement Pool. As of December 31, 2017, 499,913 ordinary shares were authorized and available for future grants under the 2014 Non-Employee Equity Plan.

Stock Options

The following table summarizes stock option activity during the year ended December 31, 2017:

	Options	Weighted Average Exercise Price	Weighted Average Contractual Term Remaining (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2016	13,627,519	$ 18.17	7.60	$ 35,157
Granted	2,077,215	16.40		
Exercised	(338,467)	6.27		
Forfeited	(644,752)	18.37		
Expired	(446,199)	22.75		
Outstanding as of December 31, 2017	**14,275,316**	**18.04**	**6.97**	**25,005**
Vested and Expected to vest as of December 31, 2017	**13,789,210**	**18.02**	**6.92**	**24,960**
Exercisable as of December 31, 2017	**9,365,306**	**$ 16.96**	**6.36**	**$ 24,158**

Stock options typically have a contractual term of ten years from grant date.

The following table summarizes the Company's outstanding stock options at December 31, 2017:

	Options Outstanding			Options Exercisable		
Exercise Price Ranges	Number of options outstanding	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (in years)	Number Exercisable	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (in years)
$2.01 - $4.00	742,582	$ 2.67	5.08	742,582	$ 2.67	5.08
$4.01- $8.00	1,209,543	6.29	4.57	1,199,789	6.28	4.56
$8.01 - $12.00	721,063	9.19	5.41	677,499	9.17	5.34
$12.01 - $17.00	2,552,212	14.12	6.87	1,810,195	14.05	6.11
$17.01 - $22.00	3,252,701	18.11	8.33	1,018,088	18.83	7.51
$22.01 - $28.00	3,412,700	22.31	7.24	2,342,100	22.30	7.23
$28.01 - $36.00	2,384,515	29.47	7.14	1,575,053	29.39	7.01
	14,275,316	**$ 18.04**	**6.97**	**9,365,306**	**$ 16.96**	**6.36**

During the years ended December 31, 2017, 2016 and 2015, the Company granted stock options to purchase an aggregate of 2,077,215, 2,057,247 and 8,010,638 ordinary shares, respectively, with a weighted average grant date fair value of $7.96, $11.58 and $16.07, respectively.

The total intrinsic value of the options exercised during the years ended December 31, 2017, 2016 and 2015 was $2.6 million, $6.9 million and $15.6 million, respectively. The total fair value of stock options vested during the years ended December 31, 2017, 2016 and 2015 was $41.3 million, $55.6 million and $11.4 million, respectively.

The fair value of each stock option award is estimated on the date of grant using the Black-Scholes option pricing model. The determination of the fair value of each stock option is affected by the Company's share price on the date of grant, as well as assumptions regarding a number of highly complex and subjective variables. These variables include, but are not limited to, the Company's expected share price volatility over the expected life of the awards and actual and projected stock option exercise behavior. The weighted average fair value per share of stock option awards granted during the years ended December 31, 2017, 2016 and 2015, and assumptions used to value stock options, are as follows:

	2017	2016	2015
Dividend yield	—	—	—
Risk-free interest rate	1.8%-2.2%	1.3%-2.2%	1.3% - 2.2%
Weighted average volatility	49.1%	73.2%	77.1%
Expected life (in years)	5.99	6.02	6.07
Weighted average grant date fair value per share of options granted	$ 7.96	$ 11.58	$ 16.07

Dividend yields

The Company has never paid dividends and does not anticipate paying any dividends in the near future. Additionally, the Credit Agreement (described in Note 16 above), as well as the indentures governing the 2024 Senior Notes and the 2023 Senior Notes (each as described in Note 16 above), contain covenants that restrict the Company from issuing dividends.

Risk-Free Interest Rate

The Company determined the risk-free interest rate by using a weighted average assumption equivalent to the expected term based on the U.S. Treasury constant maturity rate as of the date of grant.

Volatility

The Company used an average historical share price volatility of comparable companies to be representative of future share price volatility, as the Company did not have sufficient trading history for its ordinary shares.

Expected Term

Given the Company's limited historical exercise behavior, the expected term of options granted was determined using the "simplified" method since the Company does not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term. Under this approach, the expected term is presumed to be the average of the vesting term and the contractual life of the option.

Forfeitures

As share-based compensation expense recognized in the consolidated statements of comprehensive loss is based on awards ultimately expected to vest, it has been reduced for estimated forfeitures based on actual forfeiture experience, analysis of employee turnover and other factors. The Company adopted ASU No. 2016-09 on January 1, 2017 and has elected to retain a forfeiture rate after adoption.

Restricted Stock Units

The following table summarizes restricted stock unit activity for the year ended December 31, 2017:

	Number of Units	Weighted Average Grant-Date Fair Value Per Units
Outstanding as of December 31, 2016	3,367,871	$ 18.45
Granted	3,732,035	12.44
Vested	(1,222,920)	16.78
Forfeited	(593,136)	16.85
Outstanding as of December 31, 2017	**5,283,850**	**$ 14.77**

The grant-date fair value of restricted stock units is the closing price of the Company's shares on the date of grant.

During the years ended December 31, 2017, 2016 and 2015, the Company granted 3,732,035, 1,384,104 and 2,361,948 restricted stock units to acquire shares of the Company's ordinary shares to its employees and non-executive directors, respectively, with a weighted average grant date fair value of $12.44, $17.07 and $23.36, respectively. The restricted stock units vest annually, with a vesting period ranging from two to four years. The Company accounts for the restricted stock units as equity-settled awards in accordance with ASC 718. The total fair value of restricted stock units vested during the years ended December 31, 2017, 2016 and 2015 was $18.0 million, $16.2 million and $9.0 million, respectively.

Performance Stock Unit Awards

The following table summarizes performance stock unit awards ("PSUs") activity for the year ended December 31, 2017:

	Number of Units	Weighted Average Grant-Date Fair Value Per Unit	Average Illiquidity Discount	Recorded Weighted Average Fair Value Per Unit
Outstanding as of December 31, 2016	12,045,656			
Vested and issued	(25,000)	$ 12.36	0.0%	$ 13.30
Expired (1)	(3,927,440)	14.82	14.9%	12.60
Forfeited	(238,336)	10.86	7.5%	10.04
Outstanding as of December 31, 2017	**7,854,880**			

(1) During the year ended December 31, 2017, the first of three tranches of the Company's outstanding PSUs expired due to failure to meet the Company's minimum total compounded annual shareholder rate of return ("TSR") requirement.

In March 2015, the Committee approved the grant of 10,604,000 PSUs to certain members of the Company's executive committee, senior leadership team and other key employees. Of these PSUs, 7,998,000 were granted subject to shareholder approval of certain amendments of the 2014 EIP, which occurred on May 6, 2015. In May 2015, the Committee granted 1,264,000 PSUs to new and promoted key employees. In the third and fourth quarters of 2015, the Committee granted 1,120,000 PSUs to a new member of the Company's executive committee and key employees and 388,000 PSUs to non-executive committee members, respectively. In January 2016, the Committee approved the grant of 260,000 PSUs to certain members of the Company's senior leadership team.

All PSUs outstanding as of December 31, 2017 were granted in 2015 and 2016 and may vest if the Company's TSR over two performance measurement periods summarized below equals or exceeds a minimum of 15%.

Vesting Tranche	Percent of Total PSU Award	Beginning of Performance Measurement Period	End of Performance Measurement Period	Length of Performance Measurement Period (Years)
Tranche Two	33.3%	March 23, 2015	March 22, 2018	3.00
Tranche Three	33.3%	March 23, 2015	June 22, 2018	3.25

These outstanding PSUs may vest in amounts ranging from 25% to 100% based on the achievement of the following TSR over the two performance periods:

TSR Achieved	Vesting Amount
15%	25%
30%	50%
45%	75%
60%	100%

The TSR is based on the volume weighted average trading price ("VWAP") of the Company's ordinary shares over the twenty trading days ending on the last day of each of the two performance measurement periods versus the VWAP of the Company's ordinary shares over the twenty trading days ended March 23, 2015 of $21.50. The PSUs are subject to a post-vesting holding period of one year for 50% of the PSUs and two years for 50% of the PSUs for those who were members of the executive committee at the date of grant, and one year for 50% of the PSUs for all who were not executive committee members at the date of grant.

The Company accounts for the PSUs as equity-settled awards in accordance with ASC 718. Because the value of the PSUs is dependent upon the attainment of a level of TSR, it requires the impact of the market condition to be considered when estimating the fair value of the PSUs. As a result, the Monte Carlo model is applied and the most significant valuation assumptions used include:

	For the Years Ended December 31,		
	2017	2016	2015
Valuation date stock price	N/A	$ 17.72 - $21.07	$ 16.81 - $35.06
Expected volatility	N/A	76.8% - 77.6%	64.6% - 72.3%
Risk-free rate	N/A	1.0% - 1.2%	1.0% - 1.1%

The average estimated fair value of each outstanding PSU is as follows (allocated between groupings based on grant-date classification):

	Number of Units	Weighted Average Fair Value Per Unit	Average Illiquidity Discount	Recorded Weighted Average Fair Value Per Unit
Executive committee members	6,014,437	$ 15.16	17.1%	$ 12.57
Non-executive committee members	1,840,443	13.71	7.3%	12.71
	7,854,880	**$ 14.82**	**14.9%**	**$ 12.60**

During the years ended December 31, 2017, 2016 and 2015, the Company recorded an expense of $49.6 million, $48.6 million and $37.7 million, respectively, related to its PSUs.

Cash Long-Term Incentive Program

On November 5, 2014, the Committee approved a performance cash long-term incentive program for the members of the Company's executive committee and executive leadership team, including its executive officers (the "Cash Bonus Program"). Participants in the Cash Bonus Program were eligible for a specified cash bonus. The Cash Bonus Program pool funding of approximately $15.8 million was determined based on the Company's actual TSR over the period from November 5, 2014 to May 6, 2015, and the bonus could be earned and payable only if the TSR for the period from November 5, 2014 to November 4, 2017 was greater than 15%. The portion of the total bonus pool payable to individual participants was based on allocations established by the Committee. Participants must have remained employed by the Company through November 4, 2017 unless a participant's earlier departure from employment was due to death, disability, termination without cause or a change in control transaction. During the year ended December 31, 2017, the TSR did not exceed the minimum target requirement of 15% and the Cash Bonus Program expired without payment.

The Company accounted for the Cash Bonus Program under the liability method in accordance with ASC 718. Because vesting of the bonus pool was dependent upon the attainment of a VWAP of $18.37 or higher over the twenty trading days ended November 4, 2017, the Cash Bonus Program was considered to be subject to a "market condition" for the purposes of ASC 718. ASC 718 required the impact of the market condition to be considered when estimating the fair value of the bonus pool. As a result, the Monte Carlo simulation model was applied and the fair value was revalued at each reporting period. As of December 31, 2016, the estimated fair value was $4.8 million. During November 2017, the Cash Bonus Program expired without payout as the VWAP was not achieved. No amounts were accrued as of December 31, 2017 for the Cash Bonus Program. For the year ended December 31, 2017, the Company recorded a reduction in the expense of $3.5 million to the consolidated statement of comprehensive loss as a result of the valuation of the Cash Bonus Program. The most significant assumptions used when assessing the valuation of the Cash Bonus Program were as follows:

	For the Years Ended December 31,	
	2016	2015
Valuation date stock price	$ 16.18	$ 21.67
Expected volatility	74.7%	74.8%
Risk-free rate	0.78%	1.00%

Share-Based Compensation Expense

The following table summarizes share-based compensation expense included in the Company's consolidated statements of comprehensive (loss) income for the years ended December 31, 2017, 2016 and 2015 (in thousands):

	For the Years Ended December 31,		
	2017	2016	2015
Share-based compensation expense:			
Cost of goods sold	$ 2,469	$ 26	$ —
Research and development	9,263	9,413	6,590
Selling, general and administrative	109,821	104,705	79,196
Total share-based compensation expense	**$ 121,553**	**$ 114,144**	**$ 85,786**

During the year ended December 31, 2016, and prior to the adoption of ASU No. 2016-09, no material income tax benefit was recognized relating to share-based compensation expense and no tax benefits were realized from exercised stock options and vested restricted stock units, due to the Company's net loss position. After the adoption of ASU No. 2016-09, during the year ended December 31, 2017, the Company recognized $2.8 million of tax detriment related to share-based compensation resulting from the current share prices in effect at the time of the exercise of stock options and vesting of restricted stock units. In addition, during the year ended December 31, 2017, $16.4 million of deferred tax assets related to previously recognized share-based compensation expense related to PSUs was charged to income tax expense. As of December 31, 2017, the Company estimates that pre-tax unrecognized compensation expense of $124.9 million for all unvested share-based awards, including stock options, restricted stock units and PSUs, will be recognized through the fourth quarter of 2021. The Company expects to satisfy the exercise of stock options and future distribution of shares for restricted stock units and PSUs by issuing new ordinary shares which have been reserved under the 2014 EIP.

NOTE 22 – INCOME TAXES

The Company's (loss) income before benefit for income taxes by jurisdiction for the years ended December 31, 2017, 2016 and 2015 is as follows (in thousands):

	For the Years Ended December 31,		
	2017	2016	2015
Ireland	$ (16,956)	$ (27,955)	$ (10,746)
United States	(271,102)	(165,476)	(198,442)
Other foreign	(225,217)	(34,654)	76,476
Loss before benefit for income taxes	**$ (513,275)**	**$ (228,085)**	**$ (132,712)**

The components of the benefit for income taxes were as follows for the years ended December 31, 2017, 2016 and 2015 (in thousands):

	For the Years Ended December 31,		
	2017	2016	2015
Current provision			
Ireland	$ 2,922	$ 1,187	$ 1,924
U.S. - Federal and State	12,085	10,491	6,355
Other foreign	831	679	328
Total current provision	15,838	12,357	8,607
Deferred (benefit) provision			
Ireland	$ (6,294)	$ (2,054)	$ (5,623)
U.S. - Federal and State	(120,111)	(69,073)	(175,228)
Other foreign	7,818	(2,481)	—
Total deferred benefit	(118,587)	(73,608)	(180,851)
Total benefit for income taxes	**$ (102,749)**	**$ (61,251)**	**$ (172,244)**

Total benefit for income taxes was $102.7 million, $61.3 million and $172.2 million for the years ended December 31, 2017, 2016 and 2015, respectively. The current tax provision of $15.8 million for the year ended December 31, 2017 was primarily attributable to U.S. state income tax liabilities and U.S. federal alternative minimum tax liability. The deferred tax benefit of $118.6 million recognized during the year ended December 31, 2017, was primarily due to a provisional $74.9 million net benefit recorded following the enactment of the Tax Act, which net benefit included a $134.2 million tax benefit from the revaluation of the Company's U.S. net deferred tax liability based on the new U.S. federal tax rate of 21 percent, partially offset by the write-off of a $59.2 million deferred tax asset related to the Company's U.S. interest expense carryforwards and the U.S. deferred tax benefit incurred on U.S. pre-tax losses.

A reconciliation between the Irish income tax statutory rate to the Company's effective tax rate for 2017, 2016 and 2015 is as follows (in thousands):

	For the Years Ended December 31,		
	2017	2016	2015
Irish income tax at statutory rate (12.5%)	$ (64,159)	$ (28,510)	$ (16,586)
Foreign tax rate differential	(9,806)	(1,893)	(30,348)
Impact of the Tax Act on deferred taxes	(134,182)	—	—
Write-off of U.S. deferred tax asset related to interest expense carryforwards due to the Tax Act	59,243	—	—
Notional interest deduction	(27,020)	(35,075)	(22,848)
Non-deductible in-process research and development costs	51,148	—	—
Share-based compensation	26,811	7,125	3,776
Transaction costs	341	3,447	3,109
Disallowed interest	2,990	2,620	2,139
Disqualified compensation expense	1,305	2,555	3,949
Uncertain tax positions	4,976	2,837	3,012
Tax charges on intragroup profit	(8,888)	2,154	(9,955)
U.S. state income taxes	214	8,579	1,002
Change in U.S. state effective tax rate	(2,329)	(17,246)	(9,061)
Change in valuation allowances	(1,378)	(6,117)	(106,834)
U.S. federal and state tax credits	(3,608)	(3,613)	—
Interest expense on convertible debt inducements	—	—	(1,218)
Book loss on debt extinguishment	—	—	6,396
Other, net	1,593	1,886	1,223
Benefit for income taxes	**$ (102,749)**	**$ (61,251)**	**$ (172,244)**
Effective income tax rate	**20.0%**	**26.9%**	**129.8%**

The overall effective income tax rate for 2017 of 20.0% was a higher benefit rate than the Irish statutory rate of 12.5% primarily due to a provisional $74.9 million net benefit recorded following the enactment of the Tax Act, which net benefit included a $134.2 million tax benefit from the revaluation of the Company's U.S. net deferred tax liability based on the new U.S. federal tax rate of 21 percent, partially offset by the write-off of a $59.2 million deferred tax asset related to the Company's U.S. interest expense carryforwards. The higher 2017 benefit rate was also attributable to losses incurred in higher tax rate jurisdictions, the benefit realized on the notional interest deduction of $27.0 million, tax charges on intragroup profits of $8.9 million, U.S. federal and state tax credits of $3.6 million and $2.3 million due to a decrease in the U.S. state effective tax rate. These benefits to income taxes are partially offset by non-deductible IPR&D expenses of $51.1 million recorded in connection with the acquisition of River Vision, non-deductible share-based compensation expenses of $26.8 million, including the write-off of $16.4 million of deferred tax assets related to previously recognized share-based compensation expense related to PSUs that expired unvested in December 2017, and an increase in uncertain tax positions of $5.0 million.

The overall effective income tax rate for 2016 of 26.9% was a higher benefit rate than the Irish statutory rate of 12.5% primarily due to the benefit realized on the notional interest deduction, the benefit realized from a change in U.S. state effective tax rate, and changes in valuation allowances. These benefits to income taxes were partially offset by an increase in share-based compensation not deductible for tax purposes and an increase in U.S. state income taxes.

The overall effective income tax rate for 2015 of 129.8% was a higher benefit rate than the Irish statutory rate of 12.5% primarily due to the release of valuation allowances in the United States following the acquisition of Hyperion in 2015, the benefit realized on the foreign rate differential and the benefit realized on the notional interest deduction.

The decrease in the effective income tax rate in 2017 compared to that in 2016 was primarily due to non-deductible IPR&D expenses of $51.1 million recorded in connection with the acquisition of River Vision, an increase in non-deductible share-based compensation of $19.7 million primarily due to the write-off of $16.4 million of deferred tax assets related to previously recognized share-based compensation expense related to PSUs that expired unvested in December 2017, a $14.9 million decrease in benefit from the change in U.S. state effective tax rate, an $11.0 million decrease in the tax charges of intragroup profit, an $8.1 million decrease in the benefit realized on the notional interest deduction and a $4.7 million decrease in the changes in valuation allowances, partially offset by the provisional $74.9 million net impact of the Tax Act on deferred taxes.

The decrease in the effective income tax rate in 2016 compared to 2015 was primarily due to the one-time benefit recognized in 2015 for the release in valuation allowance.

The Company accounts for income taxes based upon an asset and liability approach. Deferred tax assets and liabilities represent the future tax consequences of the differences between the financial statement carrying amounts of assets and liabilities versus the tax basis of assets and liabilities. Under this method, deferred tax assets are recognized for future deductible temporary differences and operating loss and tax credit carryforwards. Deferred tax liabilities are recognized for future taxable temporary differences. Deferred tax assets are reduced by a valuation allowance when, in the opinion of management, it is more likely than not that some portion or all of the deferred tax assets will not be realized. The impact of tax rate changes on deferred tax assets and liabilities is recognized in the period in which the change is enacted.

The tax effects of the temporary differences, tax credits and net operating losses that give rise to significant portions of deferred tax assets and liabilities, before jurisdictional netting, are as follows (in thousands):

	As of December 31,	
	2017	2016
Deferred tax assets:		
Net operating loss carryforwards	$ 65,650	$ 99,004
Capital loss carryforwards	2,796	4,631
Alternative minimum tax credit	13,972	5,922
U.S. federal and state credits	35,465	48,758
Accrued compensation	46,420	65,733
Accruals and reserves	11,089	20,179
Contingent royalties	33,436	68,628
Intercompany interest	—	54,703
Other	2,259	—
Total deferred tax assets	**211,087**	**367,558**
Valuation allowance	(25,650)	(32,532)
Deferred tax assets, net of valuation allowance	**$ 185,437**	**$ 335,026**
Deferred tax liabilities:		
Inventories	$ 570	$ 13,077
Debt discount	23,372	23,050
Intangible assets	315,970	593,057
Other	—	1,499
Total deferred tax liabilities	339,912	630,683
Net deferred income tax liability	**$ 154,475**	**$ 295,657**

The Tax Act was enacted in December 2017. On December 22, 2017, the SEC staff issued SAB 118, which provides guidance on accounting for the tax effects of the Tax Act. SAB 118 provides a measurement period that should not extend beyond one year from the date of enactment for companies to complete the accounting under ASC 740, *Income Taxes*. In accordance with SAB 118, the Company reflected the income tax effects of those aspects of the Tax Act for which the accounting under ASC 740 was complete. To the extent that the Company's accounting for certain income tax effects of the Tax Act is incomplete but it is able to determine a reasonable estimate, the Company recorded a provisional estimate in the consolidated financial statements. As of December 31, 2017, the Company has not completed its accounting for the effects of the Tax Act. However, the Company has made reasonable estimates of the effects on its income tax provision with respect to certain items, primarily the revaluation of its existing U.S. deferred tax balances and the write-off of its U.S. deferred tax assets resulting from interest expense carryforwards under Section 163(j) of the Internal Revenue Code. In other cases, the Company has not been able to make reasonable estimates and continues to account for those items based on its existing accounting under the provisions of the tax laws that were in effect prior to enactment. The Company recognized a net income

tax benefit of $74.9 million for the year ended December 31, 2017, associated with the items it could reasonably estimate. This benefit reflects the revaluation of its U.S. net deferred tax liability based on the U.S. federal tax rate of 21 percent, partially offset by the write-off of the deferred tax asset related to its U.S. interest expense carryforwards. The Company is still analyzing the Tax Act and refining its calculations and the results of this analysis could potentially impact the provisional amounts recorded in 2017 and would be reflected in the 2018 income tax provision.

No provision has been made for income taxes on undistributed earnings of subsidiaries because it is the Company's intention to indefinitely reinvest outside of Ireland undistributed earnings of its subsidiaries. In the event of the distribution of those earnings to Ireland in the form of dividends, a sale of the subsidiaries, or certain other transactions, the Company may be liable for income taxes in Ireland. The unremitted earnings of the Company as of December 31, 2017, were $339.2 million, and the Company estimates that it would incur no additional income tax on unremitted earnings were they to be remitted to Ireland.

As of December 31, 2017, the Company had net operating loss carryforwards of approximately $114.4 million for U.S. federal, $307.4 million for various U.S. states and $149.3 million for non-U.S. losses. These net operating losses include net operating losses acquired in the acquisition of River Vision during the second quarter of 2017 and are available to reduce future taxable income, if any, in the jurisdiction in which the net operating losses have been generated. Net operating loss carryforwards for U.S. federal income tax purposes that were generated prior to January 1, 2018, have a twenty-year carryforward life and the earliest layers will begin to expire in 2020. Under the Tax Act, U.S. federal net operating losses incurred in 2018 and in future years may be carried forward indefinitely, but the deductibility of such net operating losses is limited. U.S. state net operating losses started to expire in 2016 for the earliest net operating loss layers. It is uncertain if and to what extent various U.S. states will conform to the Tax Act. Net operating loss carryovers in Switzerland have a seven-year carryforward life and started to expire in 2016 due to lack of sufficient taxable income to fully absorb the available carryover loss. Irish net operating losses may be carried forward indefinitely and therefore have no expiration. Utilization of the U.S. net operating loss carryforwards may be subject to annual limitations as prescribed by federal and state statutory provisions. The imposition of the annual limitations may result in a portion of the net operating loss carryforwards expiring unused.

Utilization of certain net operating loss and tax credit carryforwards in the United States is subject to an annual limitation due to ownership change limitations provided by Sections 382 and 383 of the Internal Revenue Code. The Company is limited under the annual limitation of $7.7 million from the year 2018 until 2028 on certain net operating losses generated before an August 2, 2012 ownership change. We continue to carry forward the annual limitation related to Hyperion of $50.0 million resulting from the last ownership change in 2014 as well as the annual limitation related to Raptor of $0.2 million from the year 2018 until 2028 for the ownership change which occurred in 2009. Further, the net operating losses acquired with River Vision are subject to an annual limitation of $12.5 million from 2018 through 2020. The U.S. federal net operating loss carryforward limitation is cumulative such that any use of the carryforwards below the limitation in a particular tax year will result in a corresponding increase in the limitation for the subsequent tax year.

At December 31, 2017, the Company had $56.6 million and $6.2 million of U.S. federal and state income tax credits, respectively, to reduce future tax liabilities. These tax credits include the tax credits acquired in the acquisition of River Vision. The federal income tax credits consisted primarily of orphan drug credits, research and development credits and alternative minimum tax credits. The U.S. state income tax credits consisted primarily of California research and development credits and the Illinois Economic Development for a Growing Economy ("EDGE") tax credits. Both the U.S. federal orphan drug credits and research and development credits have a twenty-year carryforward life. The U.S. federal orphan drug credits and the U.S. federal research and development credits will both begin to expire in 2030. The U.S. federal alternative minimum tax credits and California research and development credits have indefinite lives and therefore are not subject to expiration. The EDGE credits have a five-year carryforward life following the year of generation and will begin to expire in 2019.

As the Company's share price was lower than $31.58 for the twenty trading days ended December 23, 2017, a portion of outstanding PSUs expired unvested and $16.4 million of deferred tax assets related to previously recognized share-based compensation expense related to the expired PSUs was written off to income tax expense. Additionally, in relation to the remaining outstanding PSUs, if our share price is lower than $32.70 and $33.86 for the twenty trading days ending March 22, 2018 and June 22, 2018, respectively, approximately $9.3 million and $8.4 million, respectively, of deferred tax assets at December 31, 2017, related to previously recognized share-based compensation expense related to these PSUs will be charged to income tax expense.

A reconciliation of the beginning and ending amounts of valuation allowances for the years ended December 31, 2017, 2016 and 2015 is as follows (in thousands):

Valuation allowances at December 31, 2014	$ (111,555)
Increase for 2015 activity	(37,569)
Release of valuation allowances	117,814
Valuation allowances at December 31, 2015	**$ (31,310)**
Increase for 2016 activity	(14,636)
Release of valuation allowances	15,056
Additions to valuation allowances due to acquisitions	(1,642)
Valuation allowances at December 31, 2016	**$ (32,532)**
Increase for 2017 activity	(6,835)
Release of valuation allowances	5,313
Decreases to valuation allowances due to divestiture	8,404
Valuation allowances at December 31, 2017	**$ (25,650)**

Deferred tax valuation allowances decreased by $6.9 million during the year ended December 31, 2017, increased by $1.2 million during the year ended December 31, 2016 and decreased by $80.2 million during the year ended December 31, 2015. For the year ended December 31, 2017, the decrease in valuation allowances resulted primarily from the Chiesi divestiture and the release of valuation allowances related to expired net operating losses in certain jurisdictions, partially offset by the increase resulting from current year activity.

The Company is required to recognize the financial statement effects of a tax position when it is more likely than not, based on the technical merits, that the position will be sustained upon examination. The Company accounts for the uncertainty in income taxes by utilizing a comprehensive model for the recognition, measurement, presentation and disclosure in financial statements of any uncertain tax positions that have been taken, or are expected to be taken, on an income tax return. The changes in the Company's uncertain income tax positions for the years ended December 31, 2017, 2016 and 2015, excluding interest and penalties, consisted of the following (in thousands):

	For the Years Ended December 31,		
	2017	2016	2015
Beginning balance – uncertain tax positions	$ 17,747	$ 9,812	$ 775
Tax positions in the year:			
Additions	2,451	471	2,604
Acquired uncertain tax positions	—	5,362	6,433
Tax positions related to prior years:			
Additions	4,145	2,102	—
Settlements and lapses	(939)	—	—
Ending balance – uncertain tax positions	**$ 23,404**	**$ 17,747**	**$ 9,812**

For the year ended December 31, 2017, the increase in uncertain tax positions primarily resulted from the additional federal orphan drug credits generated during the year and the uncertain tax position resulting from certain state nexus exposures. In the Company's consolidated balance sheet, uncertain tax positions of $6.4 million were included in other long-term liabilities and an additional $17.0 million was offset against deferred tax assets.

At December 31, 2017, penalties of $0.2 million and interest of $1.3 million are included in the balance of the uncertain tax positions and penalties of $0.1 million and interest of $0.6 million were included in the balance of uncertain tax positions at December 31, 2016. The Company classifies interest and penalties with respect to income tax liabilities as a component of income tax expense. The Company assessed that its liability for uncertain tax positions will not significantly change within the next twelve months. If these uncertain tax positions are released, the impact on the Company's tax provision would be a benefit of $24.9 million, including interest and penalties.

The Company files income tax returns in Ireland, in the United States for federal and various states, as well as in certain other jurisdictions. At December 31, 2017, all open tax years in U.S. federal and certain state jurisdictions date back to 2006 due to the taxing authorities' ability to adjust operating loss carryforwards. In Ireland, the statute of limitations

expires five years from the end of the tax year or four years from the time a tax return is filed, whichever is later. Therefore the earliest year open to examination is 2013 with the lapse of statute occurring in 2018. No changes in settled tax years have occurred to date. On December 29, 2017, the Company received a letter from the U.S. Internal Revenue Service for commencement of a federal income tax examination for the tax year ended December 31, 2015. As of the filing of this Annual Report on Form 10-K, the Company does not currently anticipate material changes from the originally filed U.S. federal tax return for the 2015 year.

NOTE 23 – EMPLOYEE BENEFIT PLANS

The Company sponsors a defined contribution 401(k) retirement savings plan covering all of its U.S. employees, whereby an eligible employee may elect to contribute a portion of his or her salary on a pre-tax basis, subject to applicable federal limitations. The Company is not required to make any discretionary matching of employee contributions. The Company makes a matching contribution equal to 100% of each employee's elective contribution to the plan of up to 3% of the employee's eligible pay, and 50% for the next 2% of the employee's eligible pay. The full amount of this employer contribution is immediately vested in the plan. For the years ended December 31, 2017, 2016 and 2015, the Company recorded defined contribution expense of $4.9 million, $2.7 million and $2.1 million, respectively.

The Company's wholly owned Swiss subsidiary sponsors a defined benefit savings plan covering all of its employees in Switzerland. The Company's wholly owned German subsidiary sponsors a defined contribution plans for its employees in Germany. For the years ended December 31, 2017, 2016 and 2015, the Company recognized immaterial expenses under these plans.

The Company's wholly owned Irish subsidiary sponsors a defined contribution plan covering all of its employees in Ireland. For the years ended December 31, 2017, 2016 and 2015, the Company recognized expenses of $0.4 million, $0.4 million and $0.2 million, respectively, under this plan.

The Company has a non-qualified deferred compensation plan for executives, which was established in April 2015. The deferred compensation plan obligations are payable in cash upon retirement, termination of employment and/or certain other times in a lump-sum distribution or in installments, as elected by the participant in accordance with the plan. As of December 31, 2017 and 2016, the deferred compensation plan liabilities totaled $6.5 million and $3.1 million, respectively, and are included in "other long-term liabilities" in the consolidated balance sheet. The Company held funds of approximately $6.5 million and $3.1 million in an irrevocable grantor's rabbi trust as of December 31, 2017 and 2016, respectively, related to this plan. Rabbi trust assets are classified as trading marketable securities and are included in "other current assets" in the consolidated balance sheets. Unrealized gains and losses on these marketable securities are included in "other income" in the consolidated statements of comprehensive (loss) income. For the years ended December 31, 2017, 2016 and 2015, the Company recognized expenses of $0.8 million, $0.6 million and $0.2 million, respectively, under this plan.

NOTE 24 – SELECTED QUARTERLY FINANCIAL INFORMATION (UNAUDITED)

The following table provides a summary of selected financial results of operations by quarter for the years ended December 31, 2017 and 2016 (in thousands, except per share data):

2017	First	Second	Third	Fourth
Net sales	$ 220,859	$ 289,507	$ 271,646	$ 274,219
Gross profit	81,743	159,357	146,129	122,727
Operating loss	(105,383)	(185,667)	(25,751)	(75,568)
Net loss	(90,570)	(209,536)	(63,971)	(46,449)
Net loss per ordinary share - basic	$ (0.56)	$ (1.29)	$ (0.39)	$ (0.28)
Net loss per ordinary share - diluted	(0.56)	(1.29)	(0.39)	(0.28)

2016	First	Second	Third	Fourth
Net sales	$ 204,690	$ 257,378	$ 208,702	$ 310,350
Gross profit	127,457	176,252	123,541	160,598
Operating (loss) income	(27,204)	31,467	(21,322)	(130,108)
Net (loss) income	(45,406)	14,984	(5,870)	(130,542)
Net (loss) income per ordinary share - basic	$ (0.28)	$ 0.09	$ (0.04)	$ (0.81)
Net (loss) income per ordinary share - diluted	(0.28)	0.09	(0.04)	(0.81)

SCHEDULE II – VALUATION AND QUALIFYING ACCOUNTS

For Each of the Three Fiscal Years Ended December 31, 2017, 2016 and 2015:

Valuation and Qualifying Accounts (in thousands)	Balance at beginning of period	Acquisitions /(Divestitures)	Additions charged to costs and expenses	Deductions from reserves	Balance at end of period
Year ended December 31, 2017:					
Allowance for discounts and returns	21,916	-	125,851	(100,671)	47,096
Year ended December 31, 2016:					
Allowance for discounts and returns	14,964	1,234	81,089	(75,371)	21,916
Year ended December 31, 2015:					
Allowance for discounts and returns	4,483	236	55,702	(45,457)	14,964

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities and Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

HORIZON PHARMA PLC

Dated: February 28, 2018

By: /s/ TIMOTHY P. WALBERT
Timothy P. Walbert

President, Chief Executive Officer and
Chairman of the Board

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Timothy P. Walbert and Paul W. Hoelscher, and each of them, his true and lawful attorneys-in-fact and agents, with full power of substitution and resubstitution, for him and in his name, place and stead, in any and all capacities, to sign any and all amendments (including post-effective amendments) to this report, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as he might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or either of them, or their or his substitutes or substitute, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

SIGNATURE	TITLE	DATE
/s/ TIMOTHY P. WALBERT Timothy P. Walbert	President, Chief Executive Officer and Chairman of the Board *(Principal Executive Officer)*	February 28, 2018
/s/ PAUL W. HOELSCHER Paul W. Hoelscher	Executive Vice President and Chief Financial Officer *(Principal Financial Officer)*	February 28, 2018
/s/ MILES W. MCHUGH Miles W. McHugh	Senior Vice President and Chief Accounting Officer *(Principal Accounting Officer)*	February 28, 2018
/s/ MICHAEL GREY Michael Grey	Director	February 28, 2018
/s/ LIAM DANIEL Liam Daniel	Director	February 28, 2018
/s/ JEFF HIMAWAN Jeff Himawan, Ph.D.	Director	February 28, 2018
/s/ RONALD PAULI Ronald Pauli	Director	February 28, 2018
/s/ GINO SANTINI Gino Santini	Director	February 28, 2018
/s/ JAMES SHANNON James Shannon M.D.	Director	February 28, 2018
/s/ H. THOMAS WATKINS H. Thomas Watkins	Director	February 28, 2018
/s/ PASCALE WITZ Pascale Witz	Director	February 28, 2018

Exhibit 10.6

HORIZON PHARMA PUBLIC LIMITED COMPANY

2014 EQUITY INCENTIVE PLAN

ADOPTED BY THE BOARD OF DIRECTORS: MAY 17, 2014
APPROVED BY THE SHAREHOLDERS: SEPTEMBER 18, 2014
AMENDED BY THE BOARD OF DIRECTORS: MARCH 23, 2015
APPROVED BY THE SHAREHOLDERS: MAY 6, 2015
AMENDED BY THE COMPENSATION COMMITTEE: FEBRUARY 25, 2016
APPROVED BY THE SHAREHOLDERS: MAY 3, 2016
AMENDED BY THE COMPENSATION COMMITTEE: AUGUST 29, 2017
AMENDED BY THE COMPENSATION COMMITTEE: JANUARY 5, 2018

TERMINATION DATE: MAY 16, 2024

1. GENERAL.

(a) Relationship to Prior Plans. This Plan is intended as the successor to the Horizon Pharma, Inc. 2011 Equity Incentive Plan (the "***2011 Plan***") with respect to grants to Employees. From and after 12:01 a.m. on the Effective Date, all outstanding stock awards granted under the 2011 Plan and the Horizon Pharma, Inc. 2005 Stock Plan (the "***2005 Plan***") and, together with the 2011 Plan, the "***Prior Plans***") shall remain subject to the terms of the 2011 Plan or the 2005 Plan, as applicable; *provided, however*, any Ordinary Shares subject to outstanding stock awards granted under the Prior Plans that expire, terminate or are forfeited for any reason prior to exercise or settlement, and any Ordinary Shares that are repurchased or redeemed because of the failure to meet a contingency or condition required to vest such Ordinary Shares (the "***Returning Shares***") shall immediately be added to the Share Reserve (as described below) as and when such Ordinary Shares become Returning Shares and shall become available for issuance pursuant to Awards granted hereunder. All Awards granted on or after the Effective Date of this Plan shall be subject to the terms of this Plan.

(b) Eligible Award Recipients. The persons eligible to receive Awards are Employees. The persons eligible to receive Inducement Awards are Employees who meet the criteria set forth in Section 3(f).

(c) Available Awards. The Plan provides for the grant of the following Awards: (i) Incentive Stock Options, (ii) Nonstatutory Stock Options, (iii) Stock Appreciation Rights (iv) Restricted Stock Awards, (v) Restricted Stock Unit Awards, (vi) Performance Stock Awards, (vii) Performance Cash Awards, (viii) Inducement Awards, and (ix) Other Stock Awards.

(d) Purpose. The Company, by means of the Plan, seeks to secure and retain the services of the group of persons eligible to receive Awards as set forth in Section 1(b), to provide incentives for such persons to exert maximum efforts for the success of the Company and any Affiliate and to provide a means by which such eligible recipients may be given an opportunity to benefit from increases in value of the Ordinary Shares through the granting of Awards.

2. ADMINISTRATION.

(a) Administration by Board. The Board shall administer the Plan unless and until the Board delegates administration of the Plan to a Committee or Committees, as provided in Section 2(c). Notwithstanding anything to the contrary set forth herein, only an Inducement Committee has the power to grant Inducement Awards.

(b) Powers of Board. The Board shall have the power, subject to, and within the limitations of, the express provisions of the Plan:

(i) To determine from time to time (A) which of the persons eligible under the Plan shall be granted Awards; (B) when and how each Award shall be granted; (C) what type or combination of types of Award shall be granted; (D) the provisions of each Award granted (which need not be identical), including the time or times when a person shall be permitted to receive cash or Ordinary Shares pursuant to a Stock Award; (E) the number of Ordinary Shares with respect to which a Stock Award shall be granted to each such person; and (F) the Fair Market Value applicable to a Stock Award.

(ii) To construe and interpret the Plan and Awards granted under it, and to establish, amend and revoke rules and regulations for its administration. The Board, in the exercise of this power, may correct any defect, omission or inconsistency in the Plan or in any Stock Award Agreement or in the written terms of a Performance Cash Award, in a manner and to the extent it shall deem necessary or expedient to make the Plan or Award fully effective.

(iii) To settle all controversies regarding the Plan and Awards granted under it.

(iv) To accelerate the time at which an Award may first be exercised or the time during which an Award or any part thereof will vest in accordance with the Plan, notwithstanding the provisions in the Award stating the time at which it may first be exercised or the time during which it will vest.

(v) To suspend or terminate the Plan at any time. Suspension or termination of the Plan shall not impair rights and obligations under any Award granted while the Plan is in effect except with the written consent of the affected Participant.

(vi) To amend the Plan in any respect the Board deems necessary or advisable. However, except as provided in Section 9(a) relating to Capitalization Adjustments, to the extent required by applicable law or listing requirements, shareholder approval shall be required for any amendment of the Plan that either (A) materially increases the number of Ordinary Shares available for issuance under the Plan, (B) materially expands the class of individuals eligible to receive Awards under the Plan, (C) materially increases the benefits accruing to Participants under the Plan or materially reduces the price at which Ordinary Shares may be issued or purchased under the Plan, (D) materially extends the term of the Plan, or (E) expands the types of Awards available for issuance under the Plan. Except as provided above, rights under any Award granted before amendment of the Plan shall not be impaired by any amendment of the Plan unless (1) the Company requests the consent of the affected Participant, and (2) such Participant consents in writing.

(vii) To submit any amendment to the Plan for shareholder approval, including, but not limited to, amendments to the Plan intended to satisfy the requirements of (A) Section 162(m) of the Code regarding the exclusion of performance-based compensation from the limit on corporate deductibility of compensation paid to Covered Employees, (B) Section 422 of the Code regarding incentive stock options or (C) Rule 16b-3.

(viii) To approve forms of Award Agreements for use under the Plan and to amend the terms of any one or more Awards, including, but not limited to, amendments to provide terms more favorable to the Participant than previously provided in the Award Agreement, subject to any specified limits in the Plan that are not subject to Board discretion; *provided however*, that except with respect to amendments that disqualify or impair the status of an Incentive Stock Option, a Participant's rights under any Award shall not be impaired by any such amendment unless (A) the Company requests the consent of the affected Participant, and (B) such Participant consents in writing. Notwithstanding the foregoing, subject to the limitations of applicable law, if any, the Board may amend the terms of any one or more Awards without the affected Participant's consent if necessary to maintain the qualified status of the Award as an Incentive Stock Option or to bring the Award into compliance with Section 409A of the Code.

(ix) Generally, to exercise such powers and to perform such acts as the Board deems necessary or expedient to promote the best interests of the Company and any Affiliates and that are not in conflict with the provisions of the Plan or Awards.

(x) To adopt such procedures and sub-plans as are necessary or appropriate to permit participation in the Plan by Employees who are foreign nationals or employed outside the United States.

(c) Delegation to Committee.

(i) General. The Board may delegate some or all of the administration of the Plan to a Committee or Committees. If administration of the Plan is delegated to a Committee, the Committee shall have, in connection with the administration of the Plan, the powers theretofore possessed by the Board that have been delegated to the Committee, including the power to delegate to a subcommittee of the Committee any of the administrative powers the Committee is authorized to exercise (and references in this Plan to the Board shall thereafter be to the Committee or subcommittee), subject, however, to such resolutions, not inconsistent with the provisions of the Plan, as may be adopted from time to time by the Board. The Committee may, at any time, abolish the subcommittee and/or revest in the Committee any powers delegated to the subcommittee. The Board may retain the authority to concurrently administer the Plan with the Committee and may, at any time, revest in the Board some or all of the powers previously delegated.

(ii) Section 162(m) and Rule 16b-3 Compliance. The Committee may consist solely of two or more Outside Directors, in accordance with Section 162(m) of the Code, or solely of two or more Non-Employee Directors, in accordance with Rule 16b-3.

(iii) Inducement Awards. Notwithstanding any other provision of the Plan to the contrary, all Inducement Awards must be granted by an Inducement Committee.

(d) Effect of Board's Decision. All determinations, interpretations and constructions made by the Board in good faith shall not be subject to review by any person and shall be final, binding and conclusive on all persons.

(e) Cancellation and Re-Grant of Stock Awards. Neither the Board nor any Committee shall have the authority to: (i) reduce the exercise price of any outstanding Options or Stock Appreciation Rights under the Plan, or (ii) cancel any outstanding Options or Stock Appreciation Rights that have an exercise price or strike price greater than the current Fair Market Value of the Ordinary Shares in exchange for cash or other Stock Awards under the Plan, unless the stockholders of the Company have approved such an action within twelve (12) months prior to such an event, provided that the exercise price of any such outstanding Options or Stock Appreciation Rights under the Plan may not be reduced below the nominal value of an Ordinary Share.

3. SHARES SUBJECT TO THE PLAN.

(a) Share Reserve.

(i) Subject to Section 9(a) relating to Capitalization Adjustments, the aggregate number of Ordinary Shares of the Company that may be issued pursuant to Stock Awards after the Effective Date shall not exceed 44,052,130 shares, which is the sum of (i) 22,052,130 Ordinary Shares, which is the total reserve that was approved as of the Effective Date in connection with the adoption of the Plan, including, but not limited to, the shares remaining available for issuance under the Prior Plans and the Returning Shares, (ii) 14,000,000 additional Ordinary Shares approved by the Company's shareholders at the 2015 annual general meeting, and (iii) 6,000,000 new Ordinary Shares approved by the Company's shareholders at the 2016 annual general meeting (the total of (i), (ii) and (iii), the "***Share Reserve***") and (iv) 2,000,000 Ordinary Shares that may be issued pursuant to Inducement Awards granted under Section 3(f) of the Plan. For clarity, the limitation in this Section 3(a)(i) is a limitation on the number of Ordinary Shares that may be issued pursuant to the Plan. Accordingly, this Section 3(a)(i) does not limit the granting of Stock Awards except as provided in Section 7(a). Shares may be issued in connection with a merger or acquisition as permitted by, as applicable, NASDAQ Marketplace Rule 4350(i)(1)(A)(iii), NYSE Listed Company Manual Section 303A.08, AMEX Company Guide Section 711 or other applicable stock exchange rules, and such issuance shall not reduce the number of Ordinary Shares available for issuance under the Plan. Furthermore, if a Stock Award or any portion thereof (i) expires or otherwise terminates without all of the Ordinary Shares covered by such Stock Award having been issued or (ii) is settled in cash (*i.e.*, the Participant receives cash rather than Ordinary Shares), such expiration, termination or settlement shall not reduce (or otherwise offset) the number of Ordinary Shares that may be available for issuance under the Plan.

(ii) Subject to subsection 3(b) and except with respect to Inducement Awards, the number of Ordinary Shares available for issuance under the Plan shall be reduced by: (i) one (1) Ordinary Share for each Ordinary Share issued pursuant to (A) an Option granted under Section 5, or (B) a Stock Appreciation Right granted under Section 5 with respect to which the strike price is at least one hundred percent (100%) of the Fair Market Value of the underlying Ordinary Shares on the date of grant; and (ii) 1.29 Ordinary Shares for each Ordinary Share issued pursuant to a Restricted Stock Award, Restricted Stock Unit Award, Performance Stock Award, Other Stock Award or any other stock award granted under the Plan that is not described in subsection (i) above.

(b) Reversion of Shares to the Share Reserve.

(i) Shares Available For Subsequent Issuance. If any Stock Award is forfeited back to the Company or Ordinary Shares are redeemed or repurchased by the Company or any Affiliate (in accordance with applicable Irish law) because of the failure to meet a contingency or condition required to vest such Ordinary Shares, then the Ordinary Shares that are forfeited, redeemed or repurchased shall revert to and again become available for issuance under the Plan. Notwithstanding the provisions of this Section 3(b)(i), to the extent (i) there is issued an Ordinary Share pursuant to a Stock Award under the Plan (other than an Option or Stock Appreciation Right), and (ii) there are any Returning Shares granted under the Prior Plans pursuant to an award other than an Option or Stock Appreciation Right, and such Ordinary Share becomes available for issuance under the Plan pursuant to Section 1(a), Section 3(a)(i) or this Section 3(b)(i), then the number of Ordinary Shares available for issuance under the Plan shall increase by 1.29 shares for each such Ordinary Share. Notwithstanding the foregoing, any Inducement Shares that become available for issuance under the Plan pursuant to this subsection 3(b)(i) will only become available for issuance pursuant to Inducement Awards.

(ii) Shares Not Available For Subsequent Issuance. If any Ordinary Shares subject to a Stock Award are not delivered to a Participant because the Stock Award is exercised through a reduction of Ordinary Shares subject to the Stock Award (*i.e.*, "net exercised"), the number of Ordinary Shares that are not delivered to the Participant shall not remain available for issuance under the Plan. Also, any Ordinary Shares withheld by the Company pursuant to Section 8(g) or withheld or tendered as consideration for the exercise of an Option or purchase of any other Stock Award shall not again become available for issuance under the Plan.

(c) Incentive Stock Option Limit. Notwithstanding anything to the contrary in this Section 3 and, subject to the provisions of Section 9(a) relating to Capitalization Adjustments, the aggregate maximum number of Ordinary Shares that may be issued pursuant to the exercise of Incentive Stock Options shall be the number of shares subject to the Plan's Share Reserve.

(d) Section 162(m) Limitation on Annual Grants. Subject to the provisions of Section 9(a) relating to Capitalization Adjustments and except with respect to Inducement Awards, at such time as the Company may be subject to the applicable provisions of Section 162(m) of the Code, a maximum of three million (3,000,000) Ordinary Shares subject to Options, Stock Appreciation Rights and Other Stock Awards whose value is determined by reference to an increase over an exercise or strike price of at least one hundred percent (100%) of the Fair Market Value on the date any such Stock Award is granted may be granted to any

Participant during any calendar year. Notwithstanding the foregoing, if any additional Options, Stock Appreciation Rights or Other Stock Awards whose value is determined by reference to an increase over an exercise or strike price of at least one hundred percent (100%) of the Fair Market Value on the date the Stock Awards are granted to any Participant during any calendar year, compensation attributable to the exercise of such additional Stock Awards shall not satisfy the requirements to be considered "qualified performance-based compensation" under Section 162(m) of the Code unless such additional Stock Award is approved by the Company's shareholders.

(e) Source of Shares. The Ordinary Shares issuable under the Plan shall be authorized but unissued or reacquired Ordinary Shares, including Ordinary Shares redeemed or repurchased by the Company or any Affiliate on the open market or otherwise, in accordance with applicable Irish Law.

(f) Inducement Shares. This subsection 3(f) will apply with respect to the 2,000,000 Ordinary Shares reserved under this Plan by action of the Board (or a committee thereof) to be used exclusively for the grant of Inducement Awards in compliance with NASDAQ Listing Rule 5635(c)(4) (the "Inducement Shares"). Notwithstanding anything to the contrary in this Plan, an Inducement Award may be granted only to an Employee who has not previously been an Employee or a non-Employee Director of the Company or an Affiliate, or following a bona fide period of non-employment, as an inducement material to the individual's entering into employment with the Company within the meaning of Rule 5635(c)(4) of the NASDAQ Listing Rules.

4. ELIGIBILITY.

(a) Eligibility for Specific Stock Awards. Incentive Stock Options may be granted only to employees of the Company or a "parent corporation" or "subsidiary corporation" thereof (as such terms are defined in Sections 424(e) and (f) of the Code). Stock Awards other than Incentive Stock Options may be granted to Employees; *provided, however*, that Nonstatutory Stock Options and SARs may not be granted to Employees who are providing Continuous Service only to any "parent" of the Company, as such term is defined in Rule 405 promulgated under the Securities Act, unless the Ordinary Shares underlying such Stock Awards are treated as "service recipient stock" under Section 409A of the Code because the Stock Awards are granted pursuant to a corporate transaction (such as a spin off transaction) or unless such Stock Awards comply with the distribution requirements of Section 409A of the Code.

(b) Ten Percent Shareholders. A Ten Percent Shareholder shall not be granted an Incentive Stock Option unless the exercise price of such Option is at least one hundred ten percent (110%) of the Fair Market Value on the date of grant and the Option is not exercisable after the expiration of five (5) years from the date of grant.

5. PROVISIONS RELATING TO OPTIONS AND STOCK APPRECIATION RIGHTS.

Each Option or SAR shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. All Options shall be separately designated Incentive Stock Options or Nonstatutory Stock Options at the time of grant, and, if certificates are issued, a

separate certificate or certificates shall be issued for Ordinary Shares purchased on exercise of each type of Option. If an Option is not specifically designated as an Incentive Stock Option, then the Option shall be a Nonstatutory Stock Option. The provisions of separate Options or SARs need not be identical; *provided, however*, that each Option Agreement or Stock Appreciation Right Agreement shall conform to (through incorporation of provisions hereof by reference in the applicable Award Agreement or otherwise) the substance of each of the following provisions:

(a) Term. Subject to the provisions of Section 4(b) regarding Ten Percent Shareholders, no Option or SAR shall be exercisable after the expiration of ten (10) years from the date of its grant or such shorter period specified in the Award Agreement.

(b) Exercise Price. Subject to the provisions of Section 4(b) regarding Ten Percent Shareholders, the exercise price (or strike price) of each Option or SAR shall be not less than one hundred percent (100%) of the Fair Market Value of the Ordinary Shares subject to the Option or SAR on the date the Option or SAR is granted. Notwithstanding the foregoing, an Option or SAR may be granted with an exercise price (or strike price) lower than one hundred percent (100%) of the Fair Market Value of the Ordinary Shares subject to the Option or SAR if such Option or SAR is granted pursuant to an assumption of or substitution for another option or stock appreciation right pursuant to a Corporate Transaction and in a manner consistent with the provisions of Sections 409A and, if applicable, 424(a) of the Code, provided that in all cases the exercise price is not less than the nominal value of an Ordinary Share. Each SAR will be denominated in Ordinary Shares equivalents.

(c) Purchase Price for Options. The purchase price of Ordinary Shares acquired pursuant to the exercise of an Option shall be paid, to the extent permitted by applicable law and as determined by the Board in its sole discretion, by any combination of the methods of payment set forth below; *provided, however,* that where Ordinary Shares are issued pursuant to the exercise of an Option, the nominal value of each newly issued Ordinary Share is fully paid up. The Board shall have the authority to grant Options that do not permit all of the following methods of payment (or otherwise restrict the ability to use certain methods) and to grant Options that require the consent of the Company to utilize a particular method of payment. The permitted methods of payment are as follows:

(i) by cash, check, bank draft or money order payable to the Company;

(ii) pursuant to a program developed under Regulation T as promulgated by the Federal Reserve Board that, prior to the issuance of Ordinary Shares subject to the Option, results in either the receipt of cash (or check) by the Company or the receipt of irrevocable instructions to pay the aggregate exercise price to the Company from the sales proceeds;

(iii) if the option is a Nonstatutory Stock Option, by a "net exercise" arrangement pursuant to which the Company will reduce the number of Ordinary Shares issuable upon exercise by the largest whole number of Ordinary Shares with a Fair Market Value that does not exceed the aggregate exercise price; *provided, however*, that:

(1) the Company shall accept a cash or other payment from the Participant to the extent of any remaining balance of the aggregate exercise price not satisfied by such reduction in the number of whole Ordinary Shares to be issued;

(2) irrespective of whether a "net exercise" arrangement is used, the nominal value of each newly issued Ordinary Shares will be fully paid up in cash; and

(3) Ordinary Shares will no longer be subject to an Option and will not be exercisable thereafter to the extent that (A) Ordinary Shares issuable upon exercise are reduced to pay the exercise price pursuant to the "net exercise," (B) Ordinary Shares are delivered to the Participant as a result of such exercise, and (C) Ordinary Shares are withheld to satisfy tax withholding obligations;

(iv) deduction from salary due and payable to an Employee by the Company or any Affiliate; or

(v) in any other form of legal consideration that may be acceptable to the Board and permissible under applicable law.

(d) Exercise and Payment of a SAR. To exercise any outstanding Stock Appreciation Right, the Participant must provide written notice of exercise to the Company in compliance with the provisions of the Stock Appreciation Right Agreement evidencing such Stock Appreciation Right. The appreciation distribution payable on the exercise of a Stock Appreciation Right will be not greater than an amount equal to the excess of (A) the aggregate Fair Market Value (on the date of the exercise of the Stock Appreciation Right) of a number of Ordinary Shares equal to the number of Ordinary Shares equivalents in which the Participant is vested under such Stock Appreciation Right, and with respect to which the Participant is exercising the Stock Appreciation Right on such date, over (B) the strike price that will be determined by the Board at the time of grant of the Stock Appreciation Right. The appreciation distribution in respect to a Stock Appreciation Right may be paid in Ordinary Shares, in cash, in any combination of the two or in any other form of consideration, as determined by the Board and contained in the Stock Appreciation Right Agreement evidencing such Stock Appreciation Right, *provided, however,* that where Ordinary Shares are issued pursuant to a Stock Appreciation Right, the nominal value of each newly issued Ordinary Share is fully paid up.

(e) Transferability of Options and SARs. The Board may, in its sole discretion, impose such limitations on the transferability of Options and SARs as the Board shall determine. In the absence of such a determination by the Board to the contrary, the following restrictions on the transferability of Options and SARs shall apply:

(i) Restrictions on Transfer. An Option or SAR shall not be transferable except by will or by the laws of descent and distribution and shall be exercisable during the lifetime of the Participant only by the Participant; *provided, however*, that the Board may, in its sole discretion, permit transfer of the Option or SAR in a manner that is not prohibited by applicable tax and securities laws upon the Participant's request. Except as explicitly provided herein, neither an Option nor a SAR may be transferred for consideration.

(ii) Domestic Relations Orders. Notwithstanding the foregoing, an Option or SAR may be transferred pursuant to a domestic relations order; *provided, however*, that if an Option is an Incentive Stock Option, such Option may be deemed to be a Nonstatutory Stock Option as a result of such transfer.

(iii) Beneficiary Designation. Notwithstanding the foregoing, the Participant may, by delivering written notice to the Company, in a form provided by or otherwise satisfactory to the Company and any broker designated by the Company to effect Option exercises, designate a third party who, in the event of the death of the Participant, shall thereafter be entitled to exercise the Option or SAR and receive the Ordinary Shares or other consideration resulting from such exercise. In the absence of such a designation, the executor or administrator of the Participant's estate shall be entitled to exercise the Option or SAR and receive the Ordinary Shares or other consideration resulting from such exercise.

(f) Vesting Generally. The total number of Ordinary Shares subject to an Option or SAR may vest and therefore become exercisable in periodic installments that may or may not be equal. The Option or SAR may be subject to such other terms and conditions on the time or times when it may or may not be exercised (which may be based on the satisfaction of Performance Goals or other criteria) as the Board may deem appropriate. The vesting provisions of individual Options or SARs may vary. The provisions of this Section 5(f) are subject to any Option or SAR provisions governing the minimum number of Ordinary Shares as to which an Option or SAR may be exercised.

(g) Termination of Continuous Service. Except as otherwise provided in the applicable Award Agreement or other agreement between the Participant and the Company or any Affiliate, if a Participant's Continuous Service terminates (other than for Cause or upon the Participant's death or Disability), the Participant may exercise his or her Option or SAR (to the extent that the Participant was entitled to exercise such Award as of the date of termination of Continuous Service) but only within such period of time ending on the earlier of (i) the date three (3) months following the termination of the Participant's Continuous Service (or such longer or shorter period specified in the applicable Award Agreement), or (ii) the expiration of the term of the Option or SAR as set forth in the Award Agreement. If, after termination of Continuous Service, the Participant does not exercise his or her Option or SAR within the time specified herein or in the Award Agreement (as applicable), the Option or SAR shall terminate.

(h) Extension of Termination Date. If the exercise of an Option or SAR following the termination of the Participant's Continuous Service (other than for Cause or upon the Participant's death or Disability) would be prohibited at any time solely because the issuance of Ordinary Shares would violate the registration requirements under the Securities Act, then the Option or SAR shall terminate on the earlier of (i) the expiration of a total period of three (3) months (that need not be consecutive) after the termination of the Participant's Continuous Service during which the exercise of the Option or SAR would not be in violation of such registration requirements, or (ii) the expiration of the term of the Option or SAR as set forth in the applicable Award Agreement. In addition, unless otherwise provided in a Participant's Award Agreement, if the immediate sale of any Ordinary Shares received upon exercise of an Option or SAR following the termination of the Participant's Continuous Service (other than for Cause) would violate the Company's insider trading policy, then the Option or SAR shall

terminate on the earlier of (i) the expiration of a period equal to the applicable post-termination exercise period after the termination of the Participant's Continuous Service during which the sale of the Ordinary Shares received upon exercise of the Option or SAR would not be in violation of the Company's insider trading policy, or (ii) the expiration of the term of the Option or SAR as set forth in the applicable Award Agreement.

(i) Disability of Participant. Except as otherwise provided in the applicable Award Agreement or other agreement between the Participant and the Company or any Affiliate, if a Participant's Continuous Service terminates as a result of the Participant's Disability, the Participant may exercise his or her Option or SAR (to the extent that the Participant was entitled to exercise such Option or SAR as of the date of termination of Continuous Service), but only within such period of time ending on the earlier of (i) the date twelve (12) months following such termination of Continuous Service (or such longer or shorter period specified in the Award Agreement), or (ii) the expiration of the term of the Option or SAR as set forth in the Award Agreement. If, after termination of Continuous Service, the Participant does not exercise his or her Option or SAR within the time specified herein or in the Award Agreement (as applicable), the Option or SAR (as applicable) shall terminate.

(j) Death of Participant. Except as otherwise provided in the applicable Award Agreement or other agreement between the Participant and the Company or any Affiliate, if (i) a Participant's Continuous Service terminates as a result of the Participant's death, or (ii) the Participant dies within the period (if any) specified in the Award Agreement for exercisability after the termination of the Participant's Continuous Service (for a reason other than death), then the Option or SAR may be exercised (to the extent the Participant was entitled to exercise such Option or SAR as of the date of death) by the Participant's estate, by a person who acquired the right to exercise the Option or SAR by bequest or inheritance or by a person designated to exercise the Option or SAR upon the Participant's death, but only within the period ending on the earlier of (i) the date eighteen (18) months following the date of death (or such longer or shorter period specified in the Award Agreement), or (ii) the expiration of the term of such Option or SAR as set forth in the Award Agreement. If, after the Participant's death, the Option or SAR is not exercised within the time specified herein or in the Award Agreement (as applicable), the Option or SAR shall terminate.

(k) Termination for Cause. Except as explicitly provided otherwise in a Participant's Award Agreement or other individual written agreement between the Company or any Affiliate and the Participant, if a Participant's Continuous Service is terminated for Cause, the Option or SAR shall terminate immediately upon such Participant's termination of Continuous Service, and the Participant shall be prohibited from exercising his or her Option or SAR from and after the time of such termination of Continuous Service.

(l) Non-Exempt Employees. No Option or SAR, whether or not vested, granted to an Employee who is a non-exempt employee for purposes of the Fair Labor Standards Act of 1938, as amended, shall be first exercisable for any Ordinary Shares until at least six months following the date of grant of the Option or SAR. Notwithstanding the foregoing, consistent with the provisions of the Worker Economic Opportunity Act, (i) in the event of the Participant's death or Disability, (ii) upon a Corporate Transaction in which such Option or SAR is not assumed, continued, or substituted, (iii) upon a Change in Control, or (iv) upon the Participant's

retirement (as such term may be defined in the Participant's Award Agreement or in another applicable agreement or in accordance with the Company's (or Affiliates, if applicable) then current employment policies and guidelines), any such vested Options and SARs may be exercised earlier than six months following the date of grant. The foregoing provision is intended to operate so that any income derived by a non-exempt employee in connection with the exercise or vesting of an Option or SAR will be exempt from his or her regular rate of pay.

6. PROVISIONS OF STOCK AWARDS OTHER THAN OPTIONS AND SARS.

(a) Restricted Stock Awards. Each Restricted Stock Award Agreement shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. To the extent consistent with the Company's Bylaws, at the Board's election, Ordinary Shares may be (i) held in book entry form subject to the Company's instructions until any restrictions relating to the Restricted Stock Award lapse; or (ii) evidenced by a certificate, which certificate shall be held in such form and manner as determined by the Board. The terms and conditions of Restricted Stock Award Agreements may change from time to time, and the terms and conditions of separate Restricted Stock Award Agreements need not be identical; *provided, however*, that each Restricted Stock Award Agreement shall conform to (through incorporation of the provisions hereof by reference in the agreement or otherwise) the substance of each of the following provisions:

(i) Consideration. A Restricted Stock Award may be awarded in consideration for (A) cash, check, bank draft or money order payable to the Company, (B) services to the Company or an Affiliate or (C) any other form of legal consideration (including future services) that may be acceptable to the Board, in its sole discretion, and permissible under applicable law, *provided however*, that where Ordinary Shares are issued pursuant to a Restricted Stock Award the nominal value of each newly issued Ordinary Share is fully paid up.

(ii) Vesting. Ordinary Shares awarded under a Restricted Stock Award Agreement may be subject to forfeiture to the Company in accordance with a vesting schedule to be determined by the Board.

(iii) Termination of Participant's Continuous Service. If a Participant's Continuous Service terminates, the Company or any Affiliate may receive through a forfeiture condition or a repurchase right any or all of the Ordinary Shares held by the Participant that have not vested as of the date of termination of Continuous Service under the terms of the Restricted Stock Award Agreement.

(iv) Transferability. Rights to acquire Ordinary Shares under the Restricted Stock Award Agreement shall be transferable by the Participant only upon such terms and conditions as are set forth in the Restricted Stock Award Agreement, as the Board shall determine in its sole discretion, so long as Ordinary Shares awarded under the Restricted Stock Award Agreement remain subject to the terms of the Restricted Stock Award Agreement.

(v) Dividends. A Restricted Stock Award Agreement may provide that any dividends paid on Restricted Stock will be subject to the same vesting and forfeiture restrictions as apply to the Ordinary Shares subject to the Restricted Stock Award to which they relate.

(b) Restricted Stock Unit Awards. Each Restricted Stock Unit Award Agreement shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. The terms and conditions of Restricted Stock Unit Award Agreements may change from time to time, and the terms and conditions of separate Restricted Stock Unit Award Agreements need not be identical; *provided, however*, that each Restricted Stock Unit Award Agreement shall conform to (through incorporation of the provisions hereof by reference in the Agreement or otherwise) the substance of each of the following provisions:

(i) Consideration. At the time of grant of a Restricted Stock Unit Award, the Board will determine the consideration, if any, to be paid by the Participant upon delivery of each share of Ordinary Shares subject to the Restricted Stock Unit Award. The consideration to be paid (if any) by the Participant for each share of Ordinary Shares subject to a Restricted Stock Unit Award may be paid in any form of legal consideration that may be acceptable to the Board, in its sole discretion, and permissible under applicable law, *provided, however,* that where Ordinary Shares are issued pursuant to a Restricted Stock Unit Award, the nominal value of each newly issued Ordinary Share is fully paid up.

(ii) Vesting. At the time of the grant of a Restricted Stock Unit Award, the Board may impose such restrictions on or conditions to the vesting of the Restricted Stock Unit Award as it, in its sole discretion, deems appropriate.

(iii) Payment. A Restricted Stock Unit Award may be settled by the delivery of Ordinary Shares, their cash equivalent, any combination thereof or in any other form of consideration, as determined by the Board and contained in the Restricted Stock Unit Award Agreement.

(iv) Additional Restrictions. At the time of the grant of a Restricted Stock Unit Award, the Board, as it deems appropriate, may impose such restrictions or conditions that delay the delivery of the Ordinary Shares (or their cash equivalent) subject to a Restricted Stock Unit Award to a time after the vesting of such Restricted Stock Unit Award.

(v) Dividend Equivalents. Dividend equivalents may be credited in respect of Ordinary Shares covered by a Restricted Stock Unit Award, as determined by the Board and contained in the Restricted Stock Unit Award Agreement. At the sole discretion of the Board, such dividend equivalents may be converted into additional Ordinary Shares covered by the Restricted Stock Unit Award in such manner as determined by the Board. Any additional Ordinary Shares covered by the Restricted Stock Unit Award credited by reason of such dividend equivalents will be subject to all of the same terms and conditions of the underlying Restricted Stock Unit Award Agreement to which they relate.

(vi) Termination of Participant's Continuous Service. Except as otherwise provided in the applicable Restricted Stock Unit Award Agreement, such portion of the Restricted Stock Unit Award that has not vested will be forfeited upon the Participant's termination of Continuous Service.

(c) Performance Awards.

(i) Performance Stock Awards. A Performance Stock Award is a Stock Award that may vest or may be exercised contingent upon the attainment during a Performance Period of certain Performance Goals. A Performance Stock Award may, but need not, require the completion of a specified period of Continuous Service. The length of any Performance Period, the Performance Goals to be achieved during the Performance Period, and the measure of whether and to what degree such Performance Goals have been attained shall be conclusively determined by the Committee, in its sole discretion. Except with respect to Inducement Awards, the maximum number of shares covered by an Award that may be granted to any Participant in a calendar year attributable to Stock Awards described in this Section 6(c)(i) (whether the grant, vesting or exercise is contingent upon the attainment during a Performance Period of the Performance Goals) shall not exceed three million (3,000,000) Ordinary Shares. The Board may provide for or, subject to such terms and conditions as the Board may specify, may permit a Participant to elect for, the payment of any Performance Stock Award to be deferred to a specified date or event. In addition, to the extent permitted by applicable law and the applicable Award Agreement, the Board may determine that cash may be used in payment of Performance Stock Awards.

(ii) Performance Cash Awards. A Performance Cash Award is a cash award that may be paid contingent upon the attainment during a Performance Period of certain Performance Goals. A Performance Cash Award may also require the completion of a specified period of Continuous Service. At the time of grant of a Performance Cash Award, the length of any Performance Period, the Performance Goals to be achieved during the Performance Period, and the measure of whether and to what degree such Performance Goals have been attained shall be conclusively determined by the Committee, in its sole discretion. In any calendar year, the Committee may not grant a Performance Cash Award that has a maximum value that may be paid to any Participant in excess of three million dollars ($3,000,000). The Board may provide for or, subject to such terms and conditions as the Board may specify, may permit a Participant to elect for, the payment of any Performance Cash Award to be deferred to a specified date or event. The Committee may specify the form of payment of Performance Cash Awards, which may be cash or other property, or may provide for a Participant to have the option for his or her Performance Cash Award, or such portion thereof as the Board may specify, to be paid in whole or in part in cash or other property.

(iii) Board Discretion. The Board retains the discretion to reduce or eliminate the compensation or economic benefit due upon attainment of Performance Goals and to define the manner of calculating the Performance Criteria it selects to use for a Performance Period.

(iv) Section 162(m) Compliance. Unless otherwise permitted in compliance with the requirements of Section 162(m) of the Code with respect to an Award intended to qualify as "performance-based compensation" thereunder, the Committee shall establish the Performance Goals applicable to, and the formula for calculating the amount payable under, the Award no later than the earlier of (a) the date ninety (90) days after the commencement of the applicable Performance Period, or (b) the date on which twenty-five percent (25%) of the Performance Period has elapsed, and in either event at a time when the achievement of the applicable Performance Goals remains substantially uncertain. Prior to the payment of any

compensation under an Award intended to qualify as "performance-based compensation" under Section 162(m) of the Code, the Committee shall certify the extent to which any Performance Goals and any other material terms under such Award have been satisfied (other than in cases where such relate solely to the increase in the value of the Ordinary Shares). Notwithstanding satisfaction or completion of any Performance Goals, to the extent specified at the time of grant of an Award to "covered employees" within the meaning of Section 162(m) of the Code, the number of Ordinary Shares, Options, cash or other benefits granted, issued, retainable and/or vested under an Award on account of satisfaction of such Performance Goals may be reduced by the Committee on the basis of such further considerations as the Committee, in its sole discretion, shall determine.

(d) Other Stock Awards. Other forms of Stock Awards valued in whole or in part by reference to, or otherwise based on, Ordinary Shares, including the appreciation in value thereof (e.g., options or share rights with an exercise price or strike price less than 100% of the Fair Market Value of the Ordinary Shares at the time of grant) may be granted either alone or in addition to Stock Awards provided for under Section 5 and the preceding provisions of this Section 6. Subject to the provisions of the Plan, the Board shall have sole and complete authority to determine the persons to whom and the time or times at which such Other Stock Awards will be granted, the number of Ordinary Shares (or the cash equivalent thereof) to be granted pursuant to such Other Stock Awards and all other terms and conditions of such Other Stock Awards; *provided, however,* that where Ordinary Shares are issued pursuant to any Other Stock Award, the nominal value of each newly issued Ordinary Share is fully paid up.

7. COVENANTS OF THE COMPANY.

(a) Availability of Shares. During the terms of the Stock Awards, the Company shall keep available at all times the authorized but unissued Ordinary Shares reasonably required to satisfy such Stock Awards.

(b) Securities Law Compliance. The Company shall seek to obtain from each regulatory commission or agency having jurisdiction over the Plan such authority as may be required to grant Stock Awards and to issue and sell Ordinary Shares upon exercise of the Stock Awards; *provided, however*, that this undertaking shall not require the Company to register under the Securities Act the Plan, any Stock Award or any Ordinary Shares issued or issuable pursuant to any such Stock Award. If, after reasonable efforts, the Company is unable to obtain from any such regulatory commission or agency the authority that counsel for the Company deems necessary for the lawful issuance and sale of Ordinary Shares under the Plan, the Company shall be relieved from any liability for failure to issue and sell Ordinary Shares upon exercise of such Stock Awards unless and until such authority is obtained. A Participant shall not be eligible for the grant of a Stock Award or the subsequent issuance of Ordinary Shares pursuant to the Stock Award if such grant or issuance would be in violation of any applicable securities law.

(c) No Obligation to Notify or Minimize Taxes. The Company and its Affiliates shall have no duty or obligation to any Participant to advise such holder as to the time or manner of exercising such Stock Award. Furthermore, the Company and its Affiliates shall have no duty or obligation to warn or otherwise advise such holder of a pending termination or expiration of a Stock Award or a possible period in which the Stock Award may not be exercised. The Company and its Affiliates have no duty or obligation to minimize the tax consequences of a Stock Award to the holder of such Stock Award.

8. MISCELLANEOUS.

(a) Use of Proceeds from Sales of Ordinary Shares. Proceeds from the sale of Ordinary Shares pursuant to Stock Awards shall constitute general funds of the Company.

(b) Corporate Action Constituting Grant of Stock Awards. Corporate action constituting a grant by the Company of a Stock Award to any Participant shall be deemed completed as of the date of such corporate action, unless otherwise determined by the Board, regardless of when the instrument, certificate, or letter evidencing the Stock Award is communicated to, or actually received or accepted by, the Participant.

(c) Shareholder Rights. No Participant shall be deemed to be the holder of, or to have any of the rights of a holder with respect to, any Ordinary Shares subject to such Stock Award unless and until (i) such Participant has satisfied all requirements for exercise of the Stock Award pursuant to its terms, if applicable, and (ii) the issuance of the Ordinary Shares subject to such Stock Award has been entered into the books and records of the Company.

(d) No Employment or Other Service Rights. Nothing in the Plan, any Stock Award Agreement or any other instrument executed thereunder or in connection with any Award granted pursuant thereto shall confer upon any Participant any right to continue to serve the Company or an Affiliate in the capacity in effect at the time the Stock Award was granted or shall affect the right of the Company or an Affiliate to terminate the employment of an Employee with or without notice and with or without cause.

(e) Incentive Stock Option $100,000 Limitation. To the extent that the aggregate Fair Market Value (determined at the time of grant) of Ordinary Shares with respect to which Incentive Stock Options are exercisable for the first time by any Optionholder during any calendar year (under all plans of the Company and any Affiliates) exceeds one hundred thousand dollars ($100,000), the Options or portions thereof that exceed such limit (according to the order in which they were granted) shall be treated as Nonstatutory Stock Options, notwithstanding any contrary provision of the applicable Option Agreement(s).

(f) Investment Assurances. The Company may require a Participant, as a condition of exercising or acquiring Ordinary Shares under any Stock Award, (i) to give written assurances satisfactory to the Company as to the Participant's knowledge and experience in financial and business matters and/or to employ a purchaser representative reasonably satisfactory to the Company who is knowledgeable and experienced in financial and business matters and that he or she is capable of evaluating, alone or together with the purchaser representative, the merits and risks of exercising the Stock Award; and (ii) to give written assurances satisfactory to the Company stating that the Participant is acquiring Ordinary Shares subject to the Stock Award for the Participant's own account and not with any present intention of selling or otherwise distributing the Ordinary Shares. The foregoing requirements, and any assurances given pursuant to such requirements, shall be inoperative if (A) the issuance of the shares upon the exercise or acquisition of Ordinary Shares under the Stock Award has been registered under a

then currently effective registration statement under the Securities Act, or (B) as to any particular requirement, a determination is made by counsel for the Company that such requirement need not be met in the circumstances under the then applicable securities laws. The Company may, upon advice of counsel to the Company, place legends on share certificates issued under the Plan as such counsel deems necessary or appropriate in order to comply with applicable securities laws, including, but not limited to, legends restricting the transfer of the Ordinary Shares.

(g) Withholding Obligations. Unless prohibited by the terms of a Stock Award Agreement, the Company or any Affiliate may, in its sole discretion, satisfy any federal, state, local or foreign tax withholding obligation, or levies or social security deduction obligation relating to an Award by any of the following means or by a combination of such means: (i) causing the Participant to tender a cash payment; (ii) withholding Ordinary Shares from the Ordinary Shares issued or otherwise issuable to the Participant in connection with the Award; *provided, however,* that no Ordinary Shares are withheld with a value exceeding the minimum amount of tax, levies and social security contribution required to be withheld by law or the practice of any revenue authority (or such lesser amount as may be necessary to avoid classification of the Stock Award as a liability for financial accounting purposes); (iii) withholding cash from an Award settled in cash; (iv) withholding payment from any amounts otherwise payable to the Participant; or (v) by such other method as may be set forth in the Award Agreement.

(h) Electronic Delivery. Any reference herein to a "written" agreement or document shall include any agreement or document delivered electronically or posted on the Company's (or Affiliate's, if applicable) intranet (or other shared electronic medium controlled by the Company or any Affiliate to which the Participant has access).

(i) Deferrals. To the extent permitted by applicable law, the Board, in its sole discretion, may determine that the delivery of Ordinary Shares or the payment of cash, upon the exercise, vesting or settlement of all or a portion of any Award may be deferred and may establish programs and procedures for deferral elections to be made by Participants. Deferrals by Participants will be made in accordance with Section 409A of the Code. Consistent with Section 409A of the Code, the Board may provide for distributions while a Participant is still an employee or otherwise providing services to the Company or an Affiliate. The Board is authorized to make deferrals of Awards and determine when, and in what annual percentages, Participants may receive payments, including lump sum payments, following the Participant's termination of Continuous Service, and implement such other terms and conditions consistent with the provisions of the Plan and in accordance with applicable law.

(j) Compliance with Section 409A. To the extent that the Board determines that any Award granted hereunder is subject to Section 409A of the Code, the Award Agreement evidencing such Award shall incorporate the terms and conditions necessary to avoid the consequences specified in Section 409A(a)(1) of the Code. To the extent applicable, the Plan and Award Agreements shall be interpreted in accordance with Section 409A of the Code. Notwithstanding anything to the contrary in this Plan (and unless the Award Agreement specifically provides otherwise), if the Ordinary Shares are publicly traded and a Participant holding an Award that constitutes "deferred compensation" under Section 409A of the Code is a "specified employee" for purposes of Section 409A of the Code, no distribution or payment of

any amount shall be made upon a "separation from service" before a date that is six (6) months following the date of such Participant's "separation from service" (as defined in Section 409A of the Code without regard to alternative definitions thereunder) or, if earlier, the date of the Participant's death.

(k) Personal Data. It shall be a term and condition of every Award that a Participant agrees and consents to:

(i) the collection, use and processing of his Personal Data by the Company or any Subsidiary and the transfer of his Personal Data to any third party administrator of the Plan and any broker through whom Shares are to be sold on behalf of a Participant;

(ii) the Company, its Subsidiaries or any third party administrator of the Plan, transferring the Participant's Personal Data amongst themselves for the purposes of implementing, administering and managing the Plan and the issue of Awards and the acquisition of Ordinary Shares pursuant to Awards;

(iii) the use of Personal Data by any such person for any such purposes; and

(iv) the transfer to and retention of Personal Data by third parties (including any situated outside the European Economic Area) for or in connection with such purposes.

9. ADJUSTMENTS UPON CHANGES IN ORDINARY SHARES; OTHER CORPORATE EVENTS.

(a) Capitalization Adjustments. In the event of a Capitalization Adjustment, the Board shall appropriately and proportionately adjust: (i) the class(es) and maximum number of securities subject to the Plan pursuant to Section 3(a)(i) and 3(f), (ii) the class(es) and maximum number of securities that may be issued pursuant to the exercise of Incentive Stock Options pursuant to Section 3(a)(ii), (iii) the class(es) and maximum number of securities that may be awarded to any person pursuant to Sections 3(d) and 6(c)(i), and (iv) the class(es) and number of securities and price per Ordinary Share subject to outstanding Stock Awards. The Board shall make such adjustments, and its determination shall be final, binding and conclusive.

(b) Dissolution or Liquidation. Except as otherwise provided in a Stock Award Agreement, in the event of a dissolution or liquidation of the Company, all outstanding Stock Awards (other than Stock Awards consisting of vested and outstanding Ordinary Shares not subject to a forfeiture condition or the Company's or any Affiliate's right of repurchase) shall terminate immediately prior to the completion of such dissolution or liquidation, and any Ordinary Shares subject to the Company's or any Affiliate's repurchase rights or subject to a forfeiture condition may be repurchased or reacquired by the Company or an Affiliate notwithstanding the fact that the holder of such Stock Award is providing Continuous Service, *provided, however*, that the Board may, in its sole discretion, cause some or all Stock Awards to become fully vested, exercisable and/or no longer subject to repurchase or forfeiture (to the extent such Stock Awards have not previously expired or terminated) before the dissolution or liquidation is completed but contingent on its completion.

(c) Corporate Transaction. The following provisions shall apply to Stock Awards in the event of a Corporate Transaction unless otherwise provided in the instrument evidencing

the Stock Award or any other written agreement between the Company or any Affiliate and the Participant or unless otherwise expressly provided by the Board at the time of grant of a Stock Award.

(i) Stock Awards May Be Assumed. In the event of a Corporate Transaction, any surviving corporation or acquiring corporation (or the surviving or acquiring corporation's parent company) may assume or continue any or all Stock Awards outstanding under the Plan or may substitute similar stock awards for Stock Awards outstanding under the Plan (including but not limited to, awards to acquire the same consideration paid to the shareholders of the Company pursuant to the Corporate Transaction), and any reacquisition or repurchase rights held by the Company in respect of Ordinary Shares issued pursuant to Stock Awards may be assigned by the Company to the successor of the Company (or the successor's parent company, if any) in connection with such Corporate Transaction. A surviving corporation or acquiring corporation (or its parent) may choose to assume or continue only a portion of a Stock Award or substitute a similar stock award for only a portion of a Stock Award, or may choose to assume or continue the Stock Awards held by some, but not all Participants. The terms of any assumption, continuation or substitution shall be set by the Board.

(ii) Stock Awards Held by Current Participants. In the event of a Corporate Transaction in which the surviving corporation or acquiring corporation (or its parent company) does not assume or continue such outstanding Stock Awards or substitute similar stock awards for such outstanding Stock Awards, then with respect to Stock Awards that have not been assumed, continued or substituted and that are held by Participants whose Continuous Service has not terminated prior to the effective time of the Corporate Transaction (referred to as the "***Current Participants***"), the vesting of such Stock Awards (and, with respect to Options and Stock Appreciation Rights, the time when such Stock Awards may be exercised) shall be accelerated in full to a date prior to the effective time of such Corporate Transaction (contingent upon the effectiveness of the Corporate Transaction) as the Board shall determine (or, if the Board shall not determine such a date, to the date that is five (5) days prior to the effective time of the Corporate Transaction), and such Stock Awards shall terminate if not exercised (if applicable) at or prior to the effective time of the Corporate Transaction, and any reacquisition or repurchase rights held by the Company with respect to such Stock Awards shall lapse (contingent upon the effectiveness of the Corporate Transaction).

(iii) Stock Awards Held by Persons other than Current Participants. In the event of a Corporate Transaction in which the surviving corporation or acquiring corporation (or its parent company) does not assume or continue such outstanding Stock Awards or substitute similar stock awards for such outstanding Stock Awards, then with respect to Stock Awards that have not been assumed, continued or substituted and that are held by persons other than Current Participants, such Stock Awards shall terminate if not exercised (if applicable) prior to the effective time of the Corporate Transaction; *provided, however*, that any reacquisition or repurchase rights held by the Company with respect to such Stock Awards shall not terminate and may continue to be exercised notwithstanding the Corporate Transaction.

(iv) Payment for Stock Awards in Lieu of Exercise. Notwithstanding the foregoing, in the event a Stock Award will terminate if not exercised prior to the effective time of a Corporate Transaction, the Board may provide, in its sole discretion, that the holder of such

Stock Award may not exercise such Stock Award but will receive a payment, in such form as may be determined by the Board, equal in value, at the effective time, to the excess, if any, of (A) the value of the property the Participant would have received upon the exercise of the Stock Award (including, at the discretion of the Board, any unvested portion of such Stock Award), over (B) any exercise price payable by such holder in connection with such exercise.

(d) Change in Control. A Stock Award may be subject to additional acceleration of vesting and exercisability upon or after a Change in Control as may be provided in the Stock Award Agreement for such Stock Award or as may be provided in any other written agreement between the Company or any Affiliate and the Participant, but in the absence of such provision, no such acceleration shall occur.

10. TERMINATION OR SUSPENSION OF THE PLAN.

(a) Plan Term. The Board may suspend or terminate the Plan at any time. Unless terminated sooner by the Board, the Plan shall automatically terminate on the day before the tenth (10th) anniversary of the earlier of (i) the date the Plan is adopted by the Board, or (ii) the date the Plan is approved by the shareholders of the Company. No Awards may be granted under the Plan while the Plan is suspended or after it is terminated.

(b) No Impairment of Rights. Suspension or termination of the Plan shall not impair rights and obligations under any Award granted while the Plan is in effect except with the written consent of the affected Participant.

11. EFFECTIVE DATE OF PLAN.

The Plan shall become effective on the Effective Date.

12. CHOICE OF LAW.

The laws of the State of California shall govern all questions concerning the construction, validity and interpretation of this Plan, without regard to that state's conflict of laws rules.

13. DEFINITIONS. As used in the Plan, the following definitions shall apply to the capitalized terms indicated below:

(a) ***"2011 Plan Available Reserve"*** means the number of shares of common available for issuance pursuant to the grant of future awards under the 2011 Plan determined as of immediately prior to the Effective Date.

(b) "***Affiliate***" means, at the time of determination, any "parent" or "subsidiary" of the Company as such terms are defined in Rule 405 promulgated under the Securities Act. The Board shall have the authority to determine the time or times at which "parent" or "subsidiary" status is determined within the foregoing definition.

(c) "***Award***" means a Stock Award or a Performance Cash Award.

(d) "***Award Agreement***" means a written agreement between the Company and a Participant evidencing the terms and conditions of an Award.

(e) "***Board***" means the Board of Directors of the Company.

(f) "***Capitalization Adjustment***" means any change that is made in, or other events that occur with respect to, the Ordinary Shares subject to the Plan or subject to any Stock Award after the Effective Date without the receipt of consideration by the Company through merger, consolidation, reorganization, recapitalization, reincorporation, share dividend, dividend in property other than cash, large nonrecurring cash dividend, share split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or any similar equity restructuring transaction, as that term is used in Statement of Financial Accounting Standards No. 123 (revised). Notwithstanding the foregoing, the conversion of any convertible securities of the Company shall not be treated as a Capitalization Adjustment.

(g) "***Cause***" shall have the meaning ascribed to such term in any written agreement between the Participant and the Company defining such term and, in the absence of such agreement, such term shall mean, with respect to a Participant, the occurrence of any of the following events that has a material negative impact on the business or reputation of the Company: (i) such Participant's repeated failure to perform one or more essential duties and responsibilities to the Company; (ii) such Participant's failure to follow the lawful directives of manager(s); (iii) such Participant's material violation of any Company policy; (iv) such Participant's commission of any act of fraud, embezzlement, dishonesty or any other willful misconduct or gross misconduct; (v) such Participant's unauthorized use or disclosure of any proprietary information, confidential information or trade secrets of the Company or any other party to whom he or she owes an obligation of nondisclosure as a result of his or her relationship with the Company; or (vi) such Participant's willful breach of any of obligations under any written agreement or covenant with the Company or violation of any statutory duty owed to the Company. The determination that a termination of the Participant's Continuous Service is either for Cause or without Cause shall be made by the Company (or an Affiliate, if applicable), in its sole discretion. Any determination by the Company (or an Affiliate, if applicable) that the Continuous Service of a Participant was terminated with or without Cause for the purposes of outstanding Awards held by such Participant shall have no effect upon any determination of the rights or obligations of the Company or Affiliate or such Participant for any other purpose.

(h) "***Change in Control***" means the occurrence, in a single transaction or in a series of related transactions, of any one or more of the following events:

(i) any Exchange Act Person becomes the Owner, directly or indirectly, of securities of the Company representing more than fifty percent (50%) of the combined voting power of the Company's then outstanding securities other than by virtue of a merger, consolidation or similar transaction. Notwithstanding the foregoing, a Change in Control shall not be deemed to occur (A) on account of the acquisition of securities of the Company directly from the Company, (B) on account of the acquisition of securities of the Company by an investor, any affiliate thereof or any other Exchange Act Person that acquires the Company's securities in a transaction or series of related transactions the primary purpose of which is to obtain financing for the Company through the issuance of equity securities, or (C) solely because

the level of Ownership held by any Exchange Act Person (the "*Subject Person*") exceeds the designated percentage threshold of the outstanding voting securities as a result of a repurchase or other acquisition of voting securities by the Company or any Affiliate reducing the number of shares outstanding, provided that if a Change in Control would occur (but for the operation of this sentence) as a result of the acquisition of voting securities by the Company or any Affiliate, and after such share acquisition, the Subject Person becomes the Owner of any additional voting securities that, assuming the repurchase or other acquisition had not occurred, increases the percentage of the then outstanding voting securities Owned by the Subject Person over the designated percentage threshold, then a Change in Control shall be deemed to occur;

(ii) there is consummated a merger, consolidation or similar transaction involving (directly or indirectly) the Company and, immediately after the consummation of such merger, consolidation or similar transaction, the shareholders of the Company immediately prior thereto do not Own, directly or indirectly, either (A) outstanding voting securities representing more than fifty percent (50%) of the combined outstanding voting power of the surviving Entity in such merger, consolidation or similar transaction or (B) more than fifty percent (50%) of the combined outstanding voting power of the parent of the surviving Entity in such merger, consolidation or similar transaction, in each case in substantially the same proportions as their Ownership of the outstanding voting securities of the Company immediately prior to such transaction;

(iii) the shareholders of the Company approve or the Board approves a plan of complete dissolution or liquidation of the Company, or a complete dissolution or liquidation of the Company shall otherwise occur, except for a liquidation into a parent corporation;

(iv) there is consummated a sale, lease, exclusive license or other disposition of all or substantially all of the consolidated assets of the Company and its Subsidiaries, other than a sale, lease, license or other disposition of all or substantially all of the consolidated assets of the Company and its Subsidiaries to an Entity, more than fifty percent (50%) of the combined voting power of the voting securities of which are Owned by shareholders of the Company in substantially the same proportions as their Ownership of the outstanding voting securities of the Company immediately prior to such sale, lease, license or other disposition; or

(v) individuals who, on the date the Plan is adopted by the Board, are members of the Board (the "***Incumbent Board***") cease for any reason to constitute at least a majority of the members of the Board; *provided, however*, that if the appointment or election (or nomination for election) of any new Board member was approved or recommended by a majority vote of the members of the Incumbent Board then still in office, such new member shall, for purposes of this Plan, be considered as a member of the Incumbent Board.

For the avoidance of doubt, any one or more of the above events may be effected pursuant to (i) a compromise or arrangement sanctioned by the Irish courts under section 201 of the Companies Act 1963 (as may be amended, updated or replaced from time to time) (the "**1963 Act**") or (ii) a scheme, contract or offer which has become binding on all shareholders pursuant to Section 204 of the 1963 Act, or (iii) a bid pursuant to Regulation 23 or 24 of the European Communities (Takeover Bids (Directive 2004/25/EC)) Regulations 2006.

Notwithstanding the foregoing or any other provision of this Plan, (A) the term Change in Control shall not include a sale of assets, merger or other transaction effected exclusively for the purpose of changing the domicile of the Company, and (B) the definition of Change in Control (or any analogous term) in an individual written agreement between the Company or any Affiliate and the Participant shall supersede the foregoing definition with respect to Awards subject to such agreement; *provided, however*, that if no definition of Change in Control or any analogous term is set forth in such an individual written agreement, the foregoing definition shall apply.

(i) "***Code***" means the Internal Revenue Code of 1986, as amended, including any applicable regulations and guidance thereunder.

(j) "***Committee***" means a committee of one or more Directors to whom authority has been delegated by the Board in accordance with Section 2(c).

(k) "***Company***" means Horizon Pharma Public Limited Company, a company incorporated under the laws of Ireland.

(l) "***Consultant***" means any person, including an advisor, who is (i) engaged by the Company or an Affiliate to render consulting or advisory services and is compensated for such services, or (ii) serving as a member of the board of directors of an Affiliate and is compensated for such services. However, service solely as a Non-employee Director, or payment of a fee for such service, shall not cause a Non-employee Director to be considered a "Consultant" for purposes of the Plan. Notwithstanding the foregoing, a person is treated as a Consultant under this Plan only if a Form S-8 Registration Statement under the Securities Act is available to register either the offer or the sale of the Company's securities to such person.

(m) "***Continuous Service***" means that the Participant's service with the Company or an Affiliate, whether as an Employee, Director or Consultant, is not interrupted or terminated. A change in the capacity in which the Participant renders service to the Company or an Affiliate as an Employee, Consultant or Director or a change in the entity for which the Participant renders such service, provided that there is no interruption or termination of the Participant's service with the Company or an Affiliate, shall not terminate a Participant's Continuous Service; *provided, however,* if the Entity for which a Participant is rendering services ceases to qualify as an Affiliate, as determined by the Board, in its sole discretion, such Participant's Continuous Service shall be considered to have terminated on the date such Entity ceases to qualify as an Affiliate. To the extent permitted by law, the Board or the chief executive officer of the Company (or an Affiliate, if applicable), in that party's sole discretion, may determine whether Continuous Service shall be considered interrupted in the case of (i) any leave of absence approved by the Board or chief executive officer of the Company (or an Affiliate, if applicable), including sick leave, military leave or any other personal leave, or (ii) transfers between the Company, an Affiliate, or their successors. Notwithstanding the foregoing, a leave of absence shall be treated as Continuous Service for purposes of vesting in a Stock Award only to such extent as may be provided in the Company's (or an Affiliate's, if applicable) leave of absence policy, in the written terms of any leave of absence agreement or policy applicable to the Participant, or as otherwise required by law.

(n) "***Corporate Transaction***" means the consummation, in a single transaction or in a series of related transactions, of any one or more of the following events:

(i) a sale or other disposition of all or substantially all, as determined by the Board, in its sole discretion, of the consolidated assets of the Company and its Subsidiaries;

(ii) a sale or other disposition of at least ninety percent (90%) of the outstanding securities of the Company;

(iii) a merger, consolidation or similar transaction following which the Company is not the surviving corporation; or

(iv) a merger, consolidation or similar transaction following which the Company is the surviving corporation but the Ordinary Shares outstanding immediately preceding the merger, consolidation or similar transaction are converted or exchanged by virtue of the merger, consolidation or similar transaction into other property, whether in the form of securities, cash or otherwise.

(o) "***Covered Employee***" shall have the meaning provided in Section 162(m)(3) of the Code.

(p) "***Director***" means a member of the Board.

(q) "***Disability***" means, with respect to a Participant, the inability of such Participant to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than twelve (12) months, as provided in Sections 22(e)(3) and 409A(a)(2)(c)(i) of the Code, and shall be determined by the Board on the basis of such medical evidence as the Board deems warranted under the circumstances.

(r) "***Effective Date***" means the effective date of this Plan, which is immediately prior to the effective time of the merger between Horizon Pharma, Inc. and Horizon Pharma Public Limited Company pursuant to the Transaction Agreement and Plan of Merger dated March 18, 2014, provided that this Plan is approved by the stockholders of Horizon Pharma, Inc. prior to such merger and such merger is consummated.

(s) "***Employee***" means any person employed by the Company or an Affiliate. However, service solely as a Director, or payment of a fee for such services, shall not cause a Director to be considered an "Employee" for purposes of the Plan.

(t) "***Entity***" means a corporation, partnership, limited liability company or other entity.

(u) "***Exchange Act***" means the Securities Exchange Act of 1934, as amended, and the rules and regulations promulgated thereunder.

(v) "***Exchange Act Person***" means any natural person, Entity or "group" (within the meaning of Section 13(d) or 14(d) of the Exchange Act), except that "Exchange Act Person"

shall not include (i) the Company or any Subsidiary of the Company, (ii) any employee benefit plan of the Company or any Subsidiary of the Company or any trustee or other fiduciary holding securities under an employee benefit plan of the Company or any Subsidiary of the Company, (iii) an underwriter temporarily holding securities pursuant to a registered public offering of such securities, (iv) an Entity Owned, directly or indirectly, by the shareholders of the Company in substantially the same proportions as their Ownership of Ordinary Shares of the Company; or (v) any natural person, Entity or "group" (within the meaning of Section 13(d) or 14(d) of the Exchange Act) that, as of the Effective Date, is the Owner, directly or indirectly, of securities of the Company representing more than fifty percent (50%) of the combined voting power of the Company's then outstanding securities.

(w) "***Fair Market Value***" means, as of any date, the value of the Ordinary Shares determined as follows:

(i) If the Ordinary Shares is listed on any established stock exchange or traded on the NASDAQ Global Market or the NASDAQ Global Select Market, the Fair Market Value of a share of Ordinary Shares, unless otherwise determined by the Board, shall be the closing sales price for such Ordinary Shares as quoted on such exchange or market (or the exchange or market with the greatest volume of trading in the Ordinary Shares) on the day of determination, as reported in a source the Board deems reliable.

(ii) Unless otherwise provided by the Board, if there is no closing sales price for the Ordinary Shares on the day of determination, then the Fair Market Value shall be the closing selling price on the last preceding date for which such quotation exists.

(iii) In the absence of such markets for the Ordinary Shares, the Fair Market Value shall be determined by the Board in good faith and in a manner that complies with Sections 409A and 422 of the Code.

(x) "***Horizon"*** means Horizon Pharma, Inc. a Delaware corporation.

(y) "***Incentive Stock Option***" means an option granted pursuant to Section 5 of the Plan that is intended to be, and qualifies as, an "incentive stock option" within the meaning of Section 422 of the Code.

(z) ***"Inducement Award"*** means a Stock Award granted pursuant to Section 3(f) of the Plan.

(aa) ***"Inducement Committee"*** means a Committee consisting of the majority of the Company's independent directors or the Company's independent compensation committee, in either case in accordance with NASDAQ Listing Rule 5635(c)(4).

(bb) "***Non-Employee Director***" means a Director who either (i) is not a current employee or officer of the Company or an Affiliate, does not receive compensation, either directly or indirectly, from the Company or an Affiliate for services rendered as a consultant or in any capacity other than as a Director (except for an amount as to which disclosure would not be required under Item 404(a) of Regulation S-K promulgated pursuant to the Securities Act ("***Regulation S-K***")), does not possess an interest in any other transaction for which disclosure

would be required under Item 404(a) of Regulation S-K, and is not engaged in a business relationship for which disclosure would be required pursuant to Item 404(b) of Regulation S-K; or (ii) is otherwise considered a "non-employee director" for purposes of Rule 16b-3.

(cc) "***Nonstatutory Stock Option***" means any option granted pursuant to Section 5 of the Plan that does not qualify as an Incentive Stock Option.

(dd) "***Officer***" means a person who is an officer of the Company within the meaning of Section 16 of the Exchange Act.

(ee) "***Option***" means an Incentive Stock Option or a Nonstatutory Stock Option to purchase Ordinary Shares granted pursuant to the Plan.

(ff) "***Option Agreement***" means a written agreement between the Company and an Optionholder evidencing the terms and conditions of an Option grant. Each Option Agreement shall be subject to the terms and conditions of the Plan.

(gg) "***Optionholder***" means a person to whom an Option is granted pursuant to the Plan or, if applicable, such other person who holds an outstanding Option.

(hh) "***Ordinary Shares***" or "***Shares***" means the ordinary shares in the capital of the Company with a nominal value of US$0.0001 per share.

(ii) "***Other Stock Award***" means an award based in whole or in part by reference to the Ordinary Shares which is granted pursuant to the terms and conditions of Section 6(d).

(jj) "***Other Stock Award Agreement***" means a written agreement between the Company and a holder of an Other Stock Award evidencing the terms and conditions of an Other Stock Award grant. Each Other Stock Award Agreement shall be subject to the terms and conditions of the Plan.

(kk) "***Outside Director***" means a Director who either (i) is not a current employee of the Company or an "affiliated corporation" (within the meaning of Treasury Regulations promulgated under Section 162(m) of the Code), is not a former employee of the Company or an "affiliated corporation" who receives compensation for prior services (other than benefits under a tax-qualified retirement plan) during the taxable year, has not been an officer of the Company or an "affiliated corporation," and does not receive remuneration from the Company or an "affiliated corporation," either directly or indirectly, in any capacity other than as a Director, or (ii) is otherwise considered an "outside director" for purposes of Section 162(m) of the Code.

(ll) "***Own,***" "***Owned,***" "***Owner,***" "***Ownership***" A person or Entity shall be deemed to "Own," to have "Owned," to be the "Owner" of, or to have acquired "Ownership" of securities if such person or Entity, directly or indirectly, through any contract, arrangement, understanding, relationship or otherwise, has or shares voting power, which includes the power to vote or to direct the voting, with respect to such securities.

(mm) "***Participant***" means a person to whom an Award is granted pursuant to the Plan or, if applicable, such other person who holds an outstanding Stock Award.

(nn) "***Performance Cash Award***" means an award of cash granted pursuant to the terms and conditions of Section 6(c)(ii).

(oo) "***Performance Criteria***" means the one or more criteria that the Board shall select for purposes of establishing the Performance Goals for a Performance Period. The Performance Criteria that shall be used to establish such Performance Goals may be based on any one of, or combination of, the following as determined by the Board: (i) earnings (including earnings per share and net earnings); (ii) earnings before interest, taxes and depreciation; (iii) earnings before interest, taxes, depreciation and amortization; (iv) total shareholder return; (v) return on equity or average shareholder's equity; (vi) return on assets, investment, or capital employed; (vii) share price; (viii) margin (including gross margin); (ix) income (before or after taxes); (x) operating income; (xi) operating income after taxes; (xii) pre-tax profit; (xiii) operating cash flow; (xiv) sales or revenue targets; (xv) increases in revenue or product revenue; (xvi) expenses and cost reduction goals; (xvii) improvement in or attainment of working capital levels; (xiii) economic value added (or an equivalent metric); (xix) market share; (xx) cash flow; (xxi) cash flow per share; (xxii) share price performance; (xxiii) debt reduction; (xxiv) implementation or completion of projects or processes; (xxv) customer satisfaction; (xxvi) shareholders' equity; (xxvii) capital expenditures; (xxiii) debt levels; (xxix) operating profit or net operating profit; (xxx) workforce diversity; (xxxi) growth of net income or operating income; (xxxii) billings; and (xxxiii) to the extent that an Award is not intended to comply with
Section 162(m) of the Code, other measures of performance selected by the Board.

(pp) "***Performance Goals***" means, for a Performance Period, the one or more goals established by the Board for the Performance Period based upon the Performance Criteria. Performance Goals may be based on a Company-wide basis, with respect to one or more business units, divisions, Affiliates, or business segments, and in either absolute terms or relative to the performance of one or more comparable companies or the performance of one or more relevant indices. Unless specified otherwise by the Board (i) in the Award Agreement at the time the Award is granted or (ii) in such other document setting forth the Performance Goals at the time the Performance Goals are established, the Board shall appropriately make adjustments in the method of calculating the attainment of Performance Goals for a Performance Period as follows: (1) to exclude restructuring and/or other nonrecurring charges; (2) to exclude exchange rate effects, as applicable, for non-U.S. dollar denominated Performance Goals; (3) to exclude the effects of changes to generally accepted accounting principles; (4) to exclude the effects of any statutory adjustments to corporate tax rates; and (5) to exclude the effects of any items that are 'unusual' in nature or that occur 'infrequently' as determined under generally accepted accounting principles.

(qq) "***Performance Period***" means the period of time selected by the Board over which the attainment of one or more Performance Goals will be measured for the purpose of determining a Participant's right to and the payment of a Stock Award or a Performance Cash Award. Performance Periods may be of varying and overlapping duration, at the sole discretion of the Board.

(rr) "***Performance Stock Award***" means a Stock Award granted under the terms and conditions of Section 6(c)(i).

(ss) ***"Personal Data"*** has the same meaning as defined in the Data Protection Acts 1988 and 2003.

(tt) "***Plan***" means this Horizon Pharma Public Limited Company 2014 Equity Incentive Plan.

(uu) "***Restricted Stock Award***" means an award of Ordinary Shares which is granted pursuant to the terms and conditions of Section 6(a).

(vv) "***Restricted Stock Award Agreement***" means a written agreement between the Company and a holder of a Restricted Stock Award evidencing the terms and conditions of a Restricted Stock Award grant. Each Restricted Stock Award Agreement shall be subject to the terms and conditions of the Plan.

(ww) "***Restricted Stock Unit Award***" means a right to receive Ordinary Shares which is granted pursuant to the terms and conditions of Section 6(b).

(xx) "***Restricted Stock Unit Award Agreement***" means a written agreement between the Company and a holder of a Restricted Stock Unit Award evidencing the terms and conditions of a Restricted Stock Unit Award grant. Each Restricted Stock Unit Award Agreement shall be subject to the terms and conditions of the Plan.

(yy) "***Rule 16b-3***" means Rule 16b-3 promulgated under the Exchange Act or any successor to Rule 16b-3, as in effect from time to time.

(zz) "***Securities Act***" means the Securities Act of 1933, as amended.

(aaa) "***Stock Appreciation Right***" or "***SAR***" means a right to receive the appreciation on Ordinary Shares that is granted pursuant to the terms and conditions of Section 5.

(bbb) "***Stock Appreciation Right Agreement***" means a written agreement between the Company and a holder of a Stock Appreciation Right evidencing the terms and conditions of a Stock Appreciation Right grant. Each Stock Appreciation Right Agreement shall be subject to the terms and conditions of the Plan.

(ccc) "***Stock Award***" means any right to receive Ordinary Shares granted under the Plan, including an Incentive Stock Option, a Nonstatutory Stock Option, a Restricted Stock Award, a Restricted Stock Unit Award, a Stock Appreciation Right, a Performance Stock Award or any Other Stock Award.

(ddd) "***Stock Award Agreement***" means a written agreement between the Company and a Participant evidencing the terms and conditions of a Stock Award grant. Each Stock Award Agreement shall be subject to the terms and conditions of the Plan.

(eee) "***Subsidiary***" means, with respect to the Company, (i) any corporation of which more than fifty percent (50%) of the outstanding capital stock having ordinary voting power to elect a majority of the board of directors of such corporation (irrespective of whether, at the time, stock of any other class or classes of such corporation shall have or might have voting power by

reason of the happening of any contingency) is at the time, directly or indirectly, Owned by the Company, and (ii) any partnership, limited liability company or other entity in which the Company has a direct or indirect interest (whether in the form of voting or participation in profits or capital contribution) of more than fifty percent (50%).

(fff) "***Ten Percent Shareholder***" means a person who Owns (or is deemed to Own pursuant to Section 424(d) of the Code) shares possessing more than ten percent (10%) of the total combined voting power of all classes of shares of the Company or any Affiliate.

HORIZON PHARMA PUBLIC LIMITED COMPANY
2014 EQUITY INCENTIVE PLAN

OPTION AGREEMENT
(INCENTIVE STOCK OPTION OR NONSTATUTORY STOCK OPTION)

Pursuant to your Stock Option Grant Notice ("***Grant Notice***") and this Option Agreement (the "***Agreement***"), Horizon Pharma Public Limited Company (the "***Company***") has granted you an option under its 2014 Equity Incentive Plan (the "***Plan***") to purchase the number of the Company's Ordinary Shares indicated in your Grant Notice at the exercise price indicated in your Grant Notice. Capitalized terms not explicitly defined in this Agreement but defined in the Plan shall have the same definitions as in the Plan.

The details of your option are as follows:

1. VESTING. Subject to the limitations contained herein, your option will vest as provided in your Grant Notice, provided that vesting will cease upon the termination of your Continuous Service.

2. NUMBER OF SHARES AND EXERCISE PRICE. The number of Ordinary Shares subject to your option and your exercise price per share referenced in your Grant Notice may be adjusted from time to time for Capitalization Adjustments.

3. EXERCISE RESTRICTION FOR NON-EXEMPT EMPLOYEES. In the event that you are an Employee eligible for overtime compensation under the United States Fair Labor Standards Act of 1938, as amended (*i.e.*, a "***Non-Exempt Employee***"), you may not exercise your option until you have completed at least six (6) months of Continuous Service measured from the Date of Grant specified in your Grant Notice, notwithstanding any other provision of your option.

4. METHOD OF PAYMENT. Payment of the applicable exercise price is due in full upon exercise of all or any part of your option. All amounts due are payable in United States dollars based, if applicable, upon the local currency to United States dollar exchange rate published in the West Coast edition of The Wall Street Journal on the date of exercise of your option (or, if the date of exercise is not a business day in the United States, the preceding business day in the United States). You may not exercise your option, and no obligation shall arise upon the Company to procure the issue or transfer of the Ordinary Shares, unless and until the Company and/or any Affiliate are satisfied in their absolute discretion that you have fully paid up in cash (or by check) the nominal value of each Ordinary Share subject to the exercised portion of the option. You may elect to make payment of the remaining portion of the option exercise price by remittance for the amount payable or in any other manner ***permitted by your Grant Notice***, which may include one or more of the following:

a. Provided that at the time of exercise the Ordinary Shares are publicly traded and quoted regularly in a source the Board deems reliable, pursuant to a program developed under Regulation T as promulgated by the Federal Reserve Board that, prior to the issuance of Ordinary Shares, results in either the receipt of cash (or check) by the Company or the receipt of irrevocable instructions to pay the aggregate exercise price to the Company from the sales proceeds.

b. If this option is a Nonstatutory Stock Option, subject to the consent of the Company at the time of exercise, by a "net exercise" arrangement pursuant to which the Company will reduce the number of Ordinary Shares issuable upon exercise of your option by the largest whole number of Ordinary Shares with a Fair Market Value that does not exceed the aggregate exercise price; *provided, however*, that:

1) the Company shall accept a cash or other payment from you to the extent of any remaining balance of the aggregate exercise price not satisfied by such reduction in the number of whole Ordinary Shares to be issued;

2) Ordinary Shares will no longer be subject to an Option and will not be exercisable thereafter to the extent that (A) Ordinary Shares issuable upon exercise are reduced to pay the exercise price pursuant to the "net exercise," (B) Ordinary Shares are delivered to you as a result of such exercise, and (C) Ordinary Shares are withheld to satisfy tax withholding obligations.

5. WHOLE SHARES. You may exercise your option only for whole Ordinary Shares.

6. SECURITIES LAW COMPLIANCE. Notwithstanding anything to the contrary contained herein, you may not exercise your option unless the Ordinary Shares issuable upon such exercise are then registered under the Securities Act or, if such Ordinary Shares are not then so registered, the Company has determined that such exercise and issuance would be exempt from the registration requirements of the Securities Act. The exercise of your option also must comply with other applicable laws and regulations governing your option, including, without limitation, the laws and regulations of the United States and your country of residence, and you may not exercise your option if the Company determines that such exercise would not be in material compliance with such laws and regulations.

7. TERM. You may not exercise your option before the commencement of its term or after its term expires. The term of your option commences on the Date of Grant and expires upon the earliest of the following:

a. immediately upon the termination of your Continuous Service for Cause;

b. three (3) months after the termination of your Continuous Service for any reason other than Cause, Disability or death, provided that if during any part of such three (3)-month period you may not exercise your option solely because of the condition set forth in the preceding paragraph relating to "Securities Law Compliance," your option shall not expire until the earlier of the Expiration Date or until it shall have been exercisable for an aggregate period of three (3) months after the termination of your Continuous Service;

c. twelve (12) months after the termination of your Continuous Service due to your Disability;

d. eighteen (18) months after your death if you die either during your Continuous Service or within three (3) months after your Continuous Service terminates for any reason other than Cause;

e. the Expiration Date indicated in your Grant Notice; or

f. the day before the tenth (10th) anniversary of the Date of Grant.

If your option is an Incentive Stock Option, note that to obtain the US federal income tax advantages associated with an Incentive Stock Option, the Code requires that at all times beginning on the date of grant of your option and ending on the day three (3) months before the date of your option's exercise, you must be an employee of the Company or an Affiliate, except in the event of your death or your permanent and total disability, as defined in Section 22(e)(3) of the Code. The Company has provided for extended exercisability of your option under certain circumstances for your benefit but cannot guarantee that your option will necessarily be treated as an Incentive Stock Option if you continue to provide services to the Company or an Affiliate as a Consultant or Director after your employment terminates or if you otherwise exercise your option more than three (3) months after the date your employment with the Company or an Affiliate terminates.

8. EXERCISE.

a. You may exercise the vested portion of your option (and the unvested portion of your option if your Grant Notice so permits) during its term by following the option exercise instructions specified in your StockCross Financial Services brokerage account including adequate provision for payment of the option exercise price to the Company together with such additional documents as the Company may then require.

b. By exercising your option you agree that, as a condition to any exercise of your option, the Company may require you to enter into an arrangement providing for the payment by you to the Company of any tax withholding obligation of the Company arising by reason of (1) the exercise of your option, (2) the lapse of any substantial risk of forfeiture to which the Ordinary Shares are subject at the time of exercise, or (3) the disposition of Ordinary Shares acquired upon such exercise.

c. By exercising your option you agree that, as a condition to any exercise of your option, if you do not pay the nominal value of the Ordinary Shares by cash or check, such nominal value will be automatically deducted from salary or base wages due and payable to you.

d. If your option is an Incentive Stock Option, by exercising your option you agree that you will notify the Company in writing within fifteen (15) days after the date of any disposition of any of the Ordinary Shares issued upon exercise of your option that occurs within two (2) years after the date of your option grant or within one (1) year after such Ordinary Shares are transferred upon exercise of your option.

9. TRANSFERABILITY. Your option is not transferable, except by will or by the laws of descent and distribution, and is exercisable during your life only by you. Notwithstanding the foregoing, by delivering written notice to the Company, in a form satisfactory to the Company,

you may designate a third party who, in the event of your death, shall thereafter be entitled to exercise your option. In addition, if permitted by the Company you may transfer your option to a trust if you are considered to be the sole beneficial owner (determined under Section 671 of the Code and applicable state law) while the option is held in the trust, provided that you and the trustee enter into a transfer and other agreements required by the Company.

10. OPTION NOT A SERVICE CONTRACT. Your option is not an employment or service contract, and nothing in your option shall be deemed to create in any way whatsoever any obligation on your part to continue in the employ of the Company or an Affiliate, or of the Company or an Affiliate to continue your employment. In addition, nothing in your option shall obligate the Company or an Affiliate, their respective stockholders, Boards of Directors, Officers or Employees to continue any relationship that you might have as a Director or Consultant for the Company or an Affiliate.

11. WITHHOLDING OBLIGATIONS.

a. At the time you exercise your option, in whole or in part, or at any time thereafter as requested by the Company, you hereby authorize withholding from payroll and any other amounts payable to you, and otherwise agree to make adequate provision for (including by means of a "cashless exercise" pursuant to a program developed under Regulation T as promulgated by the Federal Reserve Board to the extent permitted by the Company), any sums required to satisfy the federal, state, local and foreign tax withholding obligations and social security deduction obligations of the Company or an Affiliate, if any, which arise in connection with the exercise of your option.

b. Upon your request and subject to approval by the Company, in its sole discretion, and compliance with any applicable legal conditions or restrictions, the Company may withhold from fully vested Ordinary Shares otherwise issuable to you upon the exercise of your option a number of whole Ordinary Shares having a Fair Market Value, determined by the Company as of the date of exercise, not in excess of the minimum amount of tax and social security contribution required to be withheld by law (or such lower amount as may be necessary to avoid classification of your option as a liability for financial accounting purposes). Any adverse consequences to you arising in connection with such share withholding procedure shall be your sole responsibility.

c. You may not exercise your option and no obligation shall arise upon the Company to procure the issue or transfer of the Ordinary Shares unless and until the Company and/or any Affiliate are satisfied in their absolute discretion that either (i) you have made payment, or have made arrangements satisfactory to the Company and/or any Affiliate for the payment to it of such sum as is sufficient to meet any withholding liability to Taxation (defined below) in any jurisdiction which is or would be recoverable from you following exercise of your option and/or the issue of Ordinary Shares by the Company arising from such exercise, and in respect of which the Company and/or any Affiliate is liable to account in any jurisdiction; or (ii) you have entered into an agreement with the Company and/or an Affiliate (in a form satisfactory to the Company or such Affiliate) to ensure that such a payment is made by you including, without limitation, amounts in respect of any employers' social security (or the local law equivalent thereof) or other forms of Taxation. Accordingly, you may not be able to exercise

your option when desired even though your option is vested, and the Company shall have no obligation to issue a certificate for such Ordinary Shares or release such Ordinary Shares from any escrow provided for herein unless such obligations are satisfied. "***Taxation***" shall include all forms of taxation including employees' and employers' social security, income tax and any other taxes of whatever nature in any jurisdiction together with any amount payable by an Affiliate in respect of which the Affiliate has a duty to account as a result of any laws of any jurisdiction relating to taxation.

12. PERSONAL DATA. You understand that your employer, if applicable, the Company, and/or its Affiliates hold certain personal information about you. This information include your name, home address, telephone number, date of birth, social security or equivalent tax identification number, salary, nationality, job title, and details of your option grant and all Ordinary Shares subject to such grant that have been granted, cancelled, vested, unvested, or are outstanding (the "***Personal Data***").

You hereby declare your express consent to allowing your employer to transfer your Personal Data (name, home address, telephone number, date of birth, salary, nationality, job title, and details of the option grant and all Ordinary Shares subject to such grant) outside the country in which you are employed or retained to its Affiliates, Horizon Pharma, Inc. and Horizon Pharma USA, Inc. which are located in the United States and their parent entity, Horizon Pharma Public Limited Company (together such entities are the "***Company Group***"). The legal persons for whom such Personal Data are intended are: Horizon Pharma Public Limited Company, Horizon Pharma, Inc., Horizon Pharma USA, Inc., StockCross Financial Services and any other third party entity providing option and/or Plan administration services to the Company and for the sole purpose of facilitating the transactions contemplated by this Stock Agreement. You have the right to access and correct your Personal Data by applying to the Company representative identified on the Grant Notice (the "***Representative***"). You have the right to revoke this consent at any time with future effect towards the Company Group by providing written notice to the Representative of such revocation (the "***Revocation Notice***"). You may also elect to exercise your option, to the extent such option is vested, by following the option exercise instructions specified in your StockCross Financial Services brokerage account and making provision for payment of the applicable option exercise price to the Company concurrently with your Revocation Notice, in which case your consent revocation will become effective as soon as administratively practicable following the execution of your option exercise election and the issuance of the Ordinary Shares subject to the option to you. If you do not follow the option exercise instructions specified in your StockCross Financial Services brokerage account or provide for payment of the option exercise price along with your Revocation Notice, or to the extent your option is unvested at the time you elect to provide a Revocation Notice, then as soon as administratively practicable following the Representative's receipt of the Revocation Notice your consent revocation will become effective and your option shall automatically immediately terminate and be forfeited, and you will not receive any Ordinary Shares or any other consideration in respect of such forfeited option.

13. ADDITIONAL ACKNOWLEDGEMENTS. You hereby consent and acknowledge that:

a. Participation in the Plan is voluntary and therefore you must accept the terms and conditions of the Plan and this option as a condition to participating in the Plan and receipt of this option.

b. The Plan is discretionary in nature and the Company can amend, cancel, or terminate it at any time.

c. This option and any other options under the Plan are voluntary and occasional and do not create any contractual or other right to receive future options or other benefits in lieu of future options, even if similar options have been granted repeatedly in the past.

d. All determinations with respect to any such future options, including, but not limited to, the time or times when such options are made, the number of Ordinary Shares, and performance and other conditions applied to the options, will be at the sole discretion of the Company.

e. The value of the Ordinary Shares and this option is an extraordinary item of compensation, which is outside the scope of your employment, service contract or consulting agreement, if any. This option shall not form part of any past, current or future entitlement to remuneration or benefits which you may have under any contract of employment with the Company nor form any part of any such contract of employment between you and the Company.

f. The Ordinary Shares, this option, or any income derived therefrom are a potential bonus payment not paid in lieu of any cash salary compensation and not part of normal or expected compensation or salary for any purposes, including, but not limited to, calculating any termination, severance, resignation, redundancy, end of service payments, bonuses, long-service awards, life or accident insurance benefits, pension or retirement benefits or similar payments.

g. In the event of the involuntary termination of your Continuous Service, your eligibility to receive Ordinary Shares or payments under the option or the Plan, if any, will terminate effective as of the date that you are no longer actively employed or retained regardless of any reasonable notice period mandated under local law, except as expressly provided in the option.

h. The future value of the Ordinary Shares is unknown and cannot be predicted with certainty. You do not have, and will not assert, any claim or entitlement to compensation, indemnity or damages arising from the termination of this option or diminution in value of the Ordinary Shares and you irrevocably release the Company, its Affiliates and, if applicable, your employer, if different from the Company, from any such claim that may arise.

i. The Plan and this option set forth the entire understanding between you, the Company and any Affiliate regarding the acquisition of the Ordinary Shares and supersedes all prior oral and written agreements pertaining to this option.

14. TAX CONSEQUENCES. You hereby agree that the Company does not have a duty to design or administer the Plan or its other compensation programs in a manner that minimizes your tax liabilities. You shall not make any claim against the Company, or any of its Officers,

Directors, Employees or Affiliates related to tax liabilities arising from your option or your other compensation. In particular, you acknowledge that this option is exempt from Section 409A of the Code only if the exercise price per share specified in the Grant Notice is at least equal to the "fair market value" per Ordinary Share on the Date of Grant and there is no other impermissible deferral of compensation associated with the option.

15. OTHER DOCUMENTS. You hereby acknowledge receipt or the right to receive a document providing the information required by Rule 428(b)(1) promulgated under the Securities Act, which includes the Plan prospectus. In addition, you acknowledge receipt of the Company's policy permitting officers, directors and other specified individuals to sell shares only during certain "window" periods and the Company's insider trading policy, in effect from time to time.

16. NOTICES. Any notices provided for in your option or the Plan shall be given in writing and shall be deemed effectively given upon receipt or, in the case of notices delivered by mail by the Company to you, five (5) days after deposit in the United States mail, postage prepaid, addressed to you at the last address you provided to the Company. Notwithstanding the foregoing, the Company may, in its sole discretion, decide to deliver any documents related to participation in the Plan and this option by electronic means or to request your consent to participate in the Plan by electronic means. By accepting the Option you consent to receive such documents by electronic delivery and, if requested, to agree to participate in the Plan through an on-line or electronic system established and maintained by the Company or another third party designated by the Company.

17. MISCELLANEOUS.

a. The rights and obligations of the Company under your option shall be transferable to any one or more persons or entities, and all covenants and agreements hereunder shall inure to the benefit of, and be enforceable by the Company's successors and assigns. Your rights and obligations under your option may only be assigned with the prior written consent of the Company.

b. You agree upon request to execute any further documents or instruments necessary or desirable in the sole determination of the Company to carry out the purposes or intent of your option.

c. You acknowledge and agree that you have reviewed your option in its entirety, have had an opportunity to obtain the advice of counsel prior to executing and accepting your option, and fully understand all provisions of your option.

d. This Agreement shall be subject to all applicable laws, rules, and regulations, and to such approvals by any governmental agencies or national securities exchanges as may be required.

e. All obligations of the Company under the Plan and this Agreement shall be binding on any successor to the Company, whether the existence of such successor is the result of a direct or indirect purchase, merger, consolidation, or otherwise, of all or substantially all of the business and/or assets of the Company.

18. GOVERNING PLAN DOCUMENT. Your option is subject to all the provisions of the Plan, the provisions of which are hereby made a part of your option, and is further subject to all interpretations, amendments, rules and regulations, which may from time to time be promulgated and adopted pursuant to the Plan. In the event of any conflict between the provisions of your option and those of the Plan, the provisions of the Plan shall control. In addition, your option (and any compensation paid or shares issued under your option) is subject to recoupment in accordance with The Dodd–Frank Wall Street Reform and Consumer Protection Act and any implementing regulations thereunder, any clawback policy adopted by the Company and any compensation recovery policy otherwise required by applicable law.

19. SEVERABILITY. If all or any part of this Agreement or the Plan is declared by any court or governmental authority to be unlawful or invalid, such unlawfulness or invalidity shall not invalidate any portion of this Agreement or the Plan not declared to be unlawful or invalid. Any Section of this Agreement (or part of such a Section) so declared to be unlawful or invalid shall, if possible, be construed in a manner which will give effect to the terms of such Section or part of a Section to the fullest extent possible while remaining lawful and valid.

20. EFFECT ON OTHER EMPLOYEE BENEFIT PLANS. The value of the option subject to this Agreement shall not be included as compensation, earnings, salaries, or other similar terms used when calculating the Employee's benefits under any employee benefit plan sponsored by the Company or any Affiliate, except as such plan otherwise expressly provides. The Company expressly reserves its rights to amend, modify, or terminate any of the Company's or any Affiliate's employee benefit plans.

21. AMENDMENT. This Agreement may not be modified, amended or terminated except by an instrument in writing, signed by you and by a duly authorized representative of the Company. Notwithstanding the foregoing, this Agreement may be amended solely by the Board by a writing which specifically states that it is amending this Agreement, so long as a copy of such amendment is delivered to you, and provided that no such amendment adversely affecting your rights hereunder may be made without your written consent. Without limiting the foregoing, the Board reserves the right to change, by written notice to you, the provisions of this Agreement in any way it may deem necessary or advisable to carry out the purpose of the grant as a result of any change in applicable laws or regulations or any future law, regulation, ruling, or judicial decision, provided that any such change shall be applicable only to rights relating to that portion of the option which is then subject to restrictions as provided herein.

HORIZON PHARMA PUBLIC LIMITED COMPANY
STOCK OPTION GRANT NOTICE
(2014 EQUITY INCENTIVE PLAN)

Horizon Pharma Public Limited Company (the "***Company***"), pursuant to its 2014 Equity Incentive Plan (the "***Plan***"), hereby grants to you an option (the "***Option***") to purchase the Company's Ordinary Shares. The following specific terms of the Option can be obtained by logging on to your StockCross brokerage account: [Optionholder, Date of Grant, Vesting Commencement Date, Number of Ordinary Shares Subject to Option, Exercise Price (Per Share), Total Exercise Price, Expiration Date, Type of Grant (Incentive Stock Option or Nonstatutory Stock Option), Exercise Schedule, Vesting Schedule and Payment]. These specific terms are incorporated by reference into this Grant Notice. This Option is subject to all of the terms and conditions as set forth herein and in the Option Agreement and the Plan, all of which are available on the StockCross website.

Additional Terms/Acknowledgements: You must electronically accept the Option by logging into your StockCross account. If you have not set-up your StockCross brokerage account, the following information provided below will assist you in this process. Failure to do so may result in forfeiture of the Option. By electronically accepting the Option, you acknowledge receipt of, and understand and agree to, this Stock Option Grant Notice, the Option Agreement and the Plan. You further acknowledge that as of the Date of Grant, this Stock Option Grant Notice, the Option Agreement, and the Plan set forth the entire understanding between you and the Company regarding the acquisition of shares in the Company and supersede all prior oral and written agreements on that subject with the exception of awards previously granted and delivered to you under the Plan.

STOCKCROSS FINANCIAL SERVICES BROKERAGE ACCOUNT

Horizon currently utilizes StockCross Financial Services as our online broker. StockCross Financial Services offers an internet website for viewing option data and for buying or selling your stock options.

To open your brokerage account (if you have not yet done so)

- Go to the StockCross website at www.stockcross.com
- Select the Green "Open an Account" menu item.
- Under the New Account Application screen, select "Employee Stock Plan Account" button to proceed with the brokerage application.
- If any additional documentation is needed, StockCross will contact you directly.
- Once the account is fully processed, you will receive a welcome email from StockCross, containing your account number and other useful information. This is generally within 72 hours.

If you have any questions or comments completing the brokerage application, please contact StockCross Corporate Services at 800-338-3965.

Viewing your Award

- Login to www.trading.stockcross.com using you StockCross account number and password established during registration
- Once logged into your StockCross account, select the menu item "Employee Stock Plan." This will bring you into another window screen which provides a summary of your equity grants. **Please note that to view this information, you will need to disable popup blockers.**
- Select "Portfolio." This will show you all equity grants that you have been granted.

Accepting your Award

- Login to www.trading.stockcross.com using you StockCross user name and password established during registration

- Once logged into your StockCross account, select the link to Employee Stock Plans under the menu item "Employee Stock Plan." This will bring you into another window screen which provides a summary of your equity grants. **Please note that to view this information, you will need to disable popup blockers.**
- Select "My Portfolio." This will show you all equity grants that you have been granted.
- For your new equity grant, in the first column, click on the Orange "Accept Grant" Action Button.
- This will take you to an electronic acceptance window. For your reference, the Equity Agreement applicable to the Award is provided. If you agree with the terms and conditions of your equity grant, Place your name in the signature box, type your name below, and check the agreement box. Click "Accept Grant to complete the acceptance.

IMPORTANT REMINDER: In order to avoid forfeiture of your Award, **you must electronically accept your Award 30 days *prior* to your first vesting date.**

Contact Horizon Pharma plc's Global Equity Plan Administrator Garry Devine at 224-383-3037 or email gdevine@horizonpharma.com with any further questions regarding your awards.

HORIZON PHARMA PUBLIC LIMITED COMPANY
2014 EQUITY INCENTIVE PLAN

RESTRICTED STOCK UNIT AGREEMENT

Pursuant to the Restricted Stock Unit Grant Notice (the "***Grant Notice***") and this Restricted Stock Unit Agreement (the "***Agreement***") and in consideration of your services, Horizon Pharma Public Limited Company (the "***Company***") has granted you a Restricted Stock Unit Award (the "***Award***") under its 2014 Equity Incentive Plan (the "***Plan***") for the number of restricted stock units referenced in the Grant Notice. Capitalized terms not explicitly defined in this Agreement shall have the same meanings given to them in the Plan or the Grant Notice, as applicable. Except as otherwise explicitly provided herein, in the event of any conflict between the terms in this Agreement and the Plan, the terms of the Plan shall control.

The details of your Award, in addition to those set forth in the Grant Notice and the Plan, are as follows.

1. GRANT OF THE AWARD. This Award represents your right to be issued on a future date the number of Ordinary Shares that is equal to the number of restricted stock units indicated in the Grant Notice (the "***Stock Units***") at the Purchase Price per Ordinary Share specified in your Grant Notice. As of the Date of Grant, the Company will credit to a bookkeeping account maintained by the Company for your benefit (the "***Account***") the number of Stock Units subject to the Award.

2. VESTING. Subject to the limitations contained herein, your Award will vest, if at all, in accordance with the vesting schedule provided in the Grant Notice, provided that vesting will cease upon the termination of your Continuous Service. Upon such termination of your Continuous Service, the Stock Units credited to the Account that were not vested on the date of such termination will be forfeited at no cost to the Company and you will have no further right, title or interest in such Stock Units or the Ordinary Shares to be issued in respect of such portion of the Award.

3. METHOD OF PAYMENT. On or before the time you receive a distribution of the Ordinary Shares in settlement of your Stock Units, you hereby authorize the Company or any Affiliate to satisfy the payment of the Purchase Price per Ordinary Share with respect to such Ordinary Shares by withholding such payment from payroll and any other cash amounts otherwise payable to you. If no cash amounts are otherwise payable to you by the Company and available for such deduction, you must provide timely payment of the applicable Purchase Price to the Company via cash or check and no obligation shall arise upon the Company to procure the issue or transfer of the Ordinary Shares unless and until the Company and/or any Affiliate are satisfied in their absolute discretion that you have satisfied such payment requirement. All amounts due are payable in United States dollars based, if applicable, upon the local currency to United States dollar exchange rate published in the West Coast edition of The Wall Street Journal on the applicable payment date (or, if such date is not a business day in the United States, the preceding business day in the United States).

4. NUMBER OF STOCK UNITS, ORDINARY SHARES AND PURCHASE PRICE.

a. The number of Stock Units subject to your Award and the Purchase Price per Ordinary Share may be adjusted from time to time for Capitalization Adjustments, as provided in the Plan. Furthermore, the Purchase Price per Ordinary Share will be automatically adjusted from time to time, as applicable, such that it shall at all times be equal to the nominal value per Ordinary Share as then in effect. In no event will the Purchase Price per Ordinary Share be less than the nominal value per Ordinary Share.

b. Any additional Stock Units that become subject to the Award pursuant to this Section 4, if any, shall be subject, in a manner determined by the Board, to the same forfeiture restrictions, restrictions on transferability, and time and manner of delivery as applicable to the other Stock Units covered by your Award.

c. Notwithstanding the provisions of this Section 4, no fractional shares or rights for fractional Ordinary Shares shall be created pursuant to this Section 4. The Board shall, in its discretion, determine an equivalent benefit for any fractional shares or fractional shares that might be created by the adjustments referred to in this Section 4.

5. SECURITIES LAW COMPLIANCE. You may not be issued any shares in respect of your Award unless either (i) the shares are registered under the Securities Act; or (ii) the Company has determined that such issuance would be exempt from the registration requirements of the Securities Act. Your Award also must comply with other applicable laws and regulations governing the Award, including, without limitation, the laws and regulations of the United States and your country of residence, and you will not receive such shares if the Company determines that such receipt would not be in material compliance with such laws and regulations.

6. TRANSFER RESTRICTIONS. Your Award is not transferable, except by will or by the laws of descent and distribution. In addition to any other limitation on transfer created by applicable securities laws, you agree not to assign, hypothecate, donate, encumber or otherwise dispose of any interest in any of the Ordinary Shares subject to the Award until the shares are issued to you in accordance with Section 7 of this Agreement. After the shares have been issued to you, you are free to assign, hypothecate, donate, encumber or otherwise dispose of any interest in such shares provided that any such actions are in compliance with the provisions herein, any applicable Company policies (including, but not limited to, insider trading and window period policies) and applicable securities laws. Notwithstanding the foregoing, by delivering written notice to the Company, in a form satisfactory to the Company, you may designate a third party who, in the event of your death, shall thereafter be entitled to receive any distribution of Ordinary Shares to which you were entitled at the time of your death pursuant to this Agreement.

7. DATE OF ISSUANCE.

a. To the extent the Award is exempt from application of Section 409A of the Code and any state law of similar effect (collectively **"*Section 409A*"**), the Company will deliver to you a number of Ordinary Shares equal to the number of vested Stock Units subject to your Award, including any additional Stock Units received pursuant to Section 4 above that relate to those vested Stock Units, on the applicable vesting date(s). However, if a scheduled

delivery date falls on a date that is not a business day, such delivery date shall instead fall on the next following business day. Notwithstanding the foregoing, in the event that (i) any shares covered by your Award are scheduled to be delivered on a day (the "***Original Distribution Date***") that does not occur: (A) during an open "window period" applicable to you under the Company's policy permitting officers, directors and other designated individuals to sell shares only during certain "window" periods, in effect from time to time (the "***Policy***"), (B) on a day on which you are permitted to sell Ordinary Shares pursuant to a written plan that meets the requirements of Rule 10b5-1 under the Exchange Act, as determined by the Company in accordance with the Policy, or (C) on a date when you are otherwise permitted to sell Ordinary Shares on the open market, and (ii) the Company elects not to satisfy its tax withholding obligations by withholding shares from your distribution or withholding from other compensation otherwise payable to you by the Company, then such shares shall not be delivered on such Original Distribution Date and shall instead be delivered on the first business day of the next occurring open "window period" applicable to you pursuant to such Policy (regardless of whether you are still providing continuous services at such time) or the next business day when you are not prohibited from selling Ordinary Shares in the open market, but in no event later than the fifteenth (15th) day of the third calendar month of the calendar year following the calendar year in which the shares covered by the Award vest. Delivery of the shares pursuant to the provisions of this Section 7(a) is intended to comply with the requirements for the short-term deferral exemption available under Treasury Regulations Section 1.409A-1(b)(4) and shall be construed and administered in such manner. The form of such delivery of the shares (*e.g.*, a stock certificate or electronic entry evidencing such shares) shall be determined by the Company.

b. The provisions of Appendix A to this Agreement will apply to the extent the Award is subject to, and not exempt from, application of Section 409A (a ***"Non-Exempt Award"***).

8. DIVIDENDS. You shall receive no benefit or adjustment to your Award with respect to any cash dividend, stock dividend or other distribution that does not result from a Capitalization Adjustment as provided in the Plan; provided, however, that this sentence shall not apply with respect to any Ordinary Shares that are delivered to you in connection with your Award after such shares have been delivered to you.

9. RESTRICTIVE LEGENDS. The shares issued in respect of your Award shall be endorsed with appropriate legends determined by the Company.

10. AWARD NOT A SERVICE CONTRACT.

a. Your Continuous Service with the Company or an Affiliate is not for any specified term and may be terminated by you or by the Company or an Affiliate at any time, for any reason, with or without cause and with or without notice. Nothing in this Agreement (including, but not limited to, the vesting of your Award pursuant to the schedule set forth in the Grant Notice or the issuance of the shares in respect of your Award), the Plan or any covenant of good faith and fair dealing that may be found implicit in this Agreement or the Plan shall: (i) confer upon you any right to continue in the employ of, or affiliation with, the Company or an Affiliate; (ii) constitute any promise or commitment by the Company or an Affiliate regarding the fact or nature of future positions, future work assignments, future compensation or any other

term or condition of employment or affiliation; (iii) confer any right or benefit under this Agreement or the Plan unless such right or benefit has specifically accrued under the terms of this Agreement or Plan; or (iv) deprive the Company of the right to terminate you at will and without regard to any future vesting opportunity that you may have.

b. By accepting this Award, you acknowledge and agree that the right to continue vesting in the Award pursuant to the vesting schedule provided in the Grant Notice is earned only by continuing as an employee, director or consultant at the will of the Company (not through the act of being hired, being granted this Award or any other award or benefit) and that the Company has the right to reorganize, sell, spin-out or otherwise restructure one or more of its businesses or Affiliates at any time or from time to time, as it deems appropriate (a ***"reorganization"***). You further acknowledge and agree that such a reorganization could result in the termination of your Continuous Service, or the termination of Affiliate status of your employer and the loss of benefits available to you under this Agreement, including but not limited to, the termination of the right to continue vesting in the Award. You further acknowledge and agree that this Agreement, the Plan, the transactions contemplated hereunder and the vesting schedule set forth herein or any covenant of good faith and fair dealing that may be found implicit in any of them do not constitute an express or implied promise of continued engagement as an employee or consultant for the term of this Agreement, for any period, or at all, and shall not interfere in any way with your right or the Company's right to terminate your Continuous Service at any time, with or without cause and with or without notice.

11. WITHHOLDING OBLIGATIONS.

a. On or before the time you receive a distribution of the shares subject to your Award, or at any time thereafter as requested by the Company, you hereby authorize any required withholding from the Ordinary Shares issuable to you and/or otherwise agree to make adequate provision in cash for any sums required to satisfy the federal, state, local and foreign tax withholding obligations of the Company or any Affiliate which arise in connection with your Award (the "***Withholding Taxes***"). Additionally, the Company may, in its sole discretion, satisfy all or any portion of the Withholding Taxes obligation relating to your Award by any of the following means or by a combination of such means: (i) withholding from any compensation otherwise payable to you by the Company; (ii) causing you to tender a cash payment, (iii) permitting or requiring you to enter into a "same day sale" commitment with a broker-dealer that is a member of the Financial Industry Regulatory Authority (a "***FINRA Dealer***") whereby you irrevocably elect to sell a portion of the shares to be delivered in connection with your Restricted Stock Units to satisfy the Withholding Taxes and whereby the FINRA Dealer irrevocably commits to forward the proceeds necessary to satisfy the Withholding Taxes directly to the Company and/or its Affiliates; or (iv) withholding Ordinary Shares from the Ordinary Shares issued or otherwise issuable to you in connection with the Award with a Fair Market Value (measured as of the date Ordinary Shares are issued to pursuant to Section 7) equal to the amount of such Withholding Taxes; provided, however, that the number of such Ordinary Shares so withheld shall not exceed the amount necessary to satisfy the Company's required tax withholding obligations using the minimum statutory withholding rates for federal, state, local and foreign tax purposes, including payroll taxes, that are applicable to supplemental taxable income; and provided further, that to the extent necessary to qualify for an exemption from application of Section 16(b) of the Exchange Act, such share withholding procedure shall be subject to the express prior approval of the Company's Compensation Committee.

b. Unless the tax withholding obligations of the Company and/or any Affiliate are satisfied, the Company shall have no obligation to deliver to you any Ordinary Shares pursuant to this Award.

c. No obligation shall arise upon the Company to procure the issue or transfer of the Ordinary Shares unless and until the Company and/or any Affiliate are satisfied in their absolute discretion that either (i) you have made payment, or have made arrangements satisfactory to the Company and/or any Affiliate for the payment to it of such sum as is sufficient to meet any withholding liability to Taxation (defined below) in any jurisdiction which is or would be recoverable from you in connection with the vesting or the Award or the issuance of Ordinary Shares by the Company in settlement of the Award, and in respect of which the Company and/or any Affiliate is liable to account in any jurisdiction; or (ii) you have entered into an agreement with the Company and/or an Affiliate (in a form satisfactory to the Company or such Affiliate) to ensure that such a payment is made by you including, without limitation, amounts in respect of any employers' social security (or the local law equivalent thereof) or other forms of Taxation. Accordingly, the Company shall have no obligation to issue a certificate for such Ordinary Shares or release such Ordinary Shares from any escrow provided for herein unless such obligations are satisfied. "***Taxation***" shall include all forms of taxation including employees' and employers' social security, income tax and any other taxes of whatever nature in any jurisdiction together with any amount payable by an Affiliate in respect of which the Affiliate has a duty to account as a result of any laws of any jurisdiction relating to taxation.

12. PERSONAL DATA. You understand that your employer, if applicable, the Company, and/or its Affiliates hold certain personal information about you. This information include your name, home address, telephone number, date of birth, social security or equivalent tax identification number, salary, nationality, job title, and details of your Award and all Ordinary Shares subject to your Award that have been granted, cancelled, vested, unvested, or are outstanding (the "***Personal Data***").

You hereby declare your express consent to allowing your employer to transfer your Personal Data (name, home address, telephone number, date of birth, salary, nationality, job title, and details of the Award and all Ordinary Shares subject to such grant) outside the country in which you are employed or retained to its Affiliates, Horizon Pharma, Inc. and Horizon Pharma USA, Inc. which are located in the United States and their parent entity, Horizon Pharma Public Limited Company (together such entities are the "***Company Group***"). The legal persons for whom such Personal Data are intended are: Horizon Pharma Public Limited Company, Horizon Pharma, Inc., Horizon Pharma USA, Inc., StockCross Financial Services and any other third party entity providing equity award and/or Plan administration services to the Company and for the sole purpose of facilitating the transactions contemplated by this Agreement. You have the right to access and correct your Personal Data by applying to the Company representative identified on the Grant Notice (the "***Representative***"). You have the right to revoke this consent at any time with future effect towards the Company Group by providing written notice to the Representative of such revocation (the "***Revocation Notice***") and as soon as administratively practicable following the Representative's receipt of the Revocation Notice your consent revocation will become effective and your Award shall automatically immediately terminate and be forfeited, and you will not receive any Ordinary Shares or any other consideration in respect of such forfeited Award.

13. ADDITIONAL ACKNOWLEDGEMENTS. You hereby consent and acknowledge that:

a. Participation in the Plan is voluntary and therefore you must accept the terms and conditions of the Plan and this Award as a condition to participating in the Plan and receipt of the Award.

b. The Plan is discretionary in nature and the Company can amend, cancel, or terminate it at any time.

c. This Award and any other equity awards granted under the Plan are voluntary and occasional and do not create any contractual or other right to receive future awards or other benefits in lieu of future awards, even if similar awards have been granted repeatedly in the past.

d. All determinations with respect to any such future awards, including, but not limited to, the time or times when such awards are granted, the number of Ordinary Shares, and performance and other conditions applied to the awards, will be at the sole discretion of the Company.

e. The value of the Ordinary Shares and this Award is an extraordinary item of compensation, which is outside the scope of your employment, service contract or consulting agreement, if any. This Award shall not form part of any past, current or future entitlement to remuneration or benefits which you may have under any contract of employment with the Company nor form any part of any such contract of employment between you and the Company.

f. The Ordinary Shares, this Award, or any income derived therefrom are a potential bonus payment not paid in lieu of any cash salary compensation and not part of normal or expected compensation or salary for any purposes, including, but not limited to, calculating any termination, severance, resignation, redundancy, end of service payments, bonuses, long-service awards, life or accident insurance benefits, pension or retirement benefits or similar payments.

g. In the event of the involuntary termination of your Continuous Service, your eligibility to receive Ordinary Shares or payments under the Award or the Plan, if any, will terminate effective as of the date that you are no longer actively employed or retained regardless of any reasonable notice period mandated under local law, except as expressly provided in the Agreement.

h. The future value of the Ordinary Shares is unknown and cannot be predicted with certainty. You do not have, and will not assert, any claim or entitlement to compensation, indemnity or damages arising from the termination of this award or diminution in value of the Ordinary Shares and you irrevocably release the Company, its Affiliates and, if applicable, your employer, if different from the Company, from any such claim that may arise.

i. The Plan and this Agreement set forth the entire understanding between you, the Company and any Affiliate regarding the acquisition of the Ordinary Shares and supersedes all prior oral and written agreements pertaining to this Award.

14. UNSECURED OBLIGATION. Your Award is unfunded, and as a holder of a vested Award, you shall be considered an unsecured creditor of the Company with respect to the Company's obligation, if any, to issue shares pursuant to this Agreement. You shall not have voting or any other rights as a shareholder of the Company with respect to the shares to be issued pursuant to this Agreement until such shares are issued to you pursuant to Section 7 of this Agreement. Upon such issuance, you will obtain full voting and other rights as a shareholder of the Company. Nothing contained in this Agreement, and no action taken pursuant to its provisions, shall create or be construed to create a trust of any kind or a fiduciary relationship between you and the Company or any other person.

15. OTHER DOCUMENTS. You hereby acknowledge receipt or the right to receive a document providing the information required by Rule 428(b)(1) promulgated under the Securities Act, which includes the Plan prospectus. In addition, you acknowledge receipt of the Company's policy permitting officers, directors and other specified individuals to sell shares only during certain "window" periods and the Company's insider trading policy, in effect from time to time.

16. NOTICES. Any notices provided for in your Award or the Plan shall be given in writing (including electronically) and shall be deemed effectively given upon receipt or, in the case of notices delivered by the Company to you, five (5) days after deposit in the United States mail, postage prepaid, addressed to you at the last address you provided to the Company. Notwithstanding the foregoing, the Company may, in its sole discretion, decide to deliver any documents related to participation in the Plan and this Award by electronic means or to request your consent to participate in the Plan by electronic means. By accepting this Award you consent to receive such documents by electronic delivery and, if requested, to agree to participate in the Plan through an on-line or electronic system established and maintained by the Company or another third party designated by the Company.

17. MISCELLANEOUS.

a. The rights and obligations of the Company under your Award shall be transferable to any one or more persons or entities, and all covenants and agreements hereunder shall inure to the benefit of, and be enforceable by the Company's successors and assigns. Your rights and obligations under your Award may only be assigned with the prior written consent of the Company.

b. You agree upon request to execute any further documents or instruments necessary or desirable in the sole determination of the Company to carry out the purposes or intent of your Award.

c. You acknowledge and agree that you have reviewed your Award in its entirety, have had an opportunity to obtain the advice of counsel prior to executing and accepting your Award, and fully understand all provisions of your Award.

d. This Agreement shall be subject to all applicable laws, rules, and regulations, and to such approvals by any governmental agencies or national securities exchanges as may be required.

e. All obligations of the Company under the Plan and this Agreement shall be binding on any successor to the Company, whether the existence of such successor is the result of a direct or indirect purchase, merger, consolidation, or otherwise, of all or substantially all of the business and/or assets of the Company.

18. GOVERNING PLAN DOCUMENT. Your Award is subject to all the provisions of the Plan, the provisions of which are hereby made a part of your Award, and is further subject to all interpretations, amendments, rules and regulations which may from time to time be promulgated and adopted pursuant to the Plan. Except as expressly provided in this Agreement, in the event of any conflict between the provisions of your Award and those of the Plan, the provisions of the Plan shall control. In addition, your Award (and any compensation paid or shares issued under your Award) is subject to recoupment in accordance with The Dodd–Frank Wall Street Reform and Consumer Protection Act and any implementing regulations thereunder, any clawback policy adopted by the Company and any compensation recovery policy otherwise required by applicable law.

19. SEVERABILITY. If all or any part of this Agreement or the Plan is declared by any court or governmental authority to be unlawful or invalid, such unlawfulness or invalidity shall not invalidate any portion of this Agreement or the Plan not declared to be unlawful or invalid. Any Section of this Agreement (or part of such a Section) so declared to be unlawful or invalid shall, if possible, be construed in a manner which will give effect to the terms of such Section or part of a Section to the fullest extent possible while remaining lawful and valid.

20. EFFECT ON OTHER EMPLOYEE BENEFIT PLANS. The value of the Award subject to this Agreement shall not be included as compensation, earnings, salaries, or other similar terms used when calculating the Employee's benefits under any employee benefit plan sponsored by the Company or any Affiliate, except as such plan otherwise expressly provides. The Company expressly reserves its rights to amend, modify, or terminate any of the Company's or any Affiliate's employee benefit plans.

21. AMENDMENT. This Agreement may not be modified, amended or terminated except by an instrument in writing, signed by you and by a duly authorized representative of the Company. Notwithstanding the foregoing, this Agreement may be amended solely by the Board by a writing which specifically states that it is amending this Agreement, so long as a copy of such amendment is delivered to you, and provided that no such amendment adversely affecting your rights hereunder may be made without your written consent. Without limiting the foregoing, the Board reserves the right to change, by written notice to you, the provisions of this Agreement in any way it may deem necessary or advisable to carry out the purpose of the grant as a result of any change in applicable laws or regulations or any future law, regulation, ruling, or judicial decision, provided that any such change shall be applicable only to rights relating to that portion of the Award which is then subject to restrictions as provided herein.

22. NO OBLIGATION TO MINIMIZE TAXES. The Company has no duty or obligation to minimize the tax consequences to you of this Award and will not be liable to you for any adverse tax consequences to you arising in connection with this Award. You are hereby advised to consult with your own personal tax, financial and/or legal advisors regarding the tax consequences of this Award and by signing the Grant Notice, you have agreed that you have done so or knowingly and voluntarily declined to do so.

Appendix A

The provisions set forth on this Appendix A shall apply to the extent the Award is a Non-Exempt Award and shall supersede any provisions to the contrary set forth in the Plan or in any other section of the Agreement to which this Appendix A is attached.

1. The provisions of this Section 1 are intended to apply to the extent your Award is a Non-Exempt Award because of the terms of a severance arrangement or other agreement between you and the Company, if any, that provide for acceleration of vesting of your Award and issuance of the shares in respect of the Award upon your termination of employment or separation from service (as such term is defined in Section 409A(a)(2)(A)(i) of the Code (and without regard to any alternative definition thereunder) ("***Separation from Service***") and such severance benefit does not satisfy the requirements for an exemption from application of Section 409A provided under Treasury Regulations Section 1.409A-1(b)(4) or 1.409A-1(b)(9) ("***Non-Exempt Severance Arrangement***"). To the extent your Award is a Non-Exempt Award due to application of a Non-Exempt Severance Arrangement, the following provisions in this Section 1 of Appendix A shall supersede anything to the contrary in Section 6(a) of the Award Agreement.

a. If your Award vests in the ordinary course during your Continuous Service in accordance with the vesting schedule set forth in the Grant Notice, without accelerating vesting under the terms of a Non-Exempt Severance Arrangement, in no event will the shares be issued in respect of your Award any later than the later of: (i) December 31st of the calendar year that includes the applicable vesting date and (ii) the 60th day that follows the applicable vesting date.

b. If vesting of your Award accelerates under the terms of a Non-Exempt Severance Arrangement in connection with your Separation from Service, and such vesting acceleration provisions were in effect as of the date of grant of your Award and, therefore, are part of the terms of your Award as of the date of grant, then the shares will be earlier issued in respect of your Award upon your Separation from Service in accordance with the terms of the Non-Exempt Severance Arrangement, but in no event later than the 60th day that follows the date of your Separation from Service. However, if at the time the shares would otherwise be issued you are subject to the distribution limitations contained in Section 409A applicable to "specified employees," as defined in Section 409A(a)(2)(B)(i) of the Code, such shares shall not be issued before the date that is six (6) months following the date of your Separation from Service, or, if earlier, the date of your death that occurs within such six month period.

c. If vesting of your Award accelerates under the terms of a Non-Exempt Severance Arrangement in connection with your Separation from Service, and such vesting acceleration provisions were not in effect as of the date of grant of the Award and, therefore, are not a part of the terms of your Award on the date of grant, then such acceleration of vesting of your Award shall not accelerate the issuance date of the shares, but the shares shall instead be issued on the same schedule as set forth in the Grant Notice as if they had vested in the ordinary course during your Continuous Service, notwithstanding the vesting acceleration of the Award. Such issuance schedule is intended to satisfy the requirements of payment on a specified date or pursuant to a fixed schedule, as provided under Treasury Regulations Section 1.409A-3(a)(4).

2. Permitted Treatment of Non-Exempt Awards Upon a Corporate Transaction for Employees and Consultants. The provisions in this Section 2 shall apply and shall supersede anything to the contrary that may be set forth in the Plan with respect to the permitted treatment of your Non-Exempt Award in connection with a Corporate Transaction if you were either an Employee or Consultant upon the applicable date of grant of your Non-Exempt Award.

a. Vested Non-Exempt Awards: To the extent your Non-Exempt Award has vested in accordance with its terms upon or prior to the date of a Corporate Transaction (such portion of your Non-Exempt Award is a "***Vested Non-Exempt Award***"), then the following provisions shall apply.

1) If the Corporate Transaction is also a change in the ownership or effective control of the Company, or in the ownership of a substantial portion of the Company's assets, as described in Section 409A(a)(2)(A)(v) of the Code and Treasury Regulations Section 1.409A-3(i)(5) (a "***409A Change of Control***"), then the surviving or acquiring corporation (or its parent company) (the "***Acquiring Entity***") may not assume, continue or substitute your Vested Non-Exempt Award. Upon the 409A Change of Control the settlement of your Vested Non-Exempt Award will automatically be accelerated and the shares will be immediately issued in respect of your Vested Non-Exempt Award. Alternatively, the Company may instead provide that you will receive a cash settlement equal to the Fair Market Value of the shares that would otherwise be issued to you upon the 409A Change of Control.

2) If the Corporate Transaction is not also a 409A Change of Control, then the Acquiring Entity must either assume, continue or substitute your Vested Non-Exempt Award. The shares to be issued in respect of your Vested Non-Exempt Award shall be issued to you by the Acquiring Entity on the same schedule that the shares would have been issued to you if the Corporate Transaction had not occurred. In the Acquiring Entity's discretion, in lieu of an issuance of shares, the Acquiring Entity may instead substitute a cash payment on each applicable issuance date, equal to the Fair Market Value of the shares that would otherwise be issued to you on such issuance dates, with the determination of the Fair Market Value of the shares made on the date of the Corporate Transaction.

b. Unvested Non-Exempt Awards. To the extent your Non-Exempt Award has not vested in accordance with its terms upon or prior to the date of any Corporate Transaction, (such portion of your Non-Exempt Award is an "***Unvested Non-Exempt Award***"), then the following provisions shall apply.

1) If the Acquiring Entity will not assume, substitute or continue your Unvested Non-Exempt Award, then such Award shall automatically terminate and be forfeited upon the Corporate Transaction with no consideration payable to you in respect of your forfeited Unvested Non-Exempt Award. Notwithstanding the foregoing, to the extent permitted and in compliance with the requirements of Section 409A, the Company may in its discretion determine to elect to accelerate the vesting and settlement of the Unvested Non-Exempt Award upon the Corporate Transaction, or instead substitute a cash payment equal to the Fair Market Value of such shares that would otherwise be issued to you, as further provided in Section 4(b) below. In the absence of such discretionary election by the Company, your Unvested Non-Exempt Award shall be forfeited without payment of any consideration to you if the Acquiring Entity will not assume, substitute or continue your Unvested Non-Exempt Award in connection with the Corporate Transaction.

2) The foregoing treatment shall apply with respect to all Unvested Non-Exempt Awards upon any Corporate Transaction, and regardless of whether or not such Corporate Transaction is also a 409A Change of Control.

3. Permitted Treatment of Non-Exempt Awards Upon a Corporate Transaction for Non-Employee Directors. If you were a Director but not an Employee on the applicable grant date of your Non-Exempt Award and ("***Non-Exempt Director Award***"), the following provisions shall apply and shall supersede anything to the contrary that may be set forth in the Plan with respect to the permitted treatment of your Non-Exempt Director Award in connection with a Corporate Transaction.

a. If the Corporate Transaction is also a 409A Change of Control then the Acquiring Entity may not assume, continue or substitute your Non-Exempt Director Award. Upon the 409A Change of Control the vesting and settlement of your Non-Exempt Director Award will automatically be accelerated and the shares will be immediately issued to you in respect of the Non-Exempt Director Award. Alternatively, the Company may provide that you will instead receive a cash settlement equal to the Fair Market Value of the shares that would otherwise be issued to you upon the 409A Change of Control pursuant to the preceding provision.

b. If the Corporate Transaction is not also a 409A Change of Control, then the Acquiring Entity must either assume, continue or substitute your Non-Exempt Director Award. Unless otherwise determined by the Board, your Non-Exempt Director Award will remain subject to the same vesting and forfeiture restrictions that were applicable to the Award prior to the Corporate Transaction. The shares to be issued in respect of your Non-Exempt Director Award shall be issued to your by the Acquiring Entity on the same schedule that the shares would have been issued to you if the Corporate Transaction had not occurred. In the Acquiring Entity's discretion, in lieu of an issuance of shares, the Acquiring Entity may instead substitute a cash payment on each applicable issuance date, equal to the Fair Market Value of the shares that would otherwise be issued to you on such issuance dates, with the determination of Fair Market Value made on the date of the Corporate Transaction.

4. General Superseding Provisions. The provisions in this Section 4 shall apply and supersede anything to the contrary that may be set forth in the Plan, the Grant Notice or in any other section of the Agreement with respect to the permitted treatment of your Non-Exempt Award:

a. Any exercise by the Board of discretion to accelerate the vesting of your Non-Exempt Award shall not result in any acceleration of the scheduled issuance dates for the shares in respect of the Non-Exempt Award unless earlier issuance of the shares upon the applicable vesting dates would be in compliance with the requirements of Section 409A.

b. The Company explicitly reserves the right to earlier settle your Non-Exempt Award to the extent permitted and in compliance with the requirements of Section 409A, including pursuant to any of the exemptions available in Treasury Regulations Section 1.409A-3(j)(4)(ix).

c. To the extent the terms of your Non-Exempt Award provide that it will be settled upon a Change in Control or Corporate Transaction, to the extent it is required for compliance with the requirements of Section 409A, the Change in Control or Corporate Transaction event triggering settlement must also constitute a 409A Change of Control. To the extent the terms of your Non-Exempt Award provides that it will be settled upon a termination of employment or termination of Continuous Service, to the extent it is required for compliance with the requirements of Section 409A, the termination event triggering settlement must also constitute a Separation From Service. However, if at the time the shares would otherwise be issued to you in connection with your "separation from service" you are subject to the distribution limitations contained in Section 409A applicable to "specified employees," as defined in Section 409A(a)(2)(B)(i) of the Code, such shares shall not be issued before the date that is six (6) months following the date of your Separation From Service, or, if earlier, the date of your death that occurs within such six month period.

5. Section 409A Compliance. The provisions in this Agreement for delivery of the shares in respect of the Non-Exempt Award are intended to comply with the requirements of Section 409A so that the delivery of the shares to you in respect of your Non-Exempt Award will not trigger the additional tax imposed under Section 409A, and any ambiguities herein will be so interpreted.

[Form for Section 16 Executive Officers]

HORIZON PHARMA PUBLIC LIMITED COMPANY
2014 EQUITY INCENTIVE PLAN

RESTRICTED STOCK UNIT AGREEMENT

Pursuant to the Restricted Stock Unit Grant Notice (the "***Grant Notice***") and this Restricted Stock Unit Agreement (the "***Agreement***") and in consideration of your services, Horizon Pharma Public Limited Company (the "***Company***") has granted you a Restricted Stock Unit Award (the "***Award***") under its 2014 Equity Incentive Plan (the "***Plan***") for the number of restricted stock units referenced in the Grant Notice. Capitalized terms not explicitly defined in this Agreement shall have the same meanings given to them in the Plan or the Grant Notice, as applicable. Except as otherwise explicitly provided herein, in the event of any conflict between the terms in this Agreement and the Plan, the terms of the Plan shall control.

The details of your Award, in addition to those set forth in the Grant Notice and the Plan, are as follows.

1. GRANT OF THE AWARD. This Award represents your right to be issued on a future date the number of Ordinary Shares that is equal to the number of restricted stock units indicated in the Grant Notice (the "***Stock Units***") at the Purchase Price per Ordinary Share specified in your Grant Notice. As of the Date of Grant, the Company will credit to a bookkeeping account maintained by the Company for your benefit (the "***Account***") the number of Stock Units subject to the Award.

2. VESTING. Subject to the limitations contained herein, your Award will vest, if at all, in accordance with the vesting schedule provided in the Grant Notice, provided that vesting will cease upon the termination of your Continuous Service. Upon such termination of your Continuous Service, the Stock Units credited to the Account that were not vested on the date of such termination will be forfeited at no cost to the Company and you will have no further right, title or interest in such Stock Units or the Ordinary Shares to be issued in respect of such portion of the Award.

3. METHOD OF PAYMENT. On or before the time you receive a distribution of the Ordinary Shares in settlement of your Stock Units, you hereby authorize the Company or any Affiliate to satisfy the payment of the Purchase Price per Ordinary Share with respect to such Ordinary Shares by withholding such payment from payroll and any other cash amounts otherwise payable to you. If no cash amounts are otherwise payable to you by the Company and available for such deduction, you must provide timely payment of the applicable Purchase Price to the Company via cash or check and no obligation shall arise upon the Company to procure the issue or transfer of the Ordinary Shares unless and until the Company and/or any Affiliate are satisfied in their absolute discretion that you have satisfied such payment requirement. All amounts due are payable in United States dollars based, if applicable, upon the local currency to United States dollar exchange rate published in the West Coast edition of The Wall Street Journal on the applicable payment date (or, if such date is not a business day in the United States, the preceding business day in the United States).

4. NUMBER OF STOCK UNITS, ORDINARY SHARES AND PURCHASE PRICE.

(a) The number of Stock Units subject to your Award and the Purchase Price per Ordinary Share may be adjusted from time to time for Capitalization Adjustments, as provided in the Plan. Furthermore, the Purchase Price per Ordinary Share will be automatically adjusted from time to time, as applicable, such that it shall at all times be equal to the nominal value per Ordinary Share as then in effect. In no event will the Purchase Price per Ordinary Share be less than the nominal value per Ordinary Share.

(b) Any additional Stock Units that become subject to the Award pursuant to this Section 4, if any, shall be subject, in a manner determined by the Board, to the same forfeiture restrictions, restrictions on transferability, and time and manner of delivery as applicable to the other Stock Units covered by your Award.

(c) Notwithstanding the provisions of this Section 4, no fractional shares or rights for fractional Ordinary Shares shall be created pursuant to this Section 4. The Board shall, in its discretion, determine an equivalent benefit for any fractional shares or fractional shares that might be created by the adjustments referred to in this Section 4.

5. SECURITIES LAW COMPLIANCE. You may not be issued any shares in respect of your Award unless either (i) the shares are registered under the Securities Act; or (ii) the Company has determined that such issuance would be exempt from the registration requirements of the Securities Act. Your Award also must comply with other applicable laws and regulations governing the Award, including, without limitation, the laws and regulations of the United States and your country of residence, and you will not receive such shares if the Company determines that such receipt would not be in material compliance with such laws and regulations.

6. TRANSFER RESTRICTIONS.

(a) Your Award is not transferable, except by will or by the laws of descent and distribution. In addition to any other limitation on transfer created by applicable securities laws, you agree not to assign, hypothecate, donate, encumber or otherwise dispose of any interest in any of the Ordinary Shares subject to the Award until the shares are issued to you in accordance with Section 7 of this Agreement, subject to the additional restrictions set forth in Section 6(b) below. Notwithstanding the foregoing, by delivering written notice to the Company, in a form satisfactory to the Company, you may designate a third party who, in the event of your death, shall thereafter be entitled to receive any distribution of Ordinary Shares to which you were entitled at the time of your death pursuant to this Agreement.

(b) Any Ordinary Shares issued to you in settlement of the Award may not be transferred, sold or otherwise disposed of by you within the one (1) year period that commences on the date the shares are issued to you (the "***Holding Period***"); provided that nothing in this Section 6(b) shall prohibit the disposition of Ordinary Shares in connection with a Change in Control or the withholding of shares that would otherwise be issued pursuant to the Award in satisfaction of applicable withholding taxes. After the Holding Period has expired, you are free to assign, hypothecate, donate, encumber or otherwise dispose of any interest in such issued Ordinary Shares provided that any such actions are in compliance with the provisions herein, any applicable Company policies (including, but not limited to, insider trading and window period policies) and applicable securities laws.

7. DATE OF ISSUANCE.

(a) To the extent the Award is exempt from application of Section 409A of the Code and any state law of similar effect (collectively "***Section 409A***"), the Company will deliver to you a number of Ordinary Shares equal to the number of vested Stock Units subject to your Award, including any additional Stock Units received pursuant to Section 4 above that relate to those vested Stock Units, on the applicable vesting date(s). However, if a scheduled delivery date falls on a date that is not a business day, such delivery date shall instead fall on the next following business day. Delivery of the shares pursuant to the provisions of this Section 7(a) is intended to comply with the requirements for the short-term deferral exemption available under Treasury Regulations Section 1.409A-1(b)(4) and shall be construed and administered in such manner. The form of such delivery of the shares (*e.g.*, a stock certificate or electronic entry evidencing such shares) shall be determined by the Company.

(b) The provisions of Appendix A to this Agreement will apply to the extent the Award is subject to, and not exempt from, application of Section 409A (a ***"Non-Exempt Award"***).

8. DIVIDENDS. You shall receive no benefit or adjustment to your Award with respect to any cash dividend, stock dividend or other distribution that does not result from a Capitalization Adjustment as provided in the Plan; provided, however, that this sentence shall not apply with respect to any Ordinary Shares that are delivered to you in connection with your Award after such shares have been delivered to you.

9. RESTRICTIVE LEGENDS. The shares issued in respect of your Award shall be endorsed with appropriate legends determined by the Company.

10. AWARD NOT A SERVICE CONTRACT.

(a) Your Continuous Service with the Company or an Affiliate is not for any specified term and may be terminated by you or by the Company or an Affiliate at any time, for any reason, with or without cause and with or without notice. Nothing in this Agreement (including, but not limited to, the vesting of your Award pursuant to the schedule set forth in the Grant Notice or the issuance of the shares in respect of your Award), the Plan or any covenant of good faith and fair dealing that may be found implicit in this Agreement or the Plan shall: (i) confer upon you any right to continue in the employ of, or affiliation with, the Company or an Affiliate; (ii) constitute any promise or commitment by the Company or an Affiliate regarding the fact or nature of future positions, future work assignments, future compensation or any other term or condition of employment or affiliation; (iii) confer any right or benefit under this Agreement or the Plan unless such right or benefit has specifically accrued under the terms of this Agreement or Plan; or (iv) deprive the Company of the right to terminate you at will and without regard to any future vesting opportunity that you may have.

(b) By accepting this Award, you acknowledge and agree that the right to continue vesting in the Award pursuant to the vesting schedule provided in the Grant Notice is earned only by continuing as an employee, director or consultant at the will of the Company (not through the act of being hired, being granted this Award or any other award or benefit) and that the Company has the right to reorganize, sell, spin-out or otherwise restructure one or more of its businesses or Affiliates at any time or from time to time, as it deems appropriate (a ***"reorganization"***). You further acknowledge and agree that such a reorganization could result in the termination of your Continuous Service, or the termination of Affiliate status of your employer and the loss of benefits available to you under this Agreement, including but not limited to, the termination of the right to continue vesting in the Award. You further acknowledge and agree that this Agreement, the Plan, the transactions contemplated hereunder and the vesting schedule set forth herein or any covenant of good faith and fair dealing that may be found implicit in any of them do not constitute an express or implied promise of continued engagement as an employee or consultant for the term of this Agreement, for any period, or at all, and shall not interfere in any way with your right or the Company's right to terminate your Continuous Service at any time, with or without cause and with or without notice.

11. WITHHOLDING OBLIGATIONS.

(a) On or before the time you receive a distribution of the shares subject to your Award, or at any time thereafter as requested by the Company, you hereby authorize any required withholding from the Ordinary Shares issuable to you and/or otherwise agree to make adequate provision in cash for any sums required to satisfy the federal, state, local and foreign tax withholding obligations of the Company or any Affiliate which arise in connection with your Award, as calculated based upon the maximum permitted withholding rate (the "***Withholding Taxes***"). Additionally, unless you satisfy the requirements set forth in Section 11(b) the Company will satisfy the Withholding Taxes obligation relating to your Award by withholding Ordinary Shares from the Ordinary Shares issued or otherwise issuable to you in connection with the Award with a Fair Market Value (measured as of the date Ordinary Shares are issued to pursuant to Section 7) equal to the amount of such Withholding Taxes; provided, however, that the number of such Ordinary Shares so withheld shall not exceed the amount necessary to satisfy the Company's tax withholding obligations as calculated using the maximum statutory withholding rates for federal, state, local and foreign tax purposes, including payroll taxes (the "***Share Withholding Procedure***"). Any adverse consequences to you arising in connection with such Share Withholding Procedure shall be your sole responsibility.

(b) Unless you timely provide Horizon with each of the following, a Share Withholding Procedure will be automatically applied to your Award:

(i) Written notice at least 10 days prior to the vesting date that you intend to pay the Withholding Taxes via a cash or check payment, and

(ii) Cash or check payment of the total amount of the Withholding Taxes by the vesting date.

If the Share Withholding Procedure is applied to your Award then on the Vesting Date Horizon will automatically reduce the number of shares issuable pursuant to your Award by the maximum number of whole Horizon shares with a fair market value that at such time does not exceed the Withholding Taxes, and you will be issued only the net remaining number of Horizon

shares. Any remaining portion of the Withholding Taxes that is less than the fair market value of one Horizon share will be withheld from other payroll compensation otherwise payable to you. In determining the fair market value of Horizon's shares for such purposes, the closing price of Horizon's shares on the Vesting Date will apply.

(c) Unless the tax withholding obligations of the Company and/or any Affiliate are satisfied, the Company shall have no obligation to deliver to you any Ordinary Shares pursuant to this Award.

(d) No obligation shall arise upon the Company to procure the issue or transfer of the Ordinary Shares unless and until the Company and/or any Affiliate are satisfied in their absolute discretion that either (i) you have made payment, or have made arrangements satisfactory to the Company and/or any Affiliate for the payment to it of such sum as is sufficient to meet any withholding liability to Taxation (defined below) in any jurisdiction which is or would be recoverable from you in connection with the vesting or the Award or the issuance of Ordinary Shares by the Company in settlement of the Award, and in respect of which the Company and/or any Affiliate is liable to account in any jurisdiction; or (ii) you have entered into an agreement with the Company and/or an Affiliate (in a form satisfactory to the Company or such Affiliate) to ensure that such a payment is made by you including, without limitation, amounts in respect of any employers' social security (or the local law equivalent thereof) or other forms of Taxation. Accordingly, the Company shall have no obligation to issue a certificate for such Ordinary Shares or release such Ordinary Shares from any escrow provided for herein unless such obligations are satisfied. "***Taxation***" shall include all forms of taxation including employees' and employers' social security, income tax and any other taxes of whatever nature in any jurisdiction together with any amount payable by an Affiliate in respect of which the Affiliate has a duty to account as a result of any laws of any jurisdiction relating to taxation.

12. PERSONAL DATA. You understand that your employer, if applicable, the Company, and/or its Affiliates hold certain personal information about you. This information include your name, home address, telephone number, date of birth, social security or equivalent tax identification number, salary, nationality, job title, and details of your Award and all Ordinary Shares subject to your Award that have been granted, cancelled, vested, unvested, or are outstanding (the "***Personal Data***").

You hereby declare your express consent to allowing your employer to transfer your Personal Data (name, home address, telephone number, date of birth, salary, nationality, job title, and details of the Award and all Ordinary Shares subject to such grant) outside the country in which you are employed or retained to its Affiliates, Horizon Pharma, Inc. and Horizon Pharma USA, Inc. which are located in the United States and their parent entity, Horizon Pharma Public Limited Company (together such entities are the "***Company Group***"). The legal persons for whom such Personal Data are intended are: Horizon Pharma Public Limited Company, Horizon Pharma, Inc., Horizon Pharma USA, Inc., StockCross Financial Services and any other third party entity providing equity award and/or Plan administration services to the Company and for the sole purpose of facilitating the transactions contemplated by this Agreement. You have the right to access and correct your Personal Data by applying to the Company representative identified on the Grant Notice (the "***Representative***"). You have the right to revoke this consent at any time with future effect towards the Company Group by providing written notice to the

Representative of such revocation (the "***Revocation Notice***") and as soon as administratively practicable following the Representative's receipt of the Revocation Notice your consent revocation will become effective and your Award shall automatically immediately terminate and be forfeited, and you will not receive any Ordinary Shares or any other consideration in respect of such forfeited Award.

13. ADDITIONAL ACKNOWLEDGEMENTS. You hereby consent and acknowledge that:

(a) Participation in the Plan is voluntary and therefore you must accept the terms and conditions of the Plan and this Award as a condition to participating in the Plan and receipt of the Award.

(b) The Plan is discretionary in nature and the Company can amend, cancel, or terminate it at any time.

(c) This Award and any other equity awards granted under the Plan are voluntary and occasional and do not create any contractual or other right to receive future awards or other benefits in lieu of future awards, even if similar awards have been granted repeatedly in the past.

(d) All determinations with respect to any such future awards, including, but not limited to, the time or times when such awards are granted, the number of Ordinary Shares, and performance and other conditions applied to the awards, will be at the sole discretion of the Company.

(e) The value of the Ordinary Shares and this Award is an extraordinary item of compensation, which is outside the scope of your employment, service contract or consulting agreement, if any. This Award shall not form part of any past, current or future entitlement to remuneration or benefits which you may have under any contract of employment with the Company nor form any part of any such contract of employment between you and the Company.

(f) The Ordinary Shares, this Award, or any income derived therefrom are a potential bonus payment not paid in lieu of any cash salary compensation and not part of normal or expected compensation or salary for any purposes, including, but not limited to, calculating any termination, severance, resignation, redundancy, end of service payments, bonuses, long-service awards, life or accident insurance benefits, pension or retirement benefits or similar payments.

(g) In the event of the involuntary termination of your Continuous Service, your eligibility to receive Ordinary Shares or payments under the Award or the Plan, if any, will terminate effective as of the date that you are no longer actively employed or retained regardless of any reasonable notice period mandated under local law, except as expressly provided in the Agreement.

(h) The future value of the Ordinary Shares is unknown and cannot be predicted with certainty. You do not have, and will not assert, any claim or entitlement to compensation, indemnity or damages arising from the termination of this award or diminution in value of the Ordinary Shares and you irrevocably release the Company, its Affiliates and, if applicable, your employer, if different from the Company, from any such claim that may arise.

(i) The Plan and this Agreement set forth the entire understanding between you, the Company and any Affiliate regarding the acquisition of the Ordinary Shares and supersedes all prior oral and written agreements pertaining to this Award.

14. UNSECURED OBLIGATION. Your Award is unfunded, and as a holder of a vested Award, you shall be considered an unsecured creditor of the Company with respect to the Company's obligation, if any, to issue shares pursuant to this Agreement. You shall not have voting or any other rights as a shareholder of the Company with respect to the shares to be issued pursuant to this Agreement until such shares are issued to you pursuant to Section 7 of this Agreement. Upon such issuance, you will obtain full voting and other rights as a shareholder of the Company. Nothing contained in this Agreement, and no action taken pursuant to its provisions, shall create or be construed to create a trust of any kind or a fiduciary relationship between you and the Company or any other person.

15. OTHER DOCUMENTS. You hereby acknowledge receipt or the right to receive a document providing the information required by Rule 428(b)(1) promulgated under the Securities Act, which includes the Plan prospectus. In addition, you acknowledge receipt of the Company's policy permitting officers, directors and other specified individuals to sell shares only during certain "window" periods and the Company's insider trading policy, in effect from time to time.

16. NOTICES. Any notices provided for in your Award or the Plan shall be given in writing (including electronically) and shall be deemed effectively given upon receipt or, in the case of notices delivered by the Company to you, five (5) days after deposit in the United States mail, postage prepaid, addressed to you at the last address you provided to the Company. Notwithstanding the foregoing, the Company may, in its sole discretion, decide to deliver any documents related to participation in the Plan and this Award by electronic means or to request your consent to participate in the Plan by electronic means. By accepting this Award you consent to receive such documents by electronic delivery and, if requested, to agree to participate in the Plan through an on-line or electronic system established and maintained by the Company or another third party designated by the Company.

17. MISCELLANEOUS.

(a) The rights and obligations of the Company under your Award shall be transferable to any one or more persons or entities, and all covenants and agreements hereunder shall inure to the benefit of, and be enforceable by the Company's successors and assigns. Your rights and obligations under your Award may only be assigned with the prior written consent of the Company.

(b) You agree upon request to execute any further documents or instruments necessary or desirable in the sole determination of the Company to carry out the purposes or intent of your Award.

(c) You acknowledge and agree that you have reviewed your Award in its entirety, have had an opportunity to obtain the advice of counsel prior to executing and accepting your Award, and fully understand all provisions of your Award.

(d) This Agreement shall be subject to all applicable laws, rules, and regulations, and to such approvals by any governmental agencies or national securities exchanges as may be required.

(e) All obligations of the Company under the Plan and this Agreement shall be binding on any successor to the Company, whether the existence of such successor is the result of a direct or indirect purchase, merger, consolidation, or otherwise, of all or substantially all of the business and/or assets of the Company.

18. GOVERNING PLAN DOCUMENT. Your Award is subject to all the provisions of the Plan, the provisions of which are hereby made a part of your Award, and is further subject to all interpretations, amendments, rules and regulations which may from time to time be promulgated and adopted pursuant to the Plan. Except as expressly provided in this Agreement, in the event of any conflict between the provisions of your Award and those of the Plan, the provisions of the Plan shall control.

19. CLAWBACK/RECOUPMENT. Your Award (and any compensation paid or shares issued under your Award) is subject to recoupment or recovery by the Company in accordance with the terms of: (i) the Company's Incentive Compensation Recoupment Policy, (ii) The Dodd–Frank Wall Street Reform and Consumer Protection Act and any implementing regulations thereunder, and (iii) any compensation recovery policy otherwise required by applicable law or listing requirements, in each case to the extent applicable.

20. SEVERABILITY. If all or any part of this Agreement or the Plan is declared by any court or governmental authority to be unlawful or invalid, such unlawfulness or invalidity shall not invalidate any portion of this Agreement or the Plan not declared to be unlawful or invalid. Any Section of this Agreement (or part of such a Section) so declared to be unlawful or invalid shall, if possible, be construed in a manner which will give effect to the terms of such Section or part of a Section to the fullest extent possible while remaining lawful and valid.

21. EFFECT ON OTHER EMPLOYEE BENEFIT PLANS. The value of the Award subject to this Agreement shall not be included as compensation, earnings, salaries, or other similar terms used when calculating your benefits under any employee benefit plan sponsored by the Company or any Affiliate, except as such plan otherwise expressly provides. The Company expressly reserves its rights to amend, modify, or terminate any of the Company's or any Affiliate's employee benefit plans.

22. AMENDMENT. This Agreement may not be modified, amended or terminated except by an instrument in writing, signed by you and by a duly authorized representative of the Company. Notwithstanding the foregoing, this Agreement may be amended solely by the Board by a writing which specifically states that it is amending this Agreement, so long as a copy of such amendment is delivered to you, and provided that no such amendment adversely affecting your rights hereunder may be made without your written consent. Without limiting the

foregoing, the Board reserves the right to change, by written notice to you, the provisions of this Agreement in any way it may deem necessary or advisable to carry out the purpose of the grant as a result of any change in applicable laws or regulations or any future law, regulation, ruling, or judicial decision, provided that any such change shall be applicable only to rights relating to that portion of the Award which is then subject to restrictions as provided herein.

23. NO OBLIGATION TO MINIMIZE TAXES. The Company has no duty or obligation to minimize the tax consequences to you of this Award and will not be liable to you for any adverse tax consequences to you arising in connection with this Award. You are hereby advised to consult with your own personal tax, financial and/or legal advisors regarding the tax consequences of this Award and by accepting this Award, you have agreed that you have done so or knowingly and voluntarily declined to do so.

Appendix A

The provisions set forth on this Appendix A shall apply to the extent the Award is a Non-Exempt Award and shall supersede any provisions to the contrary set forth in the Plan or in any other section of the Agreement to which this Appendix A is attached.

1. The provisions of this Section 1 are intended to apply to the extent your Award is a Non-Exempt Award because of the terms of a severance arrangement or other agreement between you and the Company, if any, that provide for acceleration of vesting of your Award and issuance of the shares in respect of the Award upon your termination of employment or separation from service (as such term is defined in Section 409A(a)(2)(A)(i) of the Code (and without regard to any alternative definition thereunder) ("***Separation from Service***") and such severance benefit does not satisfy the requirements for an exemption from application of Section 409A provided under Treasury Regulations Section 1.409A-1(b)(4) or 1.409A-1(b)(9) ("***Non-Exempt Severance Arrangement***"). To the extent your Award is a Non-Exempt Award due to application of a Non-Exempt Severance Arrangement, the following provisions in this Section 1 of Appendix A shall supersede anything to the contrary in Section 6(a) of the Award Agreement.

(a) If your Award vests in the ordinary course during your Continuous Service in accordance with the vesting schedule set forth in the Grant Notice, without accelerating vesting under the terms of a Non-Exempt Severance Arrangement, in no event will the shares be issued in respect of your Award any later than the later of: (i) December 31st of the calendar year that includes the applicable vesting date and (ii) the 60th day that follows the applicable vesting date.

(b) If vesting of your Award accelerates under the terms of a Non-Exempt Severance Arrangement in connection with your Separation from Service, and such vesting acceleration provisions were in effect as of the date of grant of your Award and, therefore, are part of the terms of your Award as of the date of grant, then the shares will be earlier issued in respect of your Award upon your Separation from Service in accordance with the terms of the Non-Exempt Severance Arrangement, but in no event later than the 60th day that follows the date of your Separation from Service. However, if at the time the shares would otherwise be issued you are subject to the distribution limitations contained in Section 409A applicable to "specified employees," as defined in Section 409A(a)(2)(B)(i) of the Code, such shares shall not be issued before the date that is six (6) months following the date of your Separation from Service, or, if earlier, the date of your death that occurs within such six month period.

(c) If vesting of your Award accelerates under the terms of a Non-Exempt Severance Arrangement in connection with your Separation from Service, and such vesting acceleration provisions were not in effect as of the date of grant of the Award and, therefore, are not a part of the terms of your Award on the date of grant, then such acceleration of vesting of your Award shall not accelerate the issuance date of the shares, but the shares shall instead be issued on the same schedule as set forth in the Grant Notice as if they had vested in the ordinary course during your Continuous Service, notwithstanding the vesting acceleration of the Award. Such issuance schedule is intended to satisfy the requirements of payment on a specified date or pursuant to a fixed schedule, as provided under Treasury Regulations Section 1.409A-3(a)(4).

2. Permitted Treatment of Non-Exempt Awards Upon a Corporate Transaction for Employees and Consultants. The provisions in this Section 2 shall apply and shall supersede anything to the contrary that may be set forth in the Plan with respect to the permitted treatment of your Non-Exempt Award in connection with a Corporate Transaction if you were either an Employee or Consultant upon the applicable date of grant of your Non-Exempt Award.

(a) Vested Non-Exempt Awards: To the extent your Non-Exempt Award has vested in accordance with its terms upon or prior to the date of a Corporate Transaction (such portion of your Non-Exempt Award is a "***Vested Non-Exempt Award***"), then the following provisions shall apply.

(i) If the Corporate Transaction is also a change in the ownership or effective control of the Company, or in the ownership of a substantial portion of the Company's assets, as described in Section 409A(a)(2)(A)(v) of the Code and Treasury Regulations Section 1.409A-3(i)(5) (a "***409A Change of Control***"), then the surviving or acquiring corporation (or its parent company) (the "***Acquiring Entity***") may not assume, continue or substitute your Vested Non-Exempt Award. Upon the 409A Change of Control the settlement of your Vested Non-Exempt Award will automatically be accelerated and the shares will be immediately issued in respect of your Vested Non-Exempt Award. Alternatively, the Company may instead provide that you will receive a cash settlement equal to the Fair Market Value of the shares that would otherwise be issued to you upon the 409A Change of Control.

(ii) If the Corporate Transaction is not also a 409A Change of Control, then the Acquiring Entity must either assume, continue or substitute your Vested Non-Exempt Award. The shares to be issued in respect of your Vested Non-Exempt Award shall be issued to you by the Acquiring Entity on the same schedule that the shares would have been issued to you if the Corporate Transaction had not occurred. In the Acquiring Entity's discretion, in lieu of an issuance of shares, the Acquiring Entity may instead substitute a cash payment on each applicable issuance date, equal to the Fair Market Value of the shares that would otherwise be issued to you on such issuance dates, with the determination of the Fair Market Value of the shares made on the date of the Corporate Transaction.

(b) Unvested Non-Exempt Awards. To the extent your Non-Exempt Award has not vested in accordance with its terms upon or prior to the date of any Corporate Transaction, (such portion of your Non-Exempt Award is an "***Unvested Non-Exempt Award***"), then the following provisions shall apply.

(i) If the Acquiring Entity will not assume, substitute or continue your Unvested Non-Exempt Award, then such Award shall automatically terminate and be forfeited upon the Corporate Transaction with no consideration payable to you in respect of your forfeited Unvested Non-Exempt Award. Notwithstanding the foregoing, to the extent permitted and in compliance with the requirements of Section 409A, the Company may in its discretion determine to elect to accelerate the vesting and settlement of the Unvested Non-Exempt Award upon the Corporate Transaction, or instead substitute a cash payment equal to the Fair Market Value of such shares that would otherwise be issued to you, as further provided in Section 4(b) below. In the absence of such discretionary election by the Company, your Unvested Non-Exempt Award shall be forfeited without payment of any consideration to you if the Acquiring Entity will not assume, substitute or continue your Unvested Non-Exempt Award in connection with the Corporate Transaction.

(ii) The foregoing treatment shall apply with respect to all Unvested Non-Exempt Awards upon any Corporate Transaction, and regardless of whether or not such Corporate Transaction is also a 409A Change of Control.

3. Permitted Treatment of Non-Exempt Awards Upon a Corporate Transaction for Non-Employee Directors. If you were a Director but not an Employee on the applicable grant date of your Non-Exempt Award and ("***Non-Exempt Director Award***"), the following provisions shall apply and shall supersede anything to the contrary that may be set forth in the Plan with respect to the permitted treatment of your Non-Exempt Director Award in connection with a Corporate Transaction.

(a) If the Corporate Transaction is also a 409A Change of Control then the Acquiring Entity may not assume, continue or substitute your Non-Exempt Director Award. Upon the 409A Change of Control the vesting and settlement of your Non-Exempt Director Award will automatically be accelerated and the shares will be immediately issued to you in respect of the Non-Exempt Director Award. Alternatively, the Company may provide that you will instead receive a cash settlement equal to the Fair Market Value of the shares that would otherwise be issued to you upon the 409A Change of Control pursuant to the preceding provision.

(b) If the Corporate Transaction is not also a 409A Change of Control, then the Acquiring Entity must either assume, continue or substitute your Non-Exempt Director Award. Unless otherwise determined by the Board, your Non-Exempt Director Award will remain subject to the same vesting and forfeiture restrictions that were applicable to the Award prior to the Corporate Transaction. The shares to be issued in respect of your Non-Exempt Director Award shall be issued to your by the Acquiring Entity on the same schedule that the shares would have been issued to you if the Corporate Transaction had not occurred. In the Acquiring Entity's discretion, in lieu of an issuance of shares, the Acquiring Entity may instead substitute a cash payment on each applicable issuance date, equal to the Fair Market Value of the shares that would otherwise be issued to you on such issuance dates, with the determination of Fair Market Value made on the date of the Corporate Transaction.

4. General Superseding Provisions. The provisions in this Section 4 shall apply and supersede anything to the contrary that may be set forth in the Plan, the Grant Notice or in any other section of the Agreement with respect to the permitted treatment of your Non-Exempt Award:

(a) Any exercise by the Board of discretion to accelerate the vesting of your Non-Exempt Award shall not result in any acceleration of the scheduled issuance dates for the shares in respect of the Non-Exempt Award unless earlier issuance of the shares upon the applicable vesting dates would be in compliance with the requirements of Section 409A.

(b) The Company explicitly reserves the right to earlier settle your Non-Exempt Award to the extent permitted and in compliance with the requirements of Section 409A, including pursuant to any of the exemptions available in Treasury Regulations Section 1.409A-3(j)(4)(ix).

(c) To the extent the terms of your Non-Exempt Award provide that it will be settled upon a Change in Control or Corporate Transaction, to the extent it is required for compliance with the requirements of Section 409A, the Change in Control or Corporate Transaction event triggering settlement must also constitute a 409A Change of Control. To the extent the terms of your Non-Exempt Award provides that it will be settled upon a termination of employment or termination of Continuous Service, to the extent it is required for compliance with the requirements of Section 409A, the termination event triggering settlement must also constitute a Separation From Service. However, if at the time the shares would otherwise be issued to you in connection with your "separation from service" you are subject to the distribution limitations contained in Section 409A applicable to "specified employees," as defined in Section 409A(a)(2)(B)(i) of the Code, such shares shall not be issued before the date that is six (6) months following the date of your Separation From Service, or, if earlier, the date of your death that occurs within such six month period.

5. **Section 409A Compliance**. The provisions in this Agreement for delivery of the shares in respect of the Non-Exempt Award are intended to comply with the requirements of Section 409A so that the delivery of the shares to you in respect of your Non-Exempt Award will not trigger the additional tax imposed under Section 409A, and any ambiguities herein will be so interpreted.

HORIZON PHARMA PUBLIC LIMITED COMPANY
RESTRICTED STOCK UNIT GRANT NOTICE
(2014 EQUITY INCENTIVE PLAN)

Horizon Pharma Public Limited Company (the "***Company***"), pursuant to its 2014 Equity Incentive Plan (the "***Plan***"), hereby grants to you a restricted stock unit award (the "***Award***") to purchase the Company's Ordinary Shares. The following specific terms of the Award can be obtained by logging on to your StockCross brokerage account: [Participant, Date of Grant, Vesting Commencement Date, Number of Restricted Stock Units, Purchase Price per Ordinary Share, Vesting Schedule and Issuance Schedule]. These specific terms are incorporated by reference into this Grant Notice. This Award is subject to all of the terms and conditions as set forth herein and in the Restricted Stock Unit Agreement (the "***Award Agreement***") and the Plan, all of which are available on the StockCross website. Capitalized terms are defined in the Plan or the Award Agreement shall have the meanings set forth in the Plan or the Award Agreement. The Purchase Price per Ordinary Share that may be issued in settlement of your Award is equal to the nominal value per Ordinary Share as of the Date of Grant and is subject to adjustment as provided in Section 4 of the Award Agreement.

Additional Terms/Acknowledgements: You must electronically accept the Award by logging into your StockCross account. If you have not set-up your StockCross brokerage account, the following information provided below will assist you in this process. Failure to do so may result in forfeiture of the Award. By electronically accepting the Award, you acknowledge receipt of, and understand and agree to, this Restricted Stock Unit Grant Notice, the Award Agreement and the Plan. You further acknowledge that as of the Date of Grant, this Restricted Stock Unit Grant Notice, the Award Agreement, and the Plan set forth the entire understanding between you and the Company regarding the acquisition of shares in the Company and supersede all prior oral and written agreements on that subject with the exception of: (i) any written employment or severance arrangement that would provide for vesting acceleration of the Award upon the terms and conditions set forth therein, or (ii) any compensation recovery policy that is adopted by the Company or is otherwise required by applicable law. By accepting this Award, the Participant consents to receive Plan documents by electronic delivery and to participate in the Plan through an on-line or electronic system established and maintained by the Company or another third party designated by the Company.

STOCKCROSS FINANCIAL SERVICES BROKERAGE ACCOUNT

Horizon currently utilizes StockCross Financial Services as our online broker. StockCross Financial Services offers an internet website for viewing option data and for buying or selling your stock options.

To open your brokerage account (if you have not yet done so)

- Go to the StockCross website at www.stockcross.com
- Select the Green "Open an Account" menu item.
- Under the New Account Application screen, select "Employee Stock Plan Account" button to proceed with the brokerage application.
- If any additional documentation is needed, StockCross will contact you directly.
- Once the account is fully processed, you will receive a welcome email from StockCross, containing your account number and other useful information. This is generally within 72 hours.

If you have any questions or comments completing the brokerage application, please contact StockCross Corporate Services at 800-338-3965.

Viewing your Award

- Login to www.trading.stockcross.com using you StockCross account number and password established during registration
- Once logged into your StockCross account, select the menu item "Employee Stock Plan." This will bring you into another window screen which provides a summary of your equity grants. **Please note that to view this information, you will need to disable popup blockers.**
- Select "Portfolio." This will show you all equity grants that you have been granted.

Accepting your Award

- Login to www.trading.stockcross.com using you StockCross user name and password established during registration
- Once logged into your StockCross account, select the link to Employee Stock Plans under the menu item "Employee Stock Plan." This will bring you into another window screen which provides a summary of your equity grants. **Please note that to view this information, you will need to disable popup blockers.**
- Select "My Portfolio." This will show you all equity grants that you have been granted.
- For your new equity grant, in the first column, click on the Orange "Accept Grant" Action Button.
- This will take you to an electronic acceptance window. For your reference, the Equity Agreement applicable to the Award is provided. If you agree with the terms and conditions of your equity grant, Place your name in the signature box, type your name below, and check the agreement box. Click "Accept Grant to complete the acceptance.

IMPORTANT REMINDER: In order to avoid forfeiture of your Award, **you must electronically accept your Award 30 days *prior* to your first vesting date.**

Contact Horizon Pharma plc's Global Equity Plan Administrator Garry Devine at 224-383-3037 or email gdevine@horizonpharma.com with any further questions regarding your awards.

HORIZON PHARMA PUBLIC LIMITED COMPANY
2014 EQUITY INCENTIVE PLAN

EQUITY LONG TERM INCENTIVE PROGRAM

RESTRICTED STOCK UNIT AGREEMENT

Pursuant to the Restricted Stock Unit Grant Notice (the "***Grant Notice***") and this Restricted Stock Unit Agreement (the "***Agreement***") and in consideration of your services, Horizon Pharma Public Limited Company (the "***Company***") has granted you a Restricted Stock Unit Award (the "***Award***") under its 2014 Equity Incentive Plan (the "***Plan***") and its Equity Long Term Incentive Program ("***Program***") for the number of restricted stock units referenced in the Grant Notice. Capitalized terms not explicitly defined in this Agreement shall have the same meanings given to them in the Plan, Program or the Grant Notice, as applicable. Except as otherwise explicitly provided herein, in the event of any conflict between the terms in this Agreement and the Plan or Program, the terms of the Plan or Program shall control.

The details of your Award, in addition to those set forth in the Grant Notice, the Program and the Plan, are as follows.

1. GRANT OF THE AWARD. This Award represents your right to be issued on a future date the number of Ordinary Shares that is equal to the number of restricted stock units indicated in the Grant Notice (the "***Stock Units***") which vest at the Purchase Price per Ordinary Share specified in your Grant Notice. As of the Date of Grant, the Company will credit to a bookkeeping account maintained by the Company for your benefit (the "***Account***") the number of Stock Units subject to the Award. As provided in the Program, the Award may be settled via a Substitute Cash Payment in lieu of an issuance of Ordinary Shares.

2. VESTING. Subject to the limitations contained herein, your Award will vest, if at all, in accordance with the Vesting Criteria. Except as otherwise specified in the Program or the Vesting Criteria, upon termination of your Continuous Service, the Stock Units credited to the Account that were not vested on the date of such termination will be forfeited at no cost to the Company and you will have no further right, title or interest in such Stock Units or the Ordinary Shares to be issued in respect of such portion of the Award.

3. METHOD OF PAYMENT. On or before the time you receive a distribution of the Ordinary Shares in settlement of your Stock Units, you hereby authorize the Company or any Affiliate to satisfy the payment of the Purchase Price per Ordinary Share with respect to such Ordinary Shares by withholding such payment from payroll and any other cash amounts otherwise payable to you. If no cash amounts are otherwise payable to you by the Company and available for such deduction, you must provide timely payment of the applicable Purchase Price to the Company via cash or check and no obligation shall arise upon the Company to procure the issue or transfer of the Ordinary Shares unless and until the Company and/or any Affiliate are satisfied in their absolute discretion that you have satisfied such payment requirement. All amounts due are payable in United States dollars based, if applicable, upon the local currency to United States dollar exchange rate published in the West Coast edition of The Wall Street Journal on the applicable payment date (or, if such date is not a business day in the United States, the preceding business day in the United States).

4. NUMBER OF STOCK UNITS, ORDINARY SHARES AND PURCHASE PRICE.

(a) The number of Stock Units subject to your Award and the Purchase Price per Ordinary Share may be adjusted from time to time for Capitalization Adjustments, as provided in the Plan. Furthermore, the Purchase Price per Ordinary Share will be automatically adjusted from time to time, as applicable, such that it shall at all times be equal to the nominal value per Ordinary Share as then in effect. In no event will the Purchase Price per Ordinary Share be less than the nominal value per Ordinary Share.

(b) Any additional Stock Units that become subject to the Award pursuant to this Section 4, if any, shall be subject, in a manner determined by the Board, to the same forfeiture restrictions, restrictions on transferability, and time and manner of delivery as applicable to the other Stock Units covered by your Award.

(c) Notwithstanding the provisions of this Section 4, no fractional shares or rights for fractional Ordinary Shares shall be created pursuant to this Section 4. The Board shall, in its discretion, determine an equivalent benefit for any fractional shares or fractional shares that might be created by the adjustments referred to in this Section 4.

5. SECURITIES LAW COMPLIANCE. You may not be issued any shares in respect of your Award unless either (i) the shares are registered under the Securities Act; or (ii) the Company has determined that such issuance would be exempt from the registration requirements of the Securities Act. Your Award also must comply with other applicable laws and regulations governing the Award, including, without limitation, the laws and regulations of the United States and your country of residence, and you will not receive such shares if the Company determines that such receipt would not be in material compliance with such laws and regulations.

6. TRANSFER RESTRICTIONS. Your Award is not transferable, except by will or by the laws of descent and distribution. In addition to any other limitation on transfer created by applicable securities laws, you agree not to assign, hypothecate, donate, encumber or otherwise dispose of any interest in any of the Ordinary Shares subject to the Award until the shares are issued to you in accordance with Section 7 of this Agreement. After the shares have been issued to you, you are free to assign, hypothecate, donate, encumber or otherwise dispose of any interest in such shares provided that any such actions are in compliance with the provisions herein, any applicable Company policies (including, but not limited to, insider trading and window period policies) and applicable securities laws. Notwithstanding the foregoing, by delivering written notice to the Company, in a form satisfactory to the Company, you may designate a third party who, in the event of your death, shall thereafter be entitled to receive any distribution of Ordinary Shares to which you were entitled at the time of your death pursuant to this Agreement.

7. DATE OF ISSUANCE. The Company will deliver to you a number of Ordinary Shares equal to the number of vested Stock Units subject to your Award, including any additional Stock Units received pursuant to Section 4 above that relate to those vested Stock Units, as soon as administratively practicable following the date of the Committee's

determination of the number of Stock Units that will vest, but in no event later than 30 days following the date of such determination. Delivery of the shares pursuant to the provisions of this Section 7(a) is intended to comply with the requirements for the short-term deferral exemption available under Treasury Regulations Section 1.409A-1(b)(4) and shall be construed and administered in such manner. The form of such delivery of the shares (*e.g.*, a stock certificate or electronic entry evidencing such shares) shall be determined by the Company.

8. DIVIDENDS. You shall receive no benefit or adjustment to your Award with respect to any cash dividend, stock dividend or other distribution that does not result from a Capitalization Adjustment as provided in the Plan; provided, however, that this sentence shall not apply with respect to any Ordinary Shares that are delivered to you in connection with your Award after such shares have been delivered to you.

9. RESTRICTIVE LEGENDS. The shares issued in respect of your Award shall be endorsed with appropriate legends determined by the Company.

10. AWARD NOT A SERVICE CONTRACT.

(a) Your Continuous Service with the Company or an Affiliate is not for any specified term and may be terminated by you or by the Company or an Affiliate at any time, for any reason, with or without cause and with or without notice. Nothing in this Agreement (including, but not limited to, the vesting of your Award pursuant to the schedule set forth in the Grant Notice or the issuance of the shares in respect of your Award), the Plan or any covenant of good faith and fair dealing that may be found implicit in this Agreement or the Plan shall: (i) confer upon you any right to continue in the employ of, or affiliation with, the Company or an Affiliate; (ii) constitute any promise or commitment by the Company or an Affiliate regarding the fact or nature of future positions, future work assignments, future compensation or any other term or condition of employment or affiliation; (iii) confer any right or benefit under this Agreement or the Plan unless such right or benefit has specifically accrued under the terms of this Agreement or Plan; or (iv) deprive the Company of the right to terminate you at will and without regard to any future vesting opportunity that you may have.

(b) By accepting this Award, you acknowledge and agree that the right to continue vesting in the Award pursuant to the vesting schedule provided in the Grant Notice is earned only by continuing as an employee, director or consultant at the will of the Company (not through the act of being hired, being granted this Award or any other award or benefit) and that the Company has the right to reorganize, sell, spin-out or otherwise restructure one or more of its businesses or Affiliates at any time or from time to time, as it deems appropriate (a ***"reorganization"***). You further acknowledge and agree that such a reorganization could result in the termination of your Continuous Service, or the termination of Affiliate status of your employer and the loss of benefits available to you under this Agreement, including but not limited to, the termination of the right to continue vesting in the Award. You further acknowledge and agree that this Agreement, the Plan, the transactions contemplated hereunder and the vesting schedule set forth herein or any covenant of good faith and fair dealing that may be found implicit in any of them do not constitute an express or implied promise of continued engagement as an employee or consultant for the term of this Agreement, for any period, or at all, and shall not interfere in any way with your right or the Company's right to terminate your Continuous Service at any time, with or without cause and with or without notice.

11. WITHHOLDING OBLIGATIONS.

(a) On or before the time you receive a distribution of the shares subject to your Award, or at any time thereafter as requested by the Company, you hereby authorize any required withholding from the Ordinary Shares issuable to you and/or otherwise agree to make adequate provision in cash for any sums required to satisfy the federal, state, local and foreign tax withholding obligations of the Company or any Affiliate which arise in connection with your Award, as calculated based upon the maximum permitted withholding rate (the "***Withholding Taxes***"). The Company will satisfy the Withholding Taxes obligation relating to your Award by withholding Ordinary Shares from the Ordinary Shares issued or otherwise issuable to you in connection with the Award with a Fair Market Value (measured as of the date Ordinary Shares are issued to pursuant to Section 7) equal to the amount of such Withholding Taxes; provided, however, that the number of such Ordinary Shares so withheld shall not exceed the amount necessary to satisfy the Company's tax withholding obligations as calculated using the maximum statutory withholding rates for federal, state, local and foreign tax purposes, including payroll taxes. Accordingly, on the applicable vesting date(s) Horizon will automatically reduce the number of shares issuable pursuant to your Award by the maximum number of whole Horizon shares with a fair market value that at such time does not exceed the Withholding Taxes, and you will be issued only the net remaining number of Horizon shares (the "***Share Withholding Procedure***").. Any remaining portion of the Withholding Taxes that is less than the fair market value of one Horizon share will be withheld from other payroll compensation otherwise payable to you. In determining the fair market value of Horizon's shares for such purposes, the closing price of Horizon's shares on the applicable vesting date will apply. Any adverse consequences to you arising in connection with such Share Withholding Procedure shall be your sole responsibility.

(b) Unless the tax withholding obligations of the Company and/or any Affiliate are satisfied, the Company shall have no obligation to deliver to you any Ordinary Shares pursuant to this Award.

12. PERSONAL DATA. You understand that your employer, if applicable, the Company, and/or its Affiliates hold certain personal information about you. This information include your name, home address, telephone number, date of birth, social security or equivalent tax identification number, salary, nationality, job title, and details of your Award and all Ordinary Shares subject to your Award that have been granted, cancelled, vested, unvested, or are outstanding (the "***Personal Data***").

You hereby declare your express consent to allowing your employer to transfer your Personal Data (name, home address, telephone number, date of birth, salary, nationality, job title, and details of the Award and all Ordinary Shares subject to such grant) outside the country in which you are employed or retained to its Affiliates, Horizon Pharma, Inc. and Horizon Pharma USA, Inc. which are located in the United States and their parent entity, Horizon Pharma Public Limited Company (together such entities are the "***Company Group***"). The legal persons for whom such Personal Data are intended are: Horizon Pharma Public Limited Company, Horizon

Pharma, Inc., Horizon Pharma USA, Inc., StockCross Financial Services and any other third party entity providing equity award and/or Plan administration services to the Company and for the sole purpose of facilitating the transactions contemplated by this Agreement. You have the right to access and correct your Personal Data by applying to the Company representative identified on the Grant Notice (the "***Representative***"). You have the right to revoke this consent at any time with future effect towards the Company Group by providing written notice to the Representative of such revocation (the "***Revocation Notice***") and as soon as administratively practicable following the Representative's receipt of the Revocation Notice your consent revocation will become effective and your Award shall automatically immediately terminate and be forfeited, and you will not receive any Ordinary Shares or any other consideration in respect of such forfeited Award.

13. ADDITIONAL ACKNOWLEDGEMENTS. You hereby consent and acknowledge that:

(a) Participation in the Plan is voluntary and therefore you must accept the terms and conditions of the Plan and this Award as a condition to participating in the Plan and receipt of the Award.

(b) The Plan is discretionary in nature and the Company can amend, cancel, or terminate it at any time.

(c) This Award and any other equity awards granted under the Plan are voluntary and occasional and do not create any contractual or other right to receive future awards or other benefits in lieu of future awards, even if similar awards have been granted repeatedly in the past.

(d) All determinations with respect to any such future awards, including, but not limited to, the time or times when such awards are granted, the number of Ordinary Shares, and performance and other conditions applied to the awards, will be at the sole discretion of the Company.

(e) The value of the Ordinary Shares and this Award is an extraordinary item of compensation, which is outside the scope of your employment, service contract or consulting agreement, if any. This Award shall not form part of any past, current or future entitlement to remuneration or benefits which you may have under any contract of employment with the Company nor form any part of any such contract of employment between you and the Company.

(f) The Ordinary Shares, this Award, or any income derived therefrom are a potential bonus payment not paid in lieu of any cash salary compensation and not part of normal or expected compensation or salary for any purposes, including, but not limited to, calculating any termination, severance, resignation, redundancy, end of service payments, bonuses, long-service awards, life or accident insurance benefits, pension or retirement benefits or similar payments.

(g) In the event of the involuntary termination of your Continuous Service, your eligibility to receive Ordinary Shares or payments under the Award or the Plan, if any, will terminate effective as of the date that you are no longer actively employed or retained regardless of any reasonable notice period mandated under local law, except as expressly provided in the Agreement.

(h) The future value of the Ordinary Shares is unknown and cannot be predicted with certainty. You do not have, and will not assert, any claim or entitlement to compensation, indemnity or damages arising from the termination of this award or diminution in value of the Ordinary Shares and you irrevocably release the Company, its Affiliates and, if applicable, your employer, if different from the Company, from any such claim that may arise.

(i) The Plan, the Program the Vesting Criteria and this Agreement set forth the entire understanding between you, the Company and any Affiliate regarding the acquisition of the Ordinary Shares and supersedes all prior oral and written agreements pertaining to this Award.

14. UNSECURED OBLIGATION. Your Award is unfunded, and as a holder of a vested Award, you shall be considered an unsecured creditor of the Company with respect to the Company's obligation, if any, to issue shares pursuant to this Agreement. You shall not have voting or any other rights as a shareholder of the Company with respect to the shares to be issued pursuant to this Agreement until such shares are issued to you pursuant to Section 7 of this Agreement. Upon such issuance, you will obtain full voting and other rights as a shareholder of the Company. Nothing contained in this Agreement, and no action taken pursuant to its provisions, shall create or be construed to create a trust of any kind or a fiduciary relationship between you and the Company or any other person.

15. OTHER DOCUMENTS. You hereby acknowledge receipt or the right to receive a document providing the information required by Rule 428(b)(1) promulgated under the Securities Act, which includes the Plan prospectus. In addition, you acknowledge receipt of the Company's policy permitting officers, directors and other specified individuals to sell shares only during certain "window" periods and the Company's insider trading policy, in effect from time to time.

16. NOTICES. Any notices provided for in your Award or the Plan shall be given in writing (including electronically) and shall be deemed effectively given upon receipt or, in the case of notices delivered by the Company to you, five (5) days after deposit in the United States mail, postage prepaid, addressed to you at the last address you provided to the Company. Notwithstanding the foregoing, the Company may, in its sole discretion, decide to deliver any documents related to participation in the Plan and this Award by electronic means or to request your consent to participate in the Plan by electronic means. By accepting this Award you consent to receive such documents by electronic delivery and, if requested, to agree to participate in the Plan through an on-line or electronic system established and maintained by the Company or another third party designated by the Company.

17. MISCELLANEOUS.

(a) The rights and obligations of the Company under your Award shall be transferable to any one or more persons or entities, and all covenants and agreements hereunder shall inure to the benefit of, and be enforceable by the Company's successors and assigns. Your rights and obligations under your Award may only be assigned with the prior written consent of the Company.

(b) You agree upon request to execute any further documents or instruments necessary or desirable in the sole determination of the Company to carry out the purposes or intent of your Award.

(c) You acknowledge and agree that you have reviewed your Award in its entirety, have had an opportunity to obtain the advice of counsel prior to executing and accepting your Award, and fully understand all provisions of your Award.

(d) This Agreement shall be subject to all applicable laws, rules, and regulations, and to such approvals by any governmental agencies or national securities exchanges as may be required.

(e) All obligations of the Company under the Plan and this Agreement shall be binding on any successor to the Company, whether the existence of such successor is the result of a direct or indirect purchase, merger, consolidation, or otherwise, of all or substantially all of the business and/or assets of the Company.

18. GOVERNING PLAN DOCUMENT. Your Award is subject to all the provisions of the Plan and the Program, the provisions of which are hereby made a part of your Award, and is further subject to all interpretations, amendments, rules and regulations which may from time to time be promulgated and adopted pursuant to the Plan and the Program. Except as expressly provided in this Agreement, in the event of any conflict between the provisions of your Award and those of the Plan or the Program, the provisions of the Plan or Program shall control.

19. CLAWBACK/RECOUPMENT. Your Award (and any compensation paid or shares issued under your Award) is subject to recoupment or recovery by the Company in accordance with the terms of: (i) the Company's Incentive Compensation Recoupment Policy, (ii) The Dodd–Frank Wall Street Reform and Consumer Protection Act and any implementing regulations thereunder, and (iii) any compensation recovery policy otherwise required by applicable law or listing requirements, in each case to the extent applicable.

20. SEVERABILITY. If all or any part of this Agreement, the Plan or the Program is declared by any court or governmental authority to be unlawful or invalid, such unlawfulness or invalidity shall not invalidate any portion of this Agreement, the Plan or the Program not declared to be unlawful or invalid. Any Section of this Agreement, the Plan or the Program (or part of such a Section) so declared to be unlawful or invalid shall, if possible, be construed in a manner which will give effect to the terms of such Section or part of a Section to the fullest extent possible while remaining lawful and valid.

21. EFFECT ON OTHER EMPLOYEE BENEFIT PLANS. The value of the Award subject to this Agreement shall not be included as compensation, earnings, salaries, or other similar terms used when calculating your benefits under any employee benefit plan sponsored by the Company or any Affiliate, except as such plan otherwise expressly provides. The Company expressly reserves its rights to amend, modify, or terminate any of the Company's or any Affiliate's employee benefit plans.

22. AMENDMENT. This Agreement may not be modified, amended or terminated except by an instrument in writing, signed by you and by a duly authorized representative of the Company. Notwithstanding the foregoing, this Agreement may be amended solely by the Board by a writing which specifically states that it is amending this Agreement, so long as a copy of such amendment is delivered to you, and provided that no such amendment adversely affecting your rights hereunder may be made without your written consent. Without limiting the foregoing, the Board reserves the right to change, by written notice to you, the provisions of this Agreement in any way it may deem necessary or advisable to carry out the purpose of the grant as a result of any change in applicable laws or regulations or any future law, regulation, ruling, or judicial decision, provided that any such change shall be applicable only to rights relating to that portion of the Award which is then subject to restrictions as provided herein.

23. NO OBLIGATION TO MINIMIZE TAXES. The Company has no duty or obligation to minimize the tax consequences to you of this Award and will not be liable to you for any adverse tax consequences to you arising in connection with this Award. You are hereby advised to consult with your own personal tax, financial and/or legal advisors regarding the tax consequences of this Award and by accepting the Award, you have agreed that you have done so or knowingly and voluntarily declined to do so.

HORIZON PHARMA PUBLIC LIMITED COMPANY
RESTRICTED STOCK UNIT GRANT NOTICE
(2014 EQUITY INCENTIVE PLAN)

EQUITY LONG TERM INCENTIVE PROGRAM

Horizon Pharma Public Limited Company (the "***Company***"), pursuant to its 2014 Equity Incentive Plan (the "***Plan***") and its Equity Long Term Incentive Program that became effective on January 5, 2018 (the "***Program"***), granted to you a restricted stock unit award (the "***Award***") to purchase the Company's Ordinary Shares. The following specific terms of the Award can be obtained by logging on to your StockCross brokerage account: Participant, Date of Grant, Number of Restricted Stock Units, Purchase Price per Ordinary Share, and Vesting Criteria.

These specific terms are incorporated by reference into this Grant Notice. This Award is subject to all of the terms and conditions as set forth herein and in the Restricted Stock Unit Agreement (the "***Award Agreement***"), the Plan, the Program, and the Vesting Criteria, all of which are available on the StockCross website. Capitalized terms are defined in the Plan or the Award Agreement shall have the meanings set forth in the Plan, the Program or the Award Agreement. The Purchase Price per Ordinary Share that may be issued in settlement of your Award is equal to the nominal value per Ordinary Share as of the Date of Grant and is subject to adjustment as provided in Section 4 of the Award Agreement. The Award is subject to all the terms and conditions of the Program and the Vesting Criteria, and in the event of any conflict between the terms of the Program or the Vesting Criteria and the terms set forth in this Restricted Stock Unit Grant Notice or the Award Agreement, the terms of the Program or Vesting Criteria shall control.

Additional Terms/Acknowledgements: You must electronically accept the Award by logging into your StockCross account. If you have not set-up your StockCross brokerage account, the following information provided below will assist you in this process. Failure to do so may result in forfeiture of the Award. By electronically accepting the Award, you acknowledge receipt of, and understand and agree to, this Restricted Stock Unit Grant Notice, the Award Agreement and the Plan. You further acknowledge that as of the Date of Grant, this Restricted Stock Unit Grant Notice, the Award Agreement, the Program and the Plan set forth the entire understanding between you and the Company regarding the acquisition of shares in the Company and supersede all prior oral and written agreements on that subject with the exception of: (i) any written employment or severance arrangement that would provide for vesting acceleration of the Award upon the terms and conditions set forth therein, or (ii) any compensation recovery policy that is adopted by the Company or is otherwise required by applicable law. By accepting this Award, the Participant consents to receive Plan documents by electronic delivery and to participate in the Plan through an on-line or electronic system established and maintained by the Company or another third party designated by the Company.

STOCKCROSS FINANCIAL SERVICES BROKERAGE ACCOUNT

Horizon currently utilizes StockCross Financial Services as our online broker. StockCross Financial Services offers an internet website for viewing Award data and for buying or selling shares that may be issued in settlement of your Award.

To open your brokerage account

- Go to the StockCross website at www.stockcross.com,
- Select the red "Employee Stock Plans" menu item.
- Under the "Get Started" window, select the blue menu button "Open an Account."
- Under the New Account Application screen, select "Employee Stock Option Plan ESOP" button to proceed with the brokerage application.
- You will receive a welcome email from StockCross within 72 hours, containing your account number and other useful information

If you have any questions or comments completing the brokerage application, please contact the StockCross New Accounts team at 800-225-6196 ext. 2442

Viewing your Award

- Login to www.stockcross.com using you StockCross account number and password established during registration
- Once logged into your StockCross account, select the menu item "Employee Stock Plan." This will bring you into another window screen which provides a summary of your equity grants. **Please note that to view this information, you will need to disable popup blockers**.
- Select "My Portfolio." This will show you all equity grants that you have been granted.

Accepting your Award

- Login to www.stockcross.com using you StockCross account number and password established during registration
- Once logged into your StockCross account, select the menu item "Employee Stock Plan." This will bring you into another window screen which provides a summary of your equity grants. **Please note that to view this information, you will need to disable popup blockers**.
- Select "My Portfolio." This will show you all equity grants that you have been granted.
- For your new equity grant in the last column, click on the "View" hyperlink.
- Selecting "View" will take you to an electronic acceptance window. For your reference, the Equity Plan Agreement applicable to the Award is provided. If you agree with the terms and conditions of your equity grant, select the green "Accept" button.

IMPORTANT REMINDER: In order to avoid forfeiture of your Award, **you must electronically accept your Award 30 days *prior* to your first vesting date.**

Contact Horizon Pharma plc's Senior Manager, Accounting and Global Equity Plan Administrator Garry Devine at 224-383-3037 or email gdevine@horizonpharma.com with any further questions regarding your awards.

Exhibit 10.30

HORIZON PHARMA, INC.

DEFERRED COMPENSATION PLAN

Amended and Restated Effective January 1, 2018

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HORIZON PHARMA, INC.
DEFERRED COMPENSATION PLAN

ARTICLE 1
ESTABLISHMENT AND PURPOSE

Horizon Pharma, Inc. (the "***Company***") originally established the Horizon Pharma, Inc. Deferred Compensation Plan (the "***Plan***"), effective April 1, 2015. The Plan is hereby amended and restated effective January 1, 2018 (the "***Restatement Effective Date***"). The purpose of the Plan is to attract and retain key employees by providing Participants with an opportunity to defer receipt of a portion of their salary, bonus, and other specified compensation. The Plan is not intended to meet the qualification requirements of Code Section 401(a), but is intended to meet the requirements of Code Section 409A, and shall be operated and interpreted consistent with that intent.

The Plan constitutes an unsecured promise by a Participating Employer to pay benefits in the future. Participants in the Plan shall have the status of general unsecured creditors of the Company or the Adopting Employer, as applicable. Each Participating Employer shall be solely responsible for payment of the benefits of its employees and their beneficiaries. The Plan is unfunded for Federal tax purposes and is intended to be an unfunded arrangement for eligible employees who are part of a select group of management or highly compensated employees of the Employer within the meaning of Sections 201(2), 301(a)(3) and 401(a)(1) of ERISA. Any amounts set aside to defray the liabilities assumed by the Company or an Adopting Employer will remain the general assets of the Company or the Adopting Employer and shall remain subject to the claims of the Company's or the Adopting Employer's creditors until such amounts are distributed to the Participants.

ARTICLE 2
DEFINITIONS

2.1 Account. Account means a bookkeeping account maintained by the Committee to record the payment obligation of a Participating Employer to a Participant as determined under the terms of the Plan. The Committee may maintain an Account to record the total obligation to a Participant and component Accounts to reflect amounts payable at different times and in different forms. Reference to an Account means any such Account established by the Committee, as the context requires. Accounts are intended to constitute unfunded obligations within the meaning of Sections 201(2), 301(a)(3) and 401(a)(1) of ERISA.

2.2 Account Balance. Account Balance means, with respect to any Account, the total payment obligation owed to a Participant from such Account as of the most recent Valuation Date.

2.3 Adopting Employer. Adopting Employer means an Affiliate who, with the consent of the Company, has adopted the Plan for the benefit of its eligible employees.

2.4 Affiliate. Affiliate means a corporation, trade or business that, together with the Company, is treated as a single employer under Code Section 414(b) or (c).

2.5 Beneficiary. Beneficiary means a natural person, estate, or trust designated by a Participant in accordance with Section 6.5 of the Plan to receive payments to which a Beneficiary is entitled in accordance with provisions of the Plan.

2.6 Business Day. Business Day means each day on which the New York Stock Exchange is open for business.

2.7 Change in Control. Change in Control means, with respect to a Participating Employer any of the following events: (i) a change in the ownership of the Participating Employer, (ii) a change in the effective control of the Participating Employer, or (iii) a change in the ownership of a substantial portion of the assets of the Participating Employer.

For purposes of this Section, a change in the ownership of the Participating Employer occurs on the date on which any one person, or more than one person acting as a group, acquires ownership of stock of the Participating Employer that, together with stock held by such person or group constitutes more than 50% of the total fair market value or total voting power of the stock of the Participating Employer. A change in the effective control of the Participating Employer occurs on the date on which either: (i) a person, or more than one person acting as a group, acquires ownership of stock of the Participating Employer possessing 50% or more of the total voting power of the stock of the Participating Employer, taking into account all such stock acquired during the 12-month period ending on the date of the most recent acquisition, or (ii) a majority of the members of the Participating Employer's Board of Directors is replaced during any 12-month period by directors whose appointment or election is not endorsed by a majority of the members of such Board of Directors prior to the date of the appointment or election, but only if no other corporation is a majority shareholder of the Participating Employer . A change in the ownership of a substantial portion of assets occurs on the date on which any one person, or more than one person acting as a group, other than a person or group of persons that is related to the Participating Employer, acquires assets from the Participating Employer that have a total gross fair market value equal to or more than 75% of the total gross fair market value of all of the assets of the Participating Employer immediately prior to such acquisition or acquisitions, taking into account all such assets acquired during the 12-month period ending on the date of the most recent acquisition.

An event constitutes a Change in Control with respect to a Participant only if the Participant performs services for the Participating Employer that has experienced the Change in Control, or the Participant's relationship to the affected Participating Employer otherwise satisfies the requirements of Treasury Regulation Section 1.409A-3(i)(5)(ii).

The determination as to the occurrence of a Change in Control shall be based on objective facts and in accordance with the requirements of Code Section 409A.

2.8 Claimant. Claimant means a Participant or Beneficiary filing a claim under Article XII of this Plan.

2.9 Code. Code means the Internal Revenue Code of 1986, as amended from time to time.

2.10 Code Section 409A. Code Section 409A means section 409A of the Code, and regulations and other guidance issued by the Treasury Department and Internal Revenue Service thereunder.

2.11 Committee. Committee means the committee appointed by the Board of Directors of the Company Parent (or the appropriate committee of such board) to administer the Plan. If no designation is made, the Compensation Committee of the Board of Directors of the Company Parent shall have and exercise the powers of the Committee.

2.12 Company. Company means Horizon Pharma, Inc.

2.13 Company Parent. Company Parent means Horizon Pharma Public Limited Company.

2.14 Company Contribution. Company Contribution means a credit by a Participating Employer to a Participant's Account(s) in accordance with the provisions of Article V of the Plan. Company Contributions are credited at the sole discretion of the Participating Employer and the fact that a Company Contribution is credited in one year shall not obligate the Participating Employer to continue to make such Company Contribution in subsequent years. Unless the context clearly indicates otherwise, a reference to Company Contribution shall include Earnings attributable to such contribution.

2.15 Company Stock. Company Stock means phantom ordinary shares issued by the Company Parent.

2.16 Compensation. Compensation means a Participant's base salary, bonus, commission, and such other cash or equity-based compensation (if any) approved by the Committee as Compensation that may be deferred under this Plan. Compensation shall not include any compensation that has been previously deferred under this Plan or any other arrangement subject to Code Section 409A.

2.17 Compensation Deferral Agreement. Compensation Deferral Agreement means an agreement between a Participant and a Participating Employer that specifies: (i) the amount of each component of Compensation that the Participant has elected to defer to the Plan in accordance with the provisions of Article IV, and (ii) the Payment Schedule applicable to one or more Accounts. The Committee may permit different deferral amounts for each component of Compensation and may establish a minimum or maximum deferral amount for each such component. Unless otherwise specified by the Committee in the Compensation Deferral Agreement, Participants may defer up to 50% of their base salary and up to 100% of other types of Compensation for a Plan Year. A Compensation Deferral Agreement may also specify the investment allocation described in Section 8.4.

2.18 Death Benefit. Death Benefit means the benefit payable under the Plan to a Participant's Beneficiary(ies) upon the Participant's death as provided in Section 6.1 of the Plan.

2.19 Deferral. Deferral means a credit to a Participant's Account(s) that records that portion of the Participant's Compensation that the Participant has elected to defer to the Plan in

accordance with the provisions of Article IV. Unless the context of the Plan clearly indicates otherwise, a reference to Deferrals includes Earnings attributable to such Deferrals.

Deferrals shall be calculated with respect to the gross cash Compensation payable to the Participant prior to any deductions or withholdings, but shall be reduced by the Committee as necessary so that it does not exceed 100% of the cash Compensation of the Participant remaining after deduction of all required income and employment taxes, 401(k) and other employee benefit deductions, and other deductions required by law. Changes to payroll withholdings that affect the amount of Compensation being deferred to the Plan shall be allowed only to the extent permissible under Code Section 409A.

2.20 Director. Director means a member of the Board of Directors of the Company, the Board of Directors of the Company Parent or the Board of Directors of any other Affiliate.

2.21 Earnings. Earnings means an adjustment to the value of an Account in accordance with Article VIII.

2.22 Eligible Employee. Eligible Employee means a member of a "select group of management or highly compensated employees" of a Participating Employer within the meaning of Sections 201(2), 301(a)(3) and 401(a)(1) of ERISA, as determined by the Committee from time to time in its sole discretion.

2.23 Employee. Employee means a common-law employee of an Employer.

2.24 Employer. Employer means, with respect to Employees it employs, the Company and each Affiliate.

2.25 ERISA. ERISA means the Employee Retirement Income Security Act of 1974, as amended from time to time.

2.26 Fiscal Year Compensation. Fiscal Year Compensation means Compensation earned during one or more consecutive fiscal years of a Participating Employer, all of which is paid after the last day of such fiscal year or years.

2.27 Participant. Participant means an Eligible Employee who has received notification of his or her eligibility to defer Compensation under the Plan under Section 3.1 and any other person with an Account Balance greater than zero, regardless of whether such individual continues to be an Eligible Employee. A Participant's continued participation in the Plan shall be governed by Section 3.2 of the Plan.

2.28 Participating Employer. Participating Employer means the Company and each Adopting Employer.

2.29 Payment Schedule. Payment Schedule means the date as of which payment of an Account under the Plan will commence and the form in which payment of such Account will be made.

2.30 Performance-Based Compensation. Performance-Based Compensation means Compensation where the amount of, or entitlement to, the Compensation is contingent on the satisfaction of pre-established organizational or individual performance criteria relating to a performance period of at least 12 consecutive months. Organizational or individual performance criteria are considered pre-established if established in writing by not later than 90 days after the commencement of the period of service to which the criteria relate, provided that the outcome is substantially uncertain at the time the criteria are established. The determination of whether Compensation qualifies as "***Performance-Based Compensation***" will be made in accordance with Treas. Reg. Section 1.409A-1(e) and subsequent guidance.

2.31 Plan. Generally, the term Plan means the "***Horizon Pharma, Inc. Deferred Compensation Plan***" as documented herein and as may be amended from time to time hereafter. However, to the extent permitted or required under Code Section 409A, the term Plan may in the appropriate context also mean a portion of the Plan that is treated as a single plan under Treas. Reg. Section 1.409A-1(c), or the Plan or portion of the Plan and any other nonqualified deferred compensation plan or portion thereof that is treated as a single plan under such section.

2.32 Plan Year. Plan Year means January 1 through December 31; provided, however, the initial Plan Year shall be the period commencing on April 1, 2015 and ending on December 31, 2015.

2.33 Pre-2018 Deferrals. Pre-2018 Deferrals means all Deferrals and Company Contributions contributed to the Participant's Account that are contributions for Plan Years commencing prior to January 1, 2018 and any related earnings.

2.34 Post-2017 Deferrals. Post-2017 Deferrals means all Deferrals and Company Contributions contributed to the Participant's Account that are contributions for Plan Years commencing on or after January 1, 2018 and any related earnings.

2.35 Retirement/Termination Account. Retirement/Termination Account means an Account established by the Committee to record the amounts payable to a Participant upon Separation from Service. Unless the Participant has established a Specified Date Account, all Deferrals and Company Contributions shall be allocated to a Retirement/Termination Account on behalf of the Participant.

2.36 Separation from Service. With respect to an Employee a "***Separation from Service***" means an Employee's termination of service with the Employer. In all cases, whether a Separation from Service has occurred shall be determined by the Committee in accordance with Code Section 409A.

Except in the case of an Employee on a bona fide leave of absence as provided below, an Employee is deemed to have incurred a Separation from Service if the Employer and the Employee reasonably anticipated that the level of services to be performed by the Employee after a date certain, whether as an Employee or in a consulting capacity, would be reduced to 20% or less of the average services rendered by the Employee during the immediately preceding 36-month period (or the total period of employment, if less than 36 months), disregarding periods during which the Employee was on a bona fide leave of absence.

An Employee who is absent from work due to military leave, sick leave, or other bona fide leave of absence shall incur a Separation from Service on the first date immediately following the later of: (i) the six month anniversary of the commencement of the leave, or (ii) the expiration of the Employee's right, if any, to reemployment under statute or contract.

If a Participant is both a Director and an Employee, the services provided as a Director shall be disregarded in determining whether there has been a Separation from Service as an Employee , provided that the Plan is not required to be aggregated with any plans in which the Participant participates as a Director in accordance with the rules of Treasury Regulation Section 1.409A-1(c)(2)(ii).

For purposes of determining whether a Separation from Service has occurred, the Employer means the Employer as defined in Section 2.24 of the Plan, except that in applying Code sections 1563(a)(1), (2) and (3) for purposes of determining whether another organization is an Affiliate of the Company under Code Section 414(b), and in applying Treasury Regulation Section 1.414(c)-2 for purposes of determining whether another organization is an Affiliate of the Company under Code Section 414(c), "at least 50 percent" shall be used instead of "at least 80 percent" each place it appears in those sections.

The Committee specifically reserves the right to determine whether a sale or other disposition of substantial assets to an unrelated party constitutes a Separation from Service with respect to a Participant providing services to the seller immediately prior to the transaction and providing services to the buyer after the transaction. Such determination shall be made in accordance with the requirements of Code Section 409A.

2.37 Specified Date Account. Specified Date Account means an Account established by the Committee to record the amounts payable at a future date as specified in the Participant's Compensation Deferral Agreement. Unless otherwise determined by the Committee, a Participant may maintain no more than five Specified Date Accounts. A Specified Date Account may be identified in enrollment materials as an "***In-Service Account***" or such other name as established by the Committee without affecting the meaning thereof.

2.38 Specified Date Benefit. Specified Date Benefit means the benefit payable to a Participant under the Plan in accordance with Section 6.1(b).

2.39 Specified Employee. Specified Employee means an Employee who, as of the date of his or her Separation from Service, is a "key employee" of the Company or any Affiliate, any stock of which is actively traded on an established securities market or otherwise.

An Employee is a key employee if he or she meets the requirements of Code Section 416(i)(1)(A)(i), (ii), or (iii) (applied in accordance with applicable regulations thereunder and without regard to Code Section 416(i)(5)) at any time during the 12-month period ending on the Specified Employee Identification Date. Such Employee shall be treated as a key employee for the entire 12-month period beginning on the Specified Employee Effective Date.

For purposes of determining whether an Employee is a Specified Employee, the compensation of the Employee shall be determined in accordance with the definition of compensation provided under Treas. Reg. Section 1.415(c)-2(d)(2) (wages, salaries, fees for

professional services, and other amounts received for personal services actually rendered in the course of employment with the employer maintaining the plan, to the extent such amounts are includible in gross income or would be includible but for an election under section 125(a), 132(f)(4), 402(e)(3), 402(h)(1)(B), 402(k) or 457(b), including the earned income of a self-employed individual); provided, however, that, with respect to a nonresident alien who is not a Participant in the Plan, compensation shall not include compensation that is not includible in the gross income of the Employee under Code Sections 872, 893, 894, 911, 931 and 933, provided such compensation is not effectively connected with the conduct of a trade or business within the United States.

In the event of corporate transactions described in Treas. Reg. Section 1.409A-1(i)6), the identification of Specified Employees shall be determined in accordance with the default rules described therein, unless the Employer elects to utilize the available alternative methodology through designations made within the timeframes specified therein.

2.40 Specified Employee Identification Date. Specified Employee Identification Date means December 31st.

2.41 Specified Employee Effective Date. Specified Employee Effective Date means the first day of the fourth month following the Specified Employee Identification Date.

2.42 Substantial Risk of Forfeiture. Substantial Risk of Forfeiture means the description specified in Treas. Reg. Section 1.409A-1(d).

2.43 Termination Benefit. Termination Benefit means the benefit payable to a Participant under the Plan following the Participant's Separation from Service.

2.44 Unforeseeable Emergency. Unforeseeable Emergency means a severe financial hardship to the Participant resulting from an illness or accident of the Participant, the Participant's spouse, the Participant's dependent (as defined in Code section 152, without regard to section 152(b)(1), (b)(2), and (d)(1)(B)), or a Beneficiary; loss of the Participant's property due to casualty (including the need to rebuild a home following damage to a home not otherwise covered by insurance, for example, as a result of a natural disaster); or other similar extraordinary and unforeseeable circumstances arising as a result of events beyond the control of the Participant. The types of events which may qualify as an Unforeseeable Emergency may be limited by the Committee.

2.45 Valuation Date. Valuation Date means each Business Day.

2.46 Year of Service. Year of Service means each 12-month period of continuous service with the Employer.

ARTICLE 3
ELIGIBILITY AND PARTICIPATION

3.1 Eligibility and Participation. An Eligible Employee becomes a Participant upon the earlier to occur of: (i) a credit of Company Contributions under Article V, or (ii) receipt of notification of eligibility to participate.

3.2 Duration. A Participant shall be eligible to defer Compensation and receive allocations of Company Contributions, subject to the terms of the Plan, for as long as such Participant remains an Eligible Employee. A Participant who is no longer an Eligible Employee but has not Separated from Service may not defer Compensation under the Plan beyond the Plan Year in which he or she became ineligible but may otherwise exercise all of the rights of a Participant under the Plan with respect to his or her Account(s). On and after a Separation from Service, a Participant shall remain a Participant as long as his or her Account Balance is greater than zero (0), and during such time may continue to make allocation elections as provided in Section 8.4. An individual shall cease being a Participant in the Plan when all benefits under the Plan to which he or she is entitled have been paid.

ARTICLE 4
DEFERRALS

4.1 Deferral Elections, Generally.

(a) A Participant may elect to defer Compensation by submitting a Compensation Deferral Agreement during the enrollment periods established by the Committee and in the manner specified by the Committee, but in any event, in accordance with Section 4.2. A Compensation Deferral Agreement that is not timely filed with respect to a service period or component of Compensation shall be considered void and shall have no effect with respect to such service period or Compensation. The Committee may modify any Compensation Deferral Agreement prior to the date the election becomes irrevocable under the rules of Section 4.2.

(b) The Participant shall specify on his or her Compensation Deferral Agreement the amount of Deferrals and whether to allocate Deferrals to a Retirement/Termination Account or to a Specified Date Account. If no designation is made, Deferrals shall be allocated to the Retirement/Termination Account. A Participant may also specify in his or her Compensation Deferral Agreement the Payment Schedule applicable to his or her Plan Accounts. If the Payment Schedule is not specified in a Compensation Deferral Agreement, the Payment Schedule shall be the Payment Schedule specified in Section 6.2.

(c) For Pre-2018 Deferrals, Participants were permitted to contribute their aggregate Deferrals for all Plan Years to a single Retirement/Termination Account and up to a maximum of five (5) Specified Date Accounts. For Post-2017 Deferrals, with respect to each Plan year Participants may make different distribution elections in their Compensation Deferral Agreement for Deferrals elected to be contributed to their Retirement/Termination Account and/or Specified Date Account, such that each Plan Year may have a separate Retirement/Termination Account and/or Specified Date Account.

4.2 Timing Requirements for Compensation Deferral Agreements.

(a) First Year of Eligibility. In the case of the first year in which an Eligible Employee becomes eligible to participate in the Plan, he or she has up to 30 days following his or her initial eligibility to submit a Compensation Deferral Agreement with respect to Compensation to be earned during such year. The Compensation Deferral Agreement described in this paragraph becomes irrevocable upon the end of such 30-day period. The determination of

whether an Eligible Employee may file a Compensation Deferral Agreement under this paragraph shall be determined in accordance with the rules of Code Section 409A, including the provisions of Treas. Reg. Section 1.409A-2(a)(7).

A Compensation Deferral Agreement filed under this paragraph applies only to Compensation earned on and after the date the Compensation Deferral Agreement becomes irrevocable.

(b) Prior Year Election. Except as otherwise provided in this Section 4.2, Participants may defer Compensation by filing a Compensation Deferral Agreement no later than December 31 of the year prior to the year in which the Compensation to be deferred is earned. A Compensation Deferral Agreement described in this paragraph shall become irrevocable with respect to such Compensation as of December 31 of the year prior to the year in which the Compensation to be deferred is earned.

(c) Performance-Based Compensation. Participants may file a Compensation Deferral Agreement with respect to Performance-Based Compensation no later than the date that is six months before the end of the performance period, provided that:

(i) the Participant performs services continuously from the later of the beginning of the performance period or the date the criteria are established through the date the Compensation Deferral Agreement is submitted and becomes irrevocable; and

(ii) the Compensation is not readily ascertainable as of the date the Compensation Deferral Agreement is filed.

A Compensation Deferral Agreement becomes irrevocable with respect to Performance-Based Compensation as of the latest date for filing such election. Any election to defer Performance-Based Compensation that is made in accordance with this paragraph and that becomes payable as a result of the Participant's death or disability (as defined in Treas. Reg. Section 1.409A-1(e)) or upon a Change in Control (as defined in Treas. Reg. Section 1.409A-3(i)(5)) prior to the satisfaction of the performance criteria, will be void.

(d) Fiscal Year Compensation. A Participant may defer Fiscal Year Compensation by filing a Compensation Deferral Agreement prior to the first day of the fiscal year or years in which such Fiscal Year Compensation is earned. The Compensation Deferral Agreement described in this paragraph becomes irrevocable on the date immediately preceding the first day of the fiscal year or years to which it applies.

(e) Short-Term Deferrals. Compensation that meets the definition of a "short-term deferral" described in Treas. Reg. Section 1.409A-1(b)(4) may be deferred in accordance with the rules of Article VII, applied as if the date the Substantial Risk of Forfeiture lapses is the date payments were originally scheduled to commence, provided, however, that the provisions of Section 7.3 shall not apply to payments attributable to a Change in Control (as defined in Treas. Reg. Section 1.409A-3(i)(5)).

(f) Certain Forfeitable Rights. With respect to a legally binding right to a payment in a subsequent year that is subject to a forfeiture condition requiring the Participant's

continued services for a period of at least 12 months from the date the Participant obtains the legally binding right, an election to defer such Compensation may be made on or before the 30th day after the Participant obtains the legally binding right to the Compensation, provided that the election is made at least 12 months in advance of the earliest date at which the forfeiture condition could lapse. The Compensation Deferral Agreement described in this paragraph becomes irrevocable upon such 30th day. If the forfeiture condition applicable to the payment lapses before the end of the required service period as a result of the Participant's death or disability (as defined in Treas. Reg. Section 1.409A-3(i)(4)) or upon a Change in Control (as defined in Treas. Reg. Section 1.409A-3(i)(5)), the Compensation Deferral Agreement will be void unless it would be considered timely under another rule described in this Section.

(g) Company Awards. Participating Employers may unilaterally provide for deferrals of Company awards prior to the date of such awards. Deferrals of Company awards (such as sign-on, retention, or severance pay) may be negotiated with a Participant prior to the date the Participant has a legally binding right to such Compensation.

(h) "Evergreen" Deferral Elections.

(i) The Committee, in its discretion, may provide in the Compensation Deferral Agreement that such Compensation Deferral Agreement will continue in effect for each subsequent year or performance period. Such "evergreen" Compensation Deferral Agreements will become effective with respect to an item of Compensation on the date such election becomes irrevocable under this Section 4.2. An evergreen Compensation Deferral Agreement may be terminated or modified prospectively with respect to Compensation for which such election remains revocable under this Section 4.2. A Participant whose Compensation Deferral Agreement is cancelled in accordance with Section 4.6 will be required to file a new Compensation Deferral Agreement under this Article IV in order to recommence Deferrals under the Plan.

(ii) With respect to Pre-2018 Deferrals, "evergreen" Compensation Deferral Agreements were in effect. Commencing with Post-2017 Deferrals, "evergreen" elections do not apply, unless otherwise set forth in the Compensation Deferral Agreement.

4.3 Allocation of Deferrals. A Compensation Deferral Agreement may allocate Deferrals to one or more Specified Date Accounts and/or to the Retirement/Termination Account. The Committee may, in its discretion, establish a minimum deferral period for the establishment of a Specified Date Account (for example, the third Plan Year following the year Compensation is allocated to such accounts.).

4.4 Deductions from Pay. The Committee has the authority to determine the payroll practices under which any component of Compensation subject to a Compensation Deferral Agreement will be deducted from a Participant's Compensation.

4.5 Vesting. Participant Deferrals shall be 100% vested at all times.

4.6 Cancellation of Deferrals. The Committee may cancel a Participant's Deferrals: (i) for the balance of the Plan Year in which an Unforeseeable Emergency occurs, (ii) if the Participant receives a hardship distribution under the Employer's qualified 401(k) plan, through

the end of the Plan Year in which the six month anniversary of the hardship distribution falls, and (iii) during periods in which the Participant is unable to perform the duties of his or her position or any substantially similar position due to a mental or physical impairment that can be expected to result in death or last for a continuous period of at least six months, provided cancellation occurs by the later of the end of the taxable year of the Participant or the 15th day of the third month following the date the Participant incurs the disability (as defined in this paragraph (iii)).

ARTICLE 5
COMPANY CONTRIBUTIONS

5.1 Discretionary Company Contributions. The Participating Employer may, from time to time in its sole and absolute discretion, credit discretionary Company Contributions to any Participant in any amount determined by the Participating Employer. Such contributions will be credited to a Participant's Retirement/Termination Account.

5.2 Matching Company Contributions. The Participating Employer may, from time to time in its sole and absolute discretion, credit matching Company Contributions to the Accounts of Participants in any amount determined by the Participating Employer. Such contributions will be credited to a Participant's Retirement/Termination Account.

5.3 Vesting. Discretionary Company Contributions described in Section 5.1, above, and the Earnings thereon, shall vest in accordance with the vesting schedule(s) established by the Committee at the time that the Company Contribution is made. Unless otherwise determined by the Company at the time such Matching Company Contributions are approved, any Matching Company Contributions described in Section 5.2 above, and the Earnings thereon, shall vest in accordance with the vesting schedule applicable to matching contributions under the Participating Employer's qualified 401(k) plan. All Company Contributions shall become 100% vested upon the occurrence of the earliest of: (i) the death of the Participant while actively employed, (ii) the Participant's disability as determined under a disability plan of the Participating Employer, or applying the disability definition under such plan if the Participant is not covered by such plan, or (iii) a Change in Control. The Participating Employer may, at any time, in its sole discretion, increase a Participant's vested interest in a Company Contribution. The portion of a Participant's Accounts that remains unvested upon his or her Separation from Service after the application of the terms of this Section 5.3 shall be immediately forfeited.

5.4 Safe Harbor Matching Contributions. Commencing January 1, 2017 the Participating Employer shall credit matching Company Contributions to Participant Accounts as provided in this Section 5.4 (the "***Safe Harbor Matching Contributions***"). With respect to each Participant, the Safe Harbor Matching Contributions will be equal to 100% of the Participant's Deferrals up to the first 3% of such Participant's Compensation plus 50% of the Participant's Deferrals between 3% and 5% of the Participant's Compensation. Any Safe Harbor Matching contributions will be credited to the Participant's Retirement/Termination Account no later than ninety (90) days following the end of the Plan Year for which the Participant Deferrals were made. Safe Harbor Matching Contributions will vest 20% on each anniversary of the Participant's date of hire so that the Participant is 100% vested in all Safe Harbor Matching Contributions on the fifth anniversary of the Participant's date of hire with the Participating

Employer, subject to the Participant's continued employment with the Participating Employer through the applicable vesting dates. All Safe Harbor Matching Contributions shall become 100% vested upon the occurrence of the earliest of: (i) the death of the Participant while actively employed, (ii) the Participant's disability as determined under a disability plan of the Participating Employer, or applying the disability definition under such plan if the Participant is not covered by such plan, a (iii) Change in Control, or (iv) the Participant attaining age 65. The Participating Employer may, at any time, in its sole discretion, increase a Participant's vested interest in a Safe Harbor Matching Contribution. The portion of a Participant's Accounts that remains unvested upon his or her Separation from Service after the application of the terms of this Section 5.4 shall be forfeited.

ARTICLE 6
BENEFITS

6.1 Benefits, Generally. A Participant shall be entitled to the following benefits under the Plan:

(a) Termination Benefit. Upon the Participant's Separation from Service for reasons other than death, he or she shall be entitled to a Termination Benefit. The Termination Benefit shall be equal to the vested portion of the Retirement/Termination Account and, if the Participant Separates from Service prior to the year payments from a Specified Date Account are scheduled to commence, the vested balances of any such Specified Date Accounts. Payment of the Termination Benefit will be made as follows:

(i) If the Participant Separates from Service on or before June 30th of a calendar year, payment of the Termination Benefit will begin on January 1st of the calendar year immediately following the calendar year in which Separation from Service occurs.

(ii) If the Participant Separates from Service on or after July 1st of a calendar year, payment of the Termination Benefit will begin on July 1st of the calendar year immediately following the calendar year in which Separation from Service occurs.

(iii) If any part of the Termination Benefit is to be paid in the form of installments, the timing of such payments shall be made as provided in Section 6.2(d).

(b) Specified Date Benefit. If the Participant has established one or more Specified Date Accounts, he or she shall be entitled to a Specified Date Benefit with respect to each such Specified Date Account. The Specified Date Benefit shall be equal to the vested portion of the Specified Date Account. Payment of the Specified Date Benefit will be made or begin in January of the year designated by the Participant; provided, however, that if a Participant Separates from Service prior to the year designated, payment will be instead made in accordance with the most recent Participant payment election applicable to the Retirement/Termination Account as provided further in Section 6.2(c)

(c) Death Benefit. In the event of the Participant's death, his or her designated Beneficiary(ies) shall be entitled to a Death Benefit. The Death Benefit shall be equal

to the vested portion of the Retirement/Termination Account and the unpaid balances of any Specified Date Accounts, with such payment made as soon as practicable following the Participant's death, but in no event later than December 31st of the calendar year following the calendar year that includes the Participant's death.

(d) Change in Control. A Participant will receive his or her Account Balances in a single lump sum payment equal to the unpaid balance of all of his or her Accounts within ninety (90) days following a Change in Control; provided, however, that with respect to any Participant who is a Specified Employee and who had a Separation from Service prior to the date of the Change in Control, such payment shall not be made until after expiration of the six month period following the date he or she Separates from Service, if later, to the extent necessary to avoid adverse tax consequences to such Participant under Section 409A.

(e) Unforeseeable Emergency Payments. A Participant who experiences an Unforeseeable Emergency may submit a written request to the Committee to receive payment of all or any portion of his or her vested Accounts. Whether a Participant or Beneficiary is faced with an Unforeseeable Emergency permitting an emergency payment shall be determined by the Committee based on the relevant facts and circumstances of each case, but, in any case, a distribution on account of Unforeseeable Emergency may not be made to the extent that such emergency is or may be reimbursed through insurance or otherwise, by liquidation of the Participant's assets, to the extent the liquidation of such assets would not cause severe financial hardship, or by cessation of Deferrals under this Plan. If an emergency payment is approved by the Committee, the amount of the payment shall not exceed the amount reasonably necessary to satisfy the need, taking into account the additional compensation that is available to the Participant as the result of cancellation of deferrals to the Plan, including amounts necessary to pay any taxes or penalties that the Participant reasonably anticipates will result from the payment. The amount of the emergency payment shall be subtracted first from the vested portion of the Participant's Retirement/Termination Account until depleted and then from the vested Specified Date Accounts, beginning with the Specified Date Account with the latest payment commencement date. Emergency payments shall be paid in a single lump sum within the 90-day period following the date the payment is approved by the Committee.

6.2 Form of Payment.

(a) Pre-2018 Deferrals Termination Benefit. A Participant who is entitled to receive a Termination Benefit with respect to Pre-2018 Deferrals shall receive payment of such benefit in a single lump sum, unless the Participant elects on his or her initial Compensation Deferral Agreement to have such benefit paid in one of the following alternative forms of payment (i) substantially equal annual installments over a period of two to twenty years, as elected by the Participant, or (ii) a lump sum payment of a percentage of the balance in the Retirement/Termination Account, with the balance paid in substantially equal annual installments over a period of two to twenty years, as elected by the Participant. Such payments will be made at the time specified in Section 6.1(a).

(b) Post-2017 Deferrals Termination Benefit. A Participant who is entitled to receive a Termination Benefit with respect to Post-2017 Deferrals shall receive payment of such benefit in a single lump sum, unless the Participant elects to have such benefit paid in

substantially equal annual installments over a period of two to ten years, as elected by the Participant. A Participant may make different payment elections for Deferrals for separate Plan Years with respect to the Termination Benefit. Such payments will be made at the time specified in Section 6.1(a).

(c) Specified Date Benefit. The Specified Date Benefit shall be paid in a single lump sum, unless the Participant elects on the Compensation Deferral Agreement with which the account was established to have the Specified Date Account paid in substantially equal annual installments over a period of two to ten years, as elected by the Participant, and such payments will be made at the time specified in Section 6.1(b); provided, however, that if a Participant Separates from Service prior to the year designated for commencement of payment(s) from a Specified Date Account, such Account will be distributed in accordance with the election applicable to the most recently effective Participant form of distribution election made for the Retirement/Termination Account pursuant to Section 6.2(b) and will instead be paid at the time specified in Section 6.1(a).

(d) Rules Applicable to Installment Payments. If a Payment Schedule specifies installment payments (without any lump sum percentage), the first installment payment shall be made on the applicable payment commencement date and subsequent installment payments shall be made on each subsequent January until the number of installment payments specified in the Payment Schedule has been paid. If a lump sum equal to less than 100% of the Retirement/Termination Account is elected (with respect to Pre-2018 Deferrals), the lump sum amount will be paid on the payment commencement date and the payment date for the first installment form of payment will be January of the following calendar year, with any subsequent installment payments to continue on each subsequent January until the number of installment payments specified in the Payment Schedule has been paid. In cases, the amount of each installment payment shall be determined by dividing (a) by (b), where (a) equals the Account Balance at the time of payment and (b) equals the remaining number of installment payments. For purposes of Article VII, installment payments will be treated as a single form of payment.

(e) Death Benefit. A designated Beneficiary who is entitled to receive a Death Benefit shall receive payment of such benefit in a single lump sum at the time specified in Section 6.1(c).

(f) Change in Control. In the event of a Change in Control each Participant will receive the value of his or her entire Account Balances in a single lump sum payment. Such payment will be made at the time specified in Section 6.1(d).

(g) Small Account Balances. The Committee shall pay the value of the entire Participant's Account Balance in a single lump sum if the Participant's entire Account Balance, including any Specified Date Account balances, at Separation from Service is less than $50,000, which payment will be made at the time specified in Section 6.1(a), as applicable. Further, the Committee may direct that all of a Participant's Account Balances will be distributed in a single lump sum if the Account Balances are not greater than the applicable dollar amount under Code Section 402(g)(1)(B), provided the payment represents the complete liquidation of the Participant's interest in the Plan.

6.3 Administrative Discretion with Regard to Timing of Payments. Notwithstanding anything to the contrary in this Article VI, the Committee may make a payment at the time specified in the preceding paragraphs or at a later date that falls in the same calendar year as the specified time or, if later, by the 15th day of the third calendar month following the time specified, provided the Participant is not permitted, directly or indirectly, to designate the taxable year in which payment will be made. Further, except as necessary so that no Termination Benefit is payable within the six month period following any Separation From Service of a Specified Employee, the Committee may make a payment up to 30 days preceding the time specified in the preceding paragraphs, provided the Participant is not permitted, directly or indirectly, to designate the taxable year in which the payment will be made.

6.4 Acceleration of or Delay in Payments. The Committee, in its sole and absolute discretion, may elect to accelerate the time or form of payment of a benefit owed to the Participant hereunder, provided such acceleration is permitted under Treas. Reg. Section 1.409A-3(j)(4) and explicitly reserves the right to make such election. The Committee may also, in its sole and absolute discretion, delay the time for payment of a benefit owed to the Participant hereunder, to the extent permitted under Treas. Reg. Section 1.409A-2(b)(7). If the Plan receives a domestic relations order (within the meaning of Code Section 414(p)(1)(B)) directing that all or a portion of a Participant's Accounts be paid to an "alternate payee," any amounts to be paid to the alternate payee(s) shall be paid in a single lump sum.

6.5 Designation of Beneficiaries.

(a) In General. The Participant shall designate a Beneficiary on the forms provided by the Committee or on such terms and conditions as the Committee may prescribe. No such designation shall become effective unless filed with the Committee during the Participant's lifetime. Any designation shall remain in effect until a new designation is filed with the Committee; provided, however, that in the event a Participant designates his or her spouse as a Beneficiary, such designation shall be automatically revoked upon the dissolution of the marriage unless, following such dissolution, the Participant submits a new designation naming the former spouse as a Beneficiary. A Participant may from time to time change his or her designated Beneficiary without the consent of a previously-designated Beneficiary by filing a new designation with the Committee.

(b) No Beneficiary. If a designated Beneficiary does not survive the Participant, or if there is no valid Beneficiary designation, amounts payable under the Plan upon the death of the Participant shall be paid to the Participant's spouse, or if there is no surviving spouse, then to the duly appointed and currently acting personal representative of the Participant's estate.

ARTICLE 7
MODIFICATIONS TO PAYMENT SCHEDULES

7.1 Participant's Right to Modify. A Participant may modify the Payment Schedules applicable to a Specified Date Account, consistent with the permissible Payment Schedules available under the Plan, provided such modification complies with the requirements of this Article VII. No modifications may be made to Payment Schedules for a Participant's Retirement/Termination Account.

7.2 Time of Election. The date on which a modification election is submitted to the Committee must be at least 12 months prior to the date on which payment is scheduled to commence under the Payment Schedule in effect prior to the modification.

7.3 Date of Payment under Modified Payment Schedule. The date payments are to commence under the modified Payment Schedule must be no earlier than five years after the date payment would have commenced under the original Payment Schedule. Under no circumstances may a modification election result in an acceleration of payments in violation of Code Section 409A.

7.4 Effective Date. A modification election submitted in accordance with this Article VII is irrevocable upon receipt by the Committee and becomes effective 12 months after such date.

7.5 Effect on Accounts. An election to modify a Payment Schedule is specific to the Account or payment event to which it applies, and shall not be construed to affect the Payment Schedules of any other Accounts.

ARTICLE 8
VALUATION OF ACCOUNT BALANCES; INVESTMENTS

8.1 Valuation. Deferrals shall be credited to appropriate Accounts on the date such Compensation would have been paid to the Participant absent the Compensation Deferral Agreement. Company Contributions shall be credited to the Retirement/Termination Account at the times determined by the Committee. Valuation of Accounts shall be performed under procedures approved by the Committee.

8.2 Earnings Credit. Each Account will be credited with Earnings on each Business Day, based upon the Participant's investment allocation among a menu of investment options selected in advance by the Committee, in accordance with the provisions of this Article VIII ("investment allocation").

8.3 Investment Options. Investment options will be determined by the Committee. The Committee, in its sole discretion, shall be permitted to add or remove investment options from the Plan menu from time to time, provided that any such additions or removals of investment options shall not be effective with respect to any period prior to the effective date of such change.

8.4 Investment Allocations. A Participant's investment allocation constitutes a deemed, not actual, investment among the investment options comprising the investment menu. At no time shall a Participant have any real or beneficial ownership in any investment option included in the investment menu, nor shall the Participating Employer or any trustee acting on its behalf have any obligation to purchase actual securities as a result of a Participant's investment allocation. A Participant's investment allocation shall be used solely for purposes of adjusting the value of a Participant's Account Balances.

A Participant shall specify an investment allocation for each of his Accounts in accordance with procedures established by the Committee. Allocation among the investment options must be designated in increments of 1%. The Participant's investment allocation will become effective on the same Business Day or, in the case of investment allocations received after a time specified by the Committee, the next Business Day.

A Participant may change an investment allocation on any Business Day, both with respect to future credits to the Plan and with respect to existing Account Balances, in accordance with procedures adopted by the Committee. Changes shall become effective on the same Business Day or, in the case of investment allocations received after a time specified by the Committee, the next Business Day, and shall be applied prospectively.

8.5 Unallocated Deferrals and Accounts. If the Participant fails to make an investment allocation with respect to an Account, such Account shall be invested in an investment option, the primary objective of which is the preservation of capital, as determined by the Committee.

8.6 Company Stock. The Committee may include Company Stock as one of the investment options described in Section 8.3. The Committee may, in its sole discretion, limit the investment allocation of Company Contributions to Company Stock. The Committee may also require Deferrals consisting of equity-based Compensation to be allocated to Company Stock.

8.7 Diversification. A Participant may not re-allocate an investment in Company Stock into another investment option. The portion of an Account that is invested in Company Stock will be paid under Article VI in the form of whole shares of Company Stock.

8.8 Effect on Installment Payments. If an Account is to be paid in installments, the Committee will determine the portion of each payment that will be paid in the form of Company Stock.

8.9 Dividend Equivalents. Dividend equivalents with respect to Company Stock will be credited to the applicable Accounts in the form of additional shares or units of Company Stock.

ARTICLE 9
ADMINISTRATION

9.1 Plan Administration. This Plan shall be administered by the Committee which shall have discretionary authority to make, amend, interpret and enforce all appropriate rules and regulations for the administration of this Plan and to utilize its discretion to decide or resolve any and all questions, including but not limited to eligibility for benefits and interpretations of this Plan and its terms, as may arise in connection with the Plan. Claims for benefits shall be filed with the Committee and resolved in accordance with the claims procedures in Article XII.

9.2 Administration Upon Change in Control. Upon a Change in Control, the Committee, as constituted immediately prior to such Change in Control, shall continue to act as the Committee. The individual who was the Chief Executive Officer of the Company Parent (or if such person is unable or unwilling to act, the next highest ranking officer) prior to the Change in Control shall have the authority (but shall not be obligated) to appoint an independent third party to act as the Committee.

Upon such Change in Control, the Company may not remove the Committee, unless 2/3rds of the members of the Board of Directors of the Company Parent and a majority of Participants and Beneficiaries with Account Balances consent to the removal and replacement of the Committee. Notwithstanding the foregoing, neither the Committee nor the officer described above shall have authority to direct investment of trust assets under any rabbi trust described in Section 11.2.

The Participating Employer shall, with respect to the Committee identified under this Section: (i) pay all reasonable expenses and fees of the Committee, (ii) indemnify the Committee (including individuals serving as Committee members) against any costs, expenses and liabilities including, without limitation, attorneys' fees and expenses arising in connection with the performance of the Committee's duties hereunder, except with respect to matters resulting from the Committee's gross negligence or willful misconduct, and (iii) supply full and timely information to the Committee on all matters related to the Plan, any rabbi trust, Participants, Beneficiaries and Accounts as the Committee may reasonably require.

9.3 Withholding. The Participating Employer shall have the right to withhold from any payment due under the Plan (or with respect to any amounts credited to the Plan) any taxes required by law to be withheld in respect of such payment (or credit). Withholdings with respect to amounts credited to the Plan shall be deducted from Compensation that has not been deferred to the Plan.

9.4 Indemnification. The Participating Employers shall indemnify and hold harmless each employee, officer, director, agent or organization, to whom or to which are delegated duties, responsibilities, and authority under the Plan or otherwise with respect to administration of the Plan, including, without limitation, the Committee and its agents, against all claims, liabilities, fines and penalties, and all expenses reasonably incurred by or imposed upon him or it (including but not limited to reasonable attorney fees) which arise as a result of his or its actions or failure to act in connection with the operation and administration of the Plan to the extent lawfully allowable and to the extent that such claim, liability, fine, penalty, or expense is not paid for by liability insurance purchased or paid for by the Participating Employer. Notwithstanding the foregoing, the Participating Employer shall not indemnify any person or organization if his or its actions or failure to act are due to gross negligence or willful misconduct or for any such amount incurred through any settlement or compromise of any action unless the Participating Employer consents in writing to such settlement or compromise.

9.5 Delegation of Authority. In the administration of this Plan, the Committee may, from time to time, employ agents and delegate to them such administrative duties as it sees fit, and may from time to time consult with legal counsel who shall be legal counsel to the Company and/or the Company Parent.

9.6 Binding Decisions or Actions. The decision or action of the Committee in respect of any question arising out of or in connection with the administration, interpretation and

application of the Plan and the rules and regulations thereunder shall be final and conclusive and binding upon all persons having any interest in the Plan.

ARTICLE 10
AMENDMENT AND TERMINATION

10.1 Amendment and Termination. The Company may at any time and from time to time amend the Plan or may terminate the Plan as provided in this Article X. Each Participating Employer may also terminate its participation in the Plan.

10.2 Amendments. The Company, by action taken by the Board of Directors of the Company Parent, may amend the Plan at any time and for any reason, provided that any such amendment shall not reduce the vested Account Balances of any Participant accrued as of the date of any such amendment or restatement (as if the Participant had incurred a voluntary Separation from Service on such date) or reduce any rights of a Participant under the Plan or other Plan features with respect to Deferrals made prior to the date of any such amendment or restatement without the consent of the Participant. The Compensation Committee of the Board of Directors of the Company Parent has the authority to amend the Plan without the consent of the Board of Directors of the Company Parent for the purpose of: (i) conforming the Plan to the requirements of law; (ii) facilitating the administration of the Plan; (iii) clarifying provisions based on the Committee's interpretation of the document; and (iv) making such other amendments as the Board of Directors of the Company Parent may authorize.

10.3 Termination. The Company, by action taken by the Board of Directors of the Company Parent, may terminate the Plan and pay Participants and Beneficiaries their Account Balances in a single lump sum at any time, to the extent and in accordance with Treas. Reg. Section 1.409A-3(j)(4)(ix). If a Participating Employer terminates its participation in the Plan, the benefits of affected Employees shall be paid at the time provided in Article VI.

10.4 Accounts Taxable Under Code Section 409A. The Plan is intended to constitute a plan of deferred compensation that meets the requirements for deferral of income taxation under Code Section 409A. The Committee, pursuant to its authority to interpret the Plan, may sever from the Plan or any Compensation Deferral Agreement any provision or exercise of a right that otherwise would result in a violation of Code Section 409A.

ARTICLE 11
INFORMAL FUNDING

11.1 General Assets. Obligations established under the terms of the Plan may be satisfied from the general funds of the Participating Employers, or a trust described in this Article XI. No Participant, spouse or Beneficiary shall have any right, title or interest whatever in assets of the Participating Employers. Nothing contained in this Plan, and no action taken pursuant to its provisions, shall create or be construed to create a trust of any kind, or a fiduciary relationship, between the Participating Employers and any Employee, spouse, or Beneficiary. To the extent that any person acquires a right to receive payments hereunder, such rights are no greater than the right of an unsecured general creditor of the Participating Employer.

11.2 Rabbi Trust. A Participating Employer may, in its sole discretion, establish a grantor trust, commonly known as a rabbi trust, as a vehicle for accumulating assets to pay benefits under the Plan. Payments under the Plan may be paid from the general assets of the Participating Employer or from the assets of any such rabbi trust. Payment from any such source shall reduce the obligation owed to the Participant or Beneficiary under the Plan.

ARTICLE 12
CLAIMS

12.1 Filing a Claim. Any controversy or claim arising out of or relating to the Plan shall be filed in writing with the Committee which shall make all determinations concerning such claim. Any claim filed with the Committee and any decision by the Committee denying such claim shall be in writing and shall be delivered to the Participant or Beneficiary filing the claim (the "***Claimant***").

(a) ***In General.*** Notice of a denial of benefits (other than Disability benefits) will be provided within 90 days of the Committee's receipt of the Claimant's claim for benefits. If the Committee determines that it needs additional time to review the claim, the Committee will provide the Claimant with a notice of the extension before the end of the initial 90-day period. The extension will not be more than 90 days from the end of the initial 90-day period and the notice of extension will explain the special circumstances that require the extension and the date by which the Committee expects to make a decision.

(b) Disability Benefits. Notice of denial of Disability benefits will be provided within forty-five (45) days of the Committee's receipt of the Claimant's claim for Disability benefits. If the Committee determines that it needs additional time to review the Disability claim, the Committee will provide the Claimant with a notice of the extension before the end of the initial 45-day period. If the Committee determines that a decision cannot be made within the first extension period due to matters beyond the control of the Committee, the time period for making a determination may be further extended for an additional 30 days. If such an additional extension is necessary, the Committee shall notify the Claimant prior to the expiration of the initial 30-day extension. Any notice of extension shall indicate the circumstances necessitating the extension of time, the date by which the Committee expects to furnish a notice of decision, the specific standards on which such entitlement to a benefit is based, the unresolved issues that prevent a decision on the claim and any additional information needed to resolve those issues. A Claimant will be provided a minimum of 45 days to submit any necessary additional information to the Committee. In the event that a 30-day extension is necessary due to a Claimant's failure to submit information necessary to decide a claim, the period for furnishing a notice of decision shall be tolled from the date on which the notice of the extension is sent to the Claimant until the earlier of the date the Claimant responds to the request for additional information or the response deadline.

(c) Contents of Notice. If a claim for benefits is completely or partially denied, notice of such denial shall be in writing and shall set forth the reasons for denial in plain language. The notice shall: (i) cite the pertinent provisions of the Plan document, and (ii) explain, where appropriate, how the Claimant can perfect the claim, including a description of any additional material or information necessary to complete the claim and why such material or

information is necessary. The claim denial also shall include an explanation of the claims review procedures and the time limits applicable to such procedures, including a statement of the Claimant's right to bring a civil action under Section 502(a) of ERISA following an adverse decision on review. In the case of a complete or partial denial of a Disability benefit claim, the notice shall provide a statement that the Committee will provide to the Claimant, upon request and free of charge, a copy of any internal rule, guideline, protocol, or other similar criterion that was relied upon in making the decision.

12.2 Appeal of Denied Claims. A Claimant whose claim has been completely or partially denied shall be entitled to appeal the claim denial by filing a written appeal with a committee designated to hear such appeals (the "***Appeals Committee***"). In the absence of any such designation, the Appeals Committee shall be the Committee. A Claimant who timely requests a review of the denied claim (or his or her authorized representative) may review, upon request and free of charge, copies of all documents, records and other information relevant to the denial and may submit written comments, documents, records and other information relevant to the claim to the Appeals Committee. All written comments, documents, records, and other information shall be considered "relevant" if the information: (i) was relied upon in making a benefits determination, (ii) was submitted, considered or generated in the course of making a benefits decision regardless of whether it was relied upon to make the decision, or (iii) demonstrates compliance with administrative processes and safeguards established for making benefit decisions. The Appeals Committee may, in its sole discretion and if it deems appropriate or necessary, decide to hold a hearing with respect to the claim appeal.

(a) In General. Appeal of a denied benefits claim (other than a Disability benefits claim) must be filed in writing with the Appeals Committee no later than 60 days after receipt of the written notification of such claim denial. The Appeals Committee shall make its decision regarding the merits of the denied claim within 60 days following receipt of the appeal (or within 120 days after such receipt, in a case where there are special circumstances requiring extension of time for reviewing the appealed claim). If an extension of time for reviewing the appeal is required because of special circumstances, written notice of the extension shall be furnished to the Claimant prior to the commencement of the extension. The notice will indicate the special circumstances requiring the extension of time and the date by which the Appeals Committee expects to render the determination on review. The review will take into account comments, documents, records and other information submitted by the Claimant relating to the claim without regard to whether such information was submitted or considered in the initial benefit determination.

(b) Disability Benefits. Appeal of a denied Disability benefits claim must be filed in writing with the Appeals Committee no later than 180 days after receipt of the written notification of such claim denial. The review shall be conducted by the Appeals Committee (exclusive of the person who made the initial adverse decision or such person's subordinate). In reviewing the appeal, the Appeals Committee shall: (i) not afford deference to the initial denial of the claim, (ii) consult a medical professional who has appropriate training and experience in the field of medicine relating to the Claimant's disability and who was neither consulted as part of the initial denial nor is the subordinate of such individual, and (iii) identify the medical or vocational experts whose advice was obtained with respect to the initial benefit denial, without regard to whether the advice was relied upon in making the decision. The Appeals Committee

shall make its decision regarding the merits of the denied claim within 45 days following receipt of the appeal (or within 90 days after such receipt, in a case where there are special circumstances requiring extension of time for reviewing the appealed claim). If an extension of time for reviewing the appeal is required because of special circumstances, written notice of the extension shall be furnished to the Claimant prior to the commencement of the extension. The notice will indicate the special circumstances requiring the extension of time and the date by which the Appeals Committee expects to render the determination on review. Following its review of any additional information submitted by the Claimant, the Appeals Committee shall render a decision on its review of the denied claim.

(c) Contents of Notice. If a benefits claim is completely or partially denied on review, notice of such denial shall be in writing and shall set forth the reasons for denial in plain language.

The decision on review shall set forth: (i) the specific reason or reasons for the denial, (ii) specific references to the pertinent Plan provisions on which the denial is based, (iii) a statement that the Claimant is entitled to receive, upon request and free of charge, reasonable access to and copies of all documents, records, or other information relevant (as defined above) to the Claimant's claim, and (iv) a statement describing any voluntary appeal procedures offered by the plan and a statement of the Claimant's right to bring an action under Section 502(a) of ERISA.

(d) For the denial of a Disability benefit, the notice will also include a statement that the Appeals Committee will provide, upon request and free of charge: (i) any internal rule, guideline, protocol or other similar criterion relied upon in making the decision, (ii) any medical opinion relied upon to make the decision, and (iii) the required statement under Section 2560.503-1(j)(5)(iii) of the Department of Labor regulations.

12.3 Claims Appeals Upon Change in Control. Upon a Change in Control, the Appeals Committee, as constituted immediately prior to such Change in Control, shall continue to act as the Appeals Committee. Upon such Change in Control, the Company may not remove any member of the Appeals Committee, but may replace resigning members if 2/3rds of the members of the Board of Directors of the Company Parent and a majority of Participants and Beneficiaries with Account Balances consent to the replacement.

The Appeals Committee shall have the exclusive authority at the appeals stage to interpret the terms of the Plan and resolve appeals under the Claims Procedure.

Each Participating Employer shall, with respect to the Committee identified under this Section: (i) pay its proportionate share of all reasonable expenses and fees of the Appeals Committee, (ii) indemnify the Appeals Committee (including individual committee members) against any costs, expenses and liabilities including, without limitation, attorneys' fees and expenses arising in connection with the performance of the Appeals Committee hereunder, except with respect to matters resulting from the Appeals Committee's gross negligence or willful misconduct, and (iii) supply full and timely information to the Appeals Committee on all matters related to the Plan, any rabbi trust, Participants, Beneficiaries and Accounts as the Appeals Committee may reasonably require.

12.4 Legal Action. A Claimant may not bring any legal action relating to a claim for benefits under the Plan unless and until the Claimant has followed the claims procedures under the Plan and exhausted his or her administrative remedies under such claims procedures.

If a Participant or Beneficiary prevails in a legal proceeding brought under the Plan to enforce the rights of such Participant or any other similarly situated Participant or Beneficiary, in whole or in part, the Participating Employer shall reimburse such Participant or Beneficiary for all legal costs, expenses, attorneys' fees and such other liabilities incurred as a result of such proceedings. If the legal proceeding is brought in connection with a Change in Control, or a "change in control" as defined in a rabbi trust described in Section 11.2, the Participant or Beneficiary may file a claim directly with the trustee for reimbursement of such costs, expenses and fees. For purposes of the preceding sentence, the amount of the claim shall be treated as if it were an addition to the Participant's or Beneficiary's Account Balance.

12.5 Discretion of Appeals Committee. All interpretations, determinations and decisions of the Appeals Committee with respect to any claim shall be made in its sole discretion, and shall be final and conclusive.

ARTICLE 13
GENERAL PROVISIONS

13.1 Assignment. No interest of any Participant, spouse or Beneficiary under this Plan and no benefit payable hereunder shall be assigned as security for a loan, and any such purported assignment shall be null, void and of no effect, nor shall any such interest or any such benefit be subject in any manner, either voluntarily or involuntarily, to anticipation, sale, transfer, assignment or encumbrance by or through any Participant, spouse or Beneficiary. Notwithstanding anything to the contrary herein, however, the Committee has the discretion to make payments to an alternate payee in accordance with the terms of a domestic relations order (as defined in Code Section 414(p)(1)(B)).

The Company may assign any or all of its liabilities under this Plan in connection with any restructuring, recapitalization, sale of assets or other similar transactions affecting a Participating Employer without the consent of the Participant.

13.2 No Legal or Equitable Rights or Interest. No Participant or other person shall have any legal or equitable rights or interest in this Plan that are not expressly granted in this Plan. Participation in this Plan does not give any person any right to be retained in the service of the Participating Employer. The right and power of a Participating Employer to dismiss or discharge an Employee is expressly reserved. The Participating Employers make no representations or warranties as to the tax consequences to a Participant or a Participant's beneficiaries resulting from a deferral of income pursuant to the Plan.

13.3 No Employment Contract. Nothing contained herein shall be construed to constitute a contract of employment between an Employee and a Participating Employer.

13.4 Notice. Any notice or filing required or permitted to be delivered to the Committee under this Plan shall be delivered in writing, in person, or through such electronic means as is established by the Committee. Notice shall be deemed given as of the date of delivery or, if delivery is made by mail, as of the date shown on the postmark on the receipt for registration or certification. Written transmission shall be sent by certified mail to:

HORIZON PHARMA, Inc.
Attn: EVP, Chief Human Resources Officer
150 South Saunders Road
Lake Forest, IL 60045

Any notice or filing required or permitted to be given to a Participant under this Plan shall be sufficient if in writing or hand-delivered, or sent by mail to the last known address of the Participant.

13.5 Headings. The headings of Sections are included solely for convenience of reference, and if there is any conflict between such headings and the text of this Plan, the text shall control.

13.6 Invalid or Unenforceable Provisions. If any provision of this Plan shall be held invalid or unenforceable, such invalidity or unenforceability shall not affect any other provisions hereof and the Committee may elect in its sole discretion to construe such invalid or unenforceable provisions in a manner that conforms to applicable law or as if such provisions, to the extent invalid or unenforceable, had not been included.

13.7 Lost Participants or Beneficiaries. Any Participant or Beneficiary who is entitled to a benefit from the Plan has the duty to keep the Committee advised of his or her current mailing address. If benefit payments are returned to the Plan or are not presented for payment after a reasonable amount of time, the Committee shall presume that the payee is missing. The Committee, after making such efforts as in its discretion it deems reasonable and appropriate to locate the payee, shall stop payment on any uncashed checks and may discontinue making future payments until contact with the payee is restored.

13.8 Facility of Payment to a Minor. If a distribution is to be made to a minor, or to a person who is otherwise incompetent, then the Committee may, in its discretion, make such distribution: (i) to the legal guardian, or if none, to a parent of a minor payee with whom the payee maintains his or her residence, or (ii) to the conservator or committee or, if none, to the person having custody of an incompetent payee. Any such distribution shall fully discharge the Committee, the Company, and the Plan from further liability on account thereof.

13.9 Governing Law. To the extent not preempted by ERISA, the laws of the State of Illinois shall govern the construction and administration of the Plan.

Exhibit 10.53

EXECUTIVE EMPLOYMENT AGREEMENT BY AND BETWEEN HORIZON PHARMA, INC., HORIZON PHARMA USA, INC. AND SHAO-LEE LIN

This Executive Employment Agreement (hereinafter referred to as the "***Agreement***"), is entered into by and between Horizon Pharma, Inc., a Delaware corporation, and its wholly owned subsidiary, Horizon Pharma USA, Inc., a Delaware corporation, each having a principal place of business at 150 S. Saunders Rd, Lake Forest IL 60045, (hereinafter referred to together as the "***Company***") and Shao-Lee Lin (hereinafter referred as to the "***Executive***"). The terms of this Agreement shall be effective commencing January 4, 2018 (the "***Effective Date***").

RECITALS

WHEREAS, the Company desires assurance of association and services of the Executive in order to retain the Executive's experience, skills, abilities, background and knowledge, and is willing to engage the Executive's services on the terms and conditions set forth in this Agreement; and

WHEREAS, Executive desires to be in the employ of the Company, and is willing to accept such employment on the terms and conditions set forth in this Agreement.

AGREEMENT

1. Employment.

1.1 Term. The Company hereby agrees to employ the Executive, and the Executive hereby accepts employment by the Company, upon the terms and conditions set forth in this Agreement. Executive's employment shall be governed under the terms set forth in this Agreement beginning on the Effective Date and shall continue until it is terminated pursuant to Section 4 herein (hereinafter referred to as the "***Term***").

1.2 Title. From and after the Effective Date the Executive will have the title of Executive Vice President, Head of Research and Development and Chief Scientific Officer (such position held by Executive during such period is hereinafter referred to as "***EVP CSO***") and Executive shall serve in such other capacity or capacities commensurate with her position as EVP CSO as the President and CEO of the Company may from time to time prescribe.

1.3 Duties. The Executive shall do and perform all services, acts or things necessary or advisable to manage and conduct the business of the Company and shall have the authority and responsibilities which are generally associated with the position of EVP CSO. The Executive shall report to the President and CEO.

1.4 Policies and Practices. The employment relationship between the Parties shall be governed by this Agreement and the policies and practices established by the Company and the Board of Directors (hereinafter referred to as the "***Board***"). In the event that the terms of this Agreement differ from or are in conflict with the Company's policies or practices or the Company's Employee Handbook, this Agreement shall control.

1.5 Location. The Executive shall perform the services the Executive is required to perform pursuant to this Agreement in at the Company's U.S. Headquarters in Lake Forest Illinois. The Company may from time to time require the Executive to travel temporarily to other locations outside of Lake Forest, Illinois area in connection with the Company's business.

2. Loyalty of Executive.

2.1 Loyalty. During the Executive's employment by the Company, the Executive shall devote the Executive's business energies, interest, abilities and productive time to the proper and efficient performance of Executive's duties under this Agreement. Subject to the prior written consent of the President and CEO, the Executive is permitted to serve on the board of directors of one other company, so long as the other company does not compete with the Company.

2.2 Exclusive Employment. Except with the prior written consent of the Chief Executive Officer, Executive shall not, during the term of this Agreement, undertake or engage in any other employment, occupation or business enterprise, other than ones in which Executive is a passive investor. Executive may engage in any civic and not-for-profit activities so long as such activities do not materially interfere with the performance of her duties hereunder or present a conflict of interest with the Company.

2.3 Agreement not to Participate in Company's Competitors. During the Term of this Agreement, the Executive agrees not to acquire, assume or participate in, directly or indirectly, any position, investment or interest known by Executive to be adverse or antagonistic to the Company, its business or prospects, financial or otherwise or in any company, person or entity that is, directly or indirectly, in competition with the business of the Company or any of its affiliates. Notwithstanding the foregoing, Executive may invest and/or maintain investments in any public or private entity up to an amount of 2% of an entity's fully diluted shares and on a passive basis.

3. Compensation to Executive.

3.1 Base Salary. The Company shall pay the Executive a base salary at the initial annualized rate of six hundred twenty five thousand dollars ($625,000.00) per year, subject to standard deductions and withholdings, or such higher rate as may be determined from time to time by the Board or the compensation committee thereof (hereinafter referred to as the "***Base Salary***"). Such Base Salary shall be paid in accordance with the Company's standard payroll practice. Payments of salary installments shall be made no less frequently than once per month. Executive's Base Salary will be reviewed annually each December and Executive shall be eligible to receive a salary increase (but not decrease) annually in an amount to be determined by the Board or the compensation committee thereof in its sole and exclusive discretion. Once increased, the new salary shall become the Base Salary for purposes of this Agreement and shall not be reduced without the Executive's written consent. Any material reduction in the Base Salary of the Executive, without her written consent, may be deemed Good Reason as set forth in and subject to Section 4.5.2 of this Agreement.

3.2 Sign-On Bonus. Executive shall be entitled to a one time sign on bonus equal to seven hundred forty thousand dollars ($740,000) (hereinafter referred to as the "***Sign On Bonus***"), subject to standard deductions and withholdings. The Sign On Bonus shall be paid to Executive as follows: (1) six hundred thousand dollars ($600,000) paid on or before January 15, 2018; and (2) one hundred forty thousand dollars ($140,000) paid on or before January 15, 2019, provided that Executive is still an employee of Company on January 15, 2019. If Executive's employment is terminated by Company for "***Cause,***" as defined in section 4.5.3 of this Agreement, or if Executive provides notice to Company of her intent to terminate this Agreement Without Good Reason, as described in section 4.2.2 of this Agreement (each hereafter referred to as a "***Termination Event,***" Executive shall reimburse Company one hundred percent (100%) of any payments made in accordance with the terms of this Section 3.2, if such Termination Event occurs during the same calendar year in which the payment is made, and fifty percent (50%) of any payment if such Termination Event occurs during the calendar year immediately following the calendar year in which such payment is made. Any reimbursement payments provide required under this Section 3.2 shall be due within 15 days of the applicable Termination Event. After the calendar year immediately following the calendar year in which such payment is made (which date is no longer than two (2) years from the date of the initial payment), the Employee does not have to reimburse the Company for any reason.

3.3 Exit Payment. Executive shall also be eligible for a payment of an amount equal to the amount Executive is required to pay her former employer due to resignation from her prior employment, but in no case shall this amount exceed seventy five thousand dollars ($75,000).

3.4 Discretionary Bonus. Provided the Executive meets the conditions stated in this Section 3.4, the Executive shall be eligible for an annual discretionary bonus (hereinafter referred to as the "***Bonus***") with a target amount of sixty percent (60%) of the Executive's Base Salary, not to exceed two hundred percent (200%) of Executive's Base Salary,, subject to standard deductions and withholdings, based on the Board's determination, in good faith, and based upon the Executive's individual achievement and company performance objectives as set by the Board or the compensation committee thereof, of whether the Executive has met such performance milestones as are established for the Executive by the Board or the compensation committee thereof, in good faith, in consultation with the Executive (hereinafter referred to as the "***Performance Milestones***"). The Performance Milestones will be based on certain factors including, but not limited to, the Executive's performance and the Company's financial performance. The Executive's Bonus target will be reviewed annually and may be adjusted by the Board or the compensation committee thereof in its discretion, provided however, that the Bonus target may only be materially reduced upon Executive's written consent. The Executive must be employed on the date the Bonus is awarded to be eligible for the Bonus, subject to the termination provisions thereof. The Bonus shall be paid during the calendar year following the performance calendar year.

3.5 Equity Awards. As an inducement to the Executive's commencement of employment with the Company, and subject to approval by the Compensation Committee, the Executive will be granted the following equity awards as "***Inducement Awards***" pursuant to and subject to the terms of the Horizon Pharma Public Limited Company 2014 Equity Incentive Plan ("***2014 Equity Incentive Plan***") and its form of stock option and restricted stock unit award agreements, in the forms to be provided to Executive (collectively the "***Equity Plan Documents***") and compliance with applicable securities laws:

3.5.1 Inducement Option. A stock option to purchase ordinary shares of Horizon Pharma plc with a fair value of $1,100,000 as of January 4, 2018 (the "***Option***"). The number of ordinary shares subject to the Option will be calculated based on the fair value of the Option determined under the Black-Scholes Method as of January 4, 2018. The Option will have an exercise price equal to the closing price of Horizon Pharma plc's ordinary shares on the applicable date of grant, which will be January 4, 2018 (the "***Vesting Commencement Date***"). All options will be issued as nonstatutory stock options. Subject to Executive's continued provision of services to the Company through the applicable vesting dates, the Option shall vest as follows: 25% of the total number of shares subject to the Option shall vest on the first anniversary of the Vesting Commencement Date or January 4, 2019 and 1/36 of the remaining number of shares subject to the Option shall vest on each monthly anniversary thereafter so that the Option would fully vest on the four (4) year anniversary of the Vesting Commencement Date subject to Executive's continued services with the Company through such date.

3.5.2 Inducement RSU. A restricted stock unit award in respect of number of ordinary shares of Horizon Pharma plc having a fair value of $1,100,000 as of January 4, 2018, which will be the applicable date of grant (the "***RSU Award***"). Subject to Executive's continued provision of services to the Company through the applicable vesting dates, the RSU Award shall vest as follows: 25% of the total number of units subject to the RSU Award shall vest on the first anniversary of the Vesting Commencement Date, and thereafter 25% of the total number of units subject to the RSU Award shall vest on each anniversary thereafter, so that the RSU Award would fully vest on the fourth anniversary of the Vesting Commencement Date, subject to Executive's continued services with the Company through such date.

3.5.3 Annual Long Term Incentive Plan. As of January 4, 2018 Executive will participate in the Annual Long-Term Incentive Plan ("***ALTIP***") currently under development by the Board of Directors for executives, subject to adoption of the ALTIP by the Board of Directors and all applicable terms which may apply. The annual grant for the Executive is anticipated to be between $2.0M—$2.7M in a mix of RSUs and PSUs. The final target amount, vesting schedule and other terms and criteria for the ALTIP are expected to be determined by the Board of Directors in late December 2017 and may be subject to shareholder approval.

3.5.4 Legal Review. Upon the Executive's submission of appropriate itemized proof and verification of reasonable and customary legal fees incurred by the Executive in obtaining legal advice associated with the review, preparation, approval, and execution of this Agreement, the Company shall pay for up to $10,000.00 of such legal fees subject to receipt of appropriate proof and verification of such legal fees no later than sixty (60) days of receipt of an invoice for legal services from the Executive and/or her attorneys. To be eligible for reimbursement, the invoice must be submitted no later than ninety (90) days after the legal fees are incurred.

3.6 Changes to Compensation. The Executive's compensation may be changed from time to time by mutual agreement of the Executive and the Company. In the event that the Executive's base salary is materially decreased without her written consent, said decrease will be Good Reason for the Executive to terminate the Agreement as set forth in and subject to Section 4.5.2 of this Agreement.

3.7 Taxes. All amounts paid under this Agreement to the Executive by the Company will be paid less applicable tax withholdings and any other withholdings required by law or authorized by the Executive.

3.8 Benefits. The Executive shall, in accordance with Company policy and the terms of the applicable plan documents, be eligible to participate in benefits under any executive benefit plan or arrangement which may be in effect from time to time and made available to the Company's executives or key management employees, provided, however, that the Executive shall be entitled to at least four (4) weeks of paid vacation annually.

4. Termination.

4.1 Termination by the Company. The Executive's employment with the Company may be terminated only under the following conditions:

4.1.1 Termination for Death or Disability. The Executive's employment with the Company shall terminate effective upon the date of the Executive's death or "***Complete Disability***" (as defined in Section 4.5.1), provided, however, that this Section 4.1.1 shall in no way limit the Company's obligations to provide such reasonable accommodations to the Executive and/or her heirs as may be required by law.

4.1.2 Termination by the Company For Cause. The Company may terminate the Executive's employment under this Agreement for "***Cause***" (as defined in Section 4.5.3) by delivery of written notice to the Executive specifying the Cause or Causes relied upon for such termination, provided that such notice is delivered within two (2) months following the occurrence or discovery of any event or events constituting "***Cause***". Any notice of termination given pursuant to this Section 4.1.2 shall effect termination as of the date of the notice or such date as specified in the notice. The Executive shall have the right to appear before the CEO before any termination for Cause becomes effective and binding upon the Executive.

4.1.3 Termination by the Company Without Cause. The Company may terminate the Executive's employment under this Agreement at any time and for any reason or no reason subject to the requirements set out in Section 4.4 of this Agreement. Such termination shall be effective on the date the Executive is so informed or as otherwise specified by the Company, pursuant to notice requirements set forth in Section 6 of this Agreement.

4.2 Termination By The Executive. The Executive may terminate her employment with the Company at any time and for any reason or no reason, including, but not limited, to the following conditions:

4.2.1 Good Reason. The Executive may terminate her employment under this Agreement for "***Good Reason***" (as defined below in Section 4.5.2) by delivery of written notice to the Company specifying the Good Reason relied upon by the Executive for such termination in accordance with the requirements of such section.

4.2.2 Without Good Reason. The Executive may terminate the Executive's employment hereunder for other than Good Reason upon thirty (30) days written notice to the Company.

4.3 Termination by Mutual Agreement of the Parties. The Executive's employment pursuant to this Agreement may be terminated at any time upon a mutual agreement in writing of the Parties. Any such termination of employment shall have the consequences specified in such mutual agreement.

4.4 Compensation to Executive Upon Termination. In connection with any termination of the Executive's employment for any reason, the Executive or the Executive's estate, as applicable, shall be entitled to any amounts payable to the Executive or the Executive's beneficiaries subject to and accordance with the terms of the Company's employee welfare benefit plans or policies (excluding any severance pay).

4.4.1 Death or Complete Disability. If the Executive's employment shall be terminated by death or Complete Disability as provided in Section 4.1.1, the Company shall pay to Executive, and/or Executive's heirs, all earned but unpaid Base Salary, any earned but unpaid discretionary bonuses for any prior period at such time as bonuses would have been paid if the Executive remained employed, all accrued but unpaid business expenses, and all accrued but unused vacation time earned through the date of termination at the rate in effect at the time of termination (hereinafter referred to as the "***Accrued Amounts***"), less standard deductions and withholdings. The Executive shall also be eligible to receive a pro-rated bonus for the year of termination, as determined by the Board or the Compensation Committee of the Board based on actual performance and the period of the year she was employed (hereinafter referred to as the "***Pro-rata Bonus***"), less standard deductions and withholdings, to be paid as a lump sum within thirty (30) days after the date of termination.

4.4.2 With Cause or Without Good Reason. If the Executive's employment shall be terminated by the Company for Cause, or if the Executive terminates employment hereunder without Good Reason, the Company shall pay the Executive's Base Salary, accrued but unpaid business expenses and accrued and unused vacation benefits earned through the date of termination at the rate in effect at the time of termination, less standard deductions and withholdings.

4.4.3 Without Cause or For Good Reason.

(i) Not in Connection With a Change in Control. If the Company terminates the Executive's employment without Cause or the Executive terminates her employment for Good Reason, and Section 4.4.3(ii) below does not apply, the Company shall pay the Accrued Amounts subject to standard deductions and withholdings, to be paid as a lump sum no later than thirty (30) days after the date of termination. In addition, subject to the limitations stated in this Agreement and upon the Executive's furnishing to the Company an executed waiver and release of claims (the form of which is attached hereto as Exhibit A) (the "***Release***") within the applicable time period set forth therein, but in no event later than forty-five days following termination of employment and permitting such Release to become effective in accordance with its terms (the "***Release Effective Date***"), and subject to Executive entering into

no later than the Release Effective Date a non-competition agreement to be effective during the Severance Period (as defined below), substantially similar to Section 2.3, and continuing to abide by its terms during the Severance Period, the Executive shall be entitled to:

(a) the equivalent of the Executive's Base Salary in effect at the time of termination will continue to be paid for a period of twelve (12) months following the date of termination (hereinafter referred to as the "***Non Change in Control Severance Period***"), less standard deductions and withholdings, to be paid during the Non Change in Control Severance Period according to the Company's regular payroll practices, subject to any delay in payment required by Section 4.6 in connection with the Release Effective Date; and

(b) in the event the Executive timely elects continued coverage under COBRA, the Company will continue to pay the same portion of Executive's COBRA health insurance premium as the percentage of health insurance premiums that it paid during the Executive's employment, including any amounts that Company paid for benefits to the qualifying family members of the Executive, following the date of termination up until the earlier of either (i) the last day of the Non Change in Control Severance Period or, (ii) the date on which the Executive begins full-time employment with another company or business entity which offers comparable health insurance coverage to the Executive (such period, the "***Non Change in Control COBRA Payment Period***"). Notwithstanding the foregoing, if the Company determines, in its sole discretion, that the Company cannot provide the COBRA premium benefits without potentially incurring financial costs or penalties under applicable law (including, without limitation, Section 2716 of the Public Health Service Act), the Company shall in lieu thereof pay Executive a taxable cash amount, which payment shall be made regardless of whether the Executive or her qualifying family members elect COBRA continuation coverage (the "***Health Care Benefit Payment***"). The Health Care Benefit Payment shall be paid in monthly or bi-weekly installments on the same schedule that the COBRA premiums would otherwise have been paid to the insurer. The Health Care Benefit Payment shall be equal to the amount that the Company otherwise would have paid for COBRA insurance premiums (which amount shall be calculated based on the premium for the first month of coverage), and shall be paid until the expiration of the Non Change in Control COBRA Payment Period.

(ii) In Connection With a Change in Control. If the Company (or its successor) terminates the Executive's employment without Cause or the Executive terminates her employment for Good Reason within the period commencing three (3) months immediately prior to a Change in Control of the Company and ending eighteen (18) months immediately following a Change in Control of the Company (as defined in Section 4.5.4 of this Agreement), the Executive shall receive the Accrued Amounts subject to standard deductions and withholdings, to be paid as a lump sum no later than thirty (30) days after the date of termination. In addition, subject to the limitations stated in this Agreement and upon the Executive's furnishing to the Company (or its successor) an executed Release within the applicable time period set forth therein, but in no event later than forty-five days following termination of employment and permitting such Release to become effective in accordance with its terms, and subject to Executive entering into no later than the Release Effective Date a non-competition agreement to be effective during the Severance Period, substantially similar to Section 2.3, and continuing to abide by its terms during the Severance Period, then in lieu of (and not additional to) the benefits provided pursuant to Section 4.4.3(i) above, the Executive shall be entitled to:

(a) the equivalent of the Executive's Base Salary in effect at the time of termination will continue to be paid for a period of eighteen (18) months following the date of termination (hereinafter referred to as the "***Change in Control Severance Period***"), less standard deductions and withholdings, to be paid during the Change in Control Severance Period according to the Company's regular payroll practices, subject to any delay in payment required by Section 4.6 in connection with the Release Effective Date;

(b) one and half (1.5) times Executive's target Bonus in effect at the time of termination, or if none, one and half (1.5) times the last target Bonus in effect for Executive, less standard deductions and withholdings, to be paid in a lump sum within ten (10) days following the later of (i) the Release Effective Date, or (ii) the effective date of the Change in Control; and

(c) in the event the Executive timely elects continued coverage under COBRA, the Company will continue to pay the same portion of Executive's COBRA health insurance premium as the percentage of health insurance premiums that it paid during the Executive's employment, including any amounts that Company paid for benefits to the qualifying family members of the Executive, following the date of termination until the expiration of the Change in Control Severance Period. Notwithstanding the foregoing, if the Company determines, in its sole discretion, that the Company cannot provide the COBRA premium benefits without potentially incurring financial costs or penalties under applicable law (including, without limitation, Section 2716 of the Public Health Service Act), the Company shall in lieu thereof pay Executive the Health Care Benefit Payment, which payment shall be made regardless of whether the Executive or her qualifying family members elect COBRA continuation coverage. The Health Care Benefit Payment shall be paid in monthly or bi-weekly installments on the same schedule that the COBRA premiums would otherwise have been paid to the insurer. The Health Care Benefit Payment shall be equal to the amount that the Company otherwise would have paid for COBRA insurance premiums (which amount shall be calculated based on the premium for the first month of coverage), and shall be paid until the expiration of the Change in Control Severance Period.

(iii) No Duplication of Benefits. For the avoidance of doubt, in no event will Executive be entitled to benefits under Section 4.4.3(i) and Section 4.4.3(4 If Executive commences to receive benefits under Section 4.4.3(i) due to a qualifying termination prior to a Change in Control and thereafter becomes entitled to benefits under Section 4.4.3(4), any benefits provided to Executive under Section 4.4.3(i) shall offset the benefits to be provided to Executive under Section 4.4.3(ii) and shall be deemed to have been provided to Executive pursuant to Section 4.4.3(ii).

4.4.4 Equity Award Acceleration.

(i) Not in Connection With a Change in Control. In the event that the Executive's employment is terminated without Cause or for Good Reason and Section 4.4.4 (ii) below does not apply, the vesting of any equity awards granted to Executive that vest solely subject to Executive's continued services to the Company (the "***Time-Based Vesting Equity Awards***") shall be deemed vested and immediately exercisable (if applicable) by the Executive with respect to such number of shares as determined in accordance with their applicable vesting schedules as if Executive had provided an additional twelve (12) months of services as of the

date of termination. Treatment of any performance based vesting equity awards will be governed solely by the terms of the agreements under which such awards were granted and will not be eligible to accelerate vesting pursuant to the foregoing provision.

(ii) In Connection With a Change in Control. In the event that the Executive's employment is terminated without Cause or for Good Reason within the three (3) months immediately preceding or during the eighteen (18) months immediately following a Change in Control of the Company (as defined in Section 4.5.4 of this Agreement), the vesting of any Time-Based Vesting Equity Awards granted to Executive shall be fully accelerated such that on the effective date of such termination (or if later, the date of the Change in Control) one hundred percent (100%) of any Time-Based Vesting Equity Awards granted to Executive prior to such termination shall be fully vested and immediately exercisable, if applicable, by the Executive. Treatment of any performance based vesting equity awards will be governed solely by the terms of the agreements under which such awards were granted and will not be eligible to accelerate vesting pursuant to the foregoing provision.

(iii) Release and Waiver. Any equity vesting acceleration pursuant to this Section 4.4.4 shall be conditioned upon and subject to the Executive's delivery to the Company of a fully effective Release in accordance with the terms specified by Section 4.4.3 hereof and such vesting acceleration benefit shall be in addition to the benefits provided by Section 4.4.3 hereof.

4.5 Definitions. For purposes of this Agreement, the following terms shall have the following meanings:

4.5.1 Complete Disability. "***Complete Disability***" shall mean the inability of the Executive to perform the Executive's duties under this Agreement, whether with or without reasonable accommodation, because the Executive has become permanently disabled within the meaning of any policy of disability income insurance covering employees of the Company then in force. In the event the Company has no policy of disability income insurance covering employees of the Company in force when the Executive becomes disabled, the term "Complete Disability" shall mean the inability of the Executive to perform the Executive's duties under this Agreement, whether with or without reasonable accommodation, by reason of any incapacity, physical or mental, which the Board, based upon medical advice or an opinion provided by a licensed physician, determines to have incapacitated the Executive from satisfactorily performing all of the Executive's usual services for the Company, with or without reasonable accommodation, for a period of at least one hundred eighty (180) days during any twelve (12) month period that need not be consecutive.

4.5.2 Good Reason. "***Good Reason***" for the Executive to terminate the Executive's employment hereunder shall mean the occurrence of any of the following events without the Executive's consent:

(i) a material reduction in the Executive's duties, authority, or responsibilities relative to the duties, authority, or responsibilities in effect immediately prior to such reduction, including by way of example, having the same title, duties, authority and responsibilities at a subsidiary level following a Change in Control;

(ii) the relocation of the Executive's primary work location to a point more than thirty-five (35) miles from the Executive's current work location set forth in Section 1.5 that requires a material increase in Executive's one-way driving distance;

(iii) a material reduction by the Company of the Executive's base salary or annual target Bonus opportunity, without the written consent of the Executive, as initially set forth herein or as the same may be increased from time to time pursuant to this Agreement; and

(iv) a material breach by the Company of Section 1.2 of this Agreement.

Provided, however that, such termination by the Executive shall only be deemed for Good Reason pursuant to the foregoing definition if (i) the Company is given written notice from the Executive within sixty (60) days following the first occurrence of the condition that she considers to constitute Good Reason describing the condition and the Company fails to satisfactorily remedy such condition within thirty (30) days following such written notice, and (ii) the Executive terminates employment within thirty (30) days following the end of the period within which the Company was entitled to remedy the condition constituting Good Reason but failed to do so.

4.5.3 Cause. "***Cause***" for the Company to terminate Executive's employment hereunder shall mean the occurrence of any of the following events, as determined reasonably and in good faith by the Board or a committee designated by the Board:

(i) the Executive's gross negligence or willful failure to substantially perform her duties and responsibilities to the Company or willful and deliberate violation of a Company policy;

(ii) the Executive's conviction of a felony or the Executive's commission of any act of fraud, embezzlement or dishonesty against the Company or involving moral turpitude that is likely to inflict or has inflicted material injury on the business of the Company, to be determined by the sole discretion of the Company;

(iii) the Executive's unauthorized use or disclosure of any proprietary information or trade secrets of the Company or any other party that the Executive owes an obligation of nondisclosure as a result of the Executive's relationship with the Company; and

(iv) the Executive's willful and deliberate breach of the obligations under this Agreement that causes material injury to the business of the Company.

4.5.4 Change in Control. For purposes of this Agreement, "***Change in Control***" means: (i) a sale of all or substantially all of the assets of the Company; (ii) a merger or consolidation in which the Company is not the surviving entity and in which the holders of the Company's outstanding voting stock immediately prior to such transaction own, immediately after such transaction, securities representing less than fifty percent (50%) of the voting power of the entity surviving such transaction or, where the surviving entity is a wholly-owned subsidiary of another entity, the surviving entity's parent; (iii) a reverse merger in which the Company is

the surviving entity but the shares of Common Stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities of the surviving entity's parent, cash or otherwise, and in which the holders of the Company's outstanding voting stock immediately prior to such transaction own, immediately after such transaction, securities representing less than fifty percent (50%) of the voting power of the Company or, where the Company is a wholly-owned subsidiary of another entity, the Company's parent; or (iv) an acquisition by any person, entity or group (excluding any employee benefit plan, or related trust, sponsored or maintained by the Company or subsidiary of the Company or other entity controlled by the Company) of the beneficial ownership of securities of the Company representing at least seventy-five percent (75%) of the combined voting power entitled to vote in the election of Directors; provided, however, that nothing in this paragraph shall apply to a sale of assets, merger or other transaction effected exclusively for the purpose of changing the domicile of the Company.

4.6 Application of Internal Revenue Code Section 409A. Notwithstanding anything to the contrary set forth herein, any payments and benefits provided under this Agreement (the "***Severance Benefits***") that constitute "deferred compensation" within the meaning of Section 409A of the Internal Revenue Code of 1986, as amended (the "***Code***") and the regulations and other guidance thereunder and any state law of similar effect (collectively "***Section 409A***") shall not commence in connection with Executive's termination of employment unless and until Executive has also incurred a "separation from service" (as such term is defined in Treasury Regulation Section 1.409A-1(h) ("***Separation From Service***"), unless the Company reasonably determines that such amounts may be provided to Executive without causing Executive to incur the additional 20% tax under Section 409A.

It is intended that each installment of the Severance Benefits payments provided for in this Agreement is a separate "payment" for purposes of Treasury Regulation Section 1.409A-2(b)(2)(i). For the avoidance of doubt, it is intended that payments of the Severance Benefits set forth in this Agreement satisfy, to the greatest extent possible, the exemptions from the application of Section 409A provided under Treasury Regulation Sections 1.409A-1(b)(4), 1.409A-1(b)(5) and 1.409A-1(b)(9). However, if the Company (or, if applicable, the successor entity thereto) determines that the Severance Benefits constitute "deferred compensation" under Section 409A and Executive is, on the termination of service, a "specified employee" of the Company or any successor entity thereto, as such term is defined in Section 409A(a)(2)(B)(i) of the Code, then, solely to the extent necessary to avoid the incurrence of the adverse personal tax consequences under Section 409A, the timing of the Severance Benefit payments shall be delayed until the earlier to occur of: (i) the date that is six months and one day after Executive's Separation From Service, or (ii) the date of Executive's death (such applicable date, the "***Specified Employee Initial Payment Date***"), the Company (or the successor entity thereto, as applicable) shall (A) pay to Executive a lump sum amount equal to the sum of the Severance Benefit payments that Executive would otherwise have received through the Specified Employee Initial Payment Date if the commencement of the payment of the Severance Benefits had not been so delayed pursuant to this Section and (B) commence paying the balance of the Severance Benefits in accordance with the applicable payment schedules set forth in this Agreement.

Notwithstanding anything to the contrary set forth herein, Executive shall receive the Severance Benefits described above, if and only if Executive duly executes and returns to the

Company within the applicable time period set forth therein, but in no event more than forty-five days following Separation From Service, the Company's standard form of release of claims in favor of the Company (attached to this Agreement as Exhibit A) (the "***Release***") and permits the release of claims contained therein to become effective in accordance with its terms (such latest permitted date, the "***Release Deadline***"). If the severance benefits are not covered by one or more exemptions from the application of Section 409A and the Release could become effective in the calendar year following the calendar year in which Executive separates from service, the Release will not be deemed effective any earlier than the Release Deadline. Notwithstanding any other payment schedule set forth in this Agreement, none of the Severance Benefits will be paid or otherwise delivered prior to the effective date (or deemed effective date) of the Release. Except to the extent that payments may be delayed until the Specified Employee Initial Payment Date pursuant to the preceding paragraph, on the first regular payroll pay day following the effective date of the Release, the Company will pay Executive the Severance Benefits Executive would otherwise have received under the Agreement on or prior to such date but for the delay in payment related to the effectiveness of the Release, with the balance of the Severance Benefits being paid as originally scheduled.

The severance benefits are intended to qualify for an exemption from application of Section 409A or comply with its requirements to the extent necessary to avoid adverse personal tax consequences under Section 409A, and any ambiguities herein shall be interpreted accordingly.

4.7 Application of Internal Revenue Code Section 280G. If any payment or benefit Executive would receive pursuant to a Change in Control from the Company or otherwise ("***Payment***") would (i) constitute a "parachute payment" within the meaning of Section 280G of the Code, and (ii) but for this sentence, be subject to the excise tax imposed by Section 4999 of the Code (the "***Excise Tax***"), then such Payment shall be equal to the Reduced Amount. The "***Reduced Amount***" shall be either (x) the largest portion of the Payment that would result in no portion of the Payment being subject to the Excise Tax or (y) the largest portion, up to and including the total, of the Payment, whichever amount, after taking into account all applicable federal, state and local employment taxes, income taxes, and the Excise Tax (all computed at the highest applicable marginal rate), results in Executive's receipt, on an after-tax basis, of the greater economic benefit notwithstanding that all or some portion of the Payment may be subject to the Excise Tax. If a reduction in payments or benefits constituting "parachute payments" is necessary so that the Payment equals the Reduced Amount, reduction shall occur in the manner that results in the greatest economic benefit for Executive. If more than one method of reduction will result in the same economic benefit, the items so reduced will be reduced pro rata.

In the event it is subsequently determined by the Internal Revenue Service that some portion of the Reduced Amount as determined pursuant to clause (x) in the preceding paragraph is subject to the Excise Tax, Executive agrees to promptly return to the Company a sufficient amount of the Payment so that no portion of the Reduced Amount is subject to the Excise Tax. For the avoidance of doubt, if the Reduced Amount is determined pursuant to clause (y) in the preceding paragraph, Executive will have no obligation to return any portion of the Payment pursuant to the preceding sentence.

Unless Executive and the Company agree on an alternative accounting firm, the accounting firm engaged by the Company for general tax compliance purposes as of the day prior to the effective date of the Change in Control shall perform the foregoing calculations. If the accounting firm so engaged by the Company is serving as accountant or auditor for the individual, entity or group effecting the Change in Control, the Company shall appoint a nationally recognized accounting firm to make the determinations required hereunder. The Company shall bear all expenses with respect to the determinations by such accounting firm required to be made hereunder.

The Company shall use commercially reasonable efforts to cause the accounting firm engaged to make the determinations hereunder to provide its calculations, together with detailed supporting documentation, to Executive and the Company within fifteen (15) calendar days after the date on which Executive's right to a Payment is triggered (if requested at that time by Executive or the Company) or such other time as requested by Executive or the Company.

4.8 Indemnification Agreements. Concurrently with the execution of this Agreement, the Company and the Executive shall enter into indemnification agreements, copies of which are attached hereto as Exhibit B-1 and Exhibit B-2.

4.9 Confidential Information and Invention Assignment Agreement. The Executive shall execute the Company's Confidential Information and Invention Assignment Agreement the terms of which shall govern the terms of Executive's employment following the Effective Date, and a copy of which is attached as Exhibit C.

4.10 No Mitigation or Offset. The Executive shall not be required to seek or accept other employment, or otherwise to mitigate damages, as a condition to receipt of the Severance Benefits, and the Severance Benefits shall not be offset by any amounts received by the Executive from any other source, except to the extent that the Executive's rights to the benefits described in Sections 4.4.3(i)(b) or 4.4.3(ii)(c), as applicable, are terminated by reason of the Executive obtaining full-time employment with another company or business entity which offers comparable health insurance coverage.

5. Assignment and Binding Effect.

This Agreement shall be binding upon the Executive and the Company and inure to the benefit of the Executive and the Executive's heirs, executors, personal representatives, assigns, administrators and legal representatives. Because of the unique and personal nature of the Executive's duties under this Agreement, neither this Agreement nor obligations under this Agreement shall be assignable by the Executive. This Agreement shall be binding upon and inure to the benefit of the Company and its successors, assigns and legal representatives, provided that the Agreement may only be assigned to an acquirer of all or substantially all of the Company's assets. Any such successor of the Company will be deemed substituted for the Company under the terms of this Agreement for all purposes. For this purpose, "successor" means any person, firm, corporation or other business entity which at any time, whether by purchase, merger or otherwise, directly or indirectly acquires all or substantially all of the assets or business of the Company.

6. Notice.

For the purposes of this Agreement, notices, demands, and all other forms of communication provided for in this Agreement shall be in writing and shall be deemed to have been duly given when delivered or (unless otherwise specified) mailed by registered mail, return receipt requested, postage prepaid, or by confirmed facsimile, addressed as set forth below, or to such other address as any party may have furnished to the other in writing in accordance herewith, except that notices of address shall be effective only upon receipt, as follows:

If to the Company:

Horizon Pharma, Inc.
150 S. Saunders Rd.
Lake Forest, IL 60045
Attention: Timothy P. Walbert, Chairman, President & CEO
Fax: 847-572-1372

If to the Executive:

1111 Evergreen Dr.
Lake Forest, IL 60045

Any such written notice shall be deemed given on the earlier of the date on which such notice is personally delivered or five (5) days after its deposit in the United States mail as specified above. Either Party may change its address for notices by giving written notice to the other Party in the manner specified in this section.

7. Choice of Law.

This Agreement shall be governed by the laws of the State of Illinois, without regard to any conflicts of law principals thereof that would call for the application of the laws of any other jurisdiction. The Parties consent to the exclusive jurisdiction and venue of the federal court in the Northern District of Illinois, and state courts located in the state of Illinois, county of Cook. Nothing in this Section 7 limits the rights of the Parties to seek appeal of a decision of an Illinois court outside of Illinois that has proper jurisdiction over the decision of a court sitting in Illinois.

8. Integration.

This Agreement, including Exhibit A, Exhibit B-1 and B-2, Exhibit C, the 2014 Equity Incentive Plan and the Equity Plan Documents, contains the complete, final and exclusive agreement of the Parties relating to the terms and conditions of the Executive's employment and the termination of Executive's employment, and supersedes all prior and contemporaneous oral and written employment agreements or arrangements between the Parties.

9. Amendment.

This Agreement cannot be amended or modified except by a written agreement signed by the Executive and the Company.

10. Waiver.

No term, covenant or condition of this Agreement or any breach thereof shall be deemed waived, except with the written consent of the Party against whom the wavier is claimed, and any waiver or any such term, covenant, condition or breach shall not be deemed to be a waiver of any preceding or succeeding breach of the same or any other term, covenant, condition or breach.

11. Severability.

The finding by a court of competent jurisdiction of the unenforceability, invalidity or illegality of any provision of this Agreement shall not render any other provision of this Agreement unenforceable, invalid or illegal. Such court shall have the authority to modify or replace the invalid or unenforceable term or provision with a valid and enforceable term or provision, which most accurately represents the Parties' intention with respect to the invalid, unenforceable, or illegal term or provision.

12. Interpretation; Construction.

The headings set forth in this Agreement are for convenience of reference only and shall not be used in interpreting this Agreement. This Agreement has been drafted and negotiated by legal counsel representing the Company and the Executive. The Parties acknowledge that each Party and its counsel has reviewed and revised, or had an opportunity to review and revise, this Agreement, and any rule of construction to the effect that any ambiguities are to be resolved against the drafting party shall not be employed in the interpretation of this Agreement.

13. Execution by Facsimile Signatures and in Counterparts.

The parties agree that facsimile signatures shall have the same force and effect as original signatures. This Agreement may be executed in one or more counterparts, each of which shall be deemed an original but all of which together shall constitute one and the same instrument.

14. Survival.

The provisions of this Agreement, and of all other agreements referenced herein, shall survive the termination of this Agreement, and of the Executive's employment by the Company for any reason, to the extent necessary to enable the parties to enforce their respective rights hereunder.

[Remainder of Page Intentionally Left Blank]

IN WITNESS WHEREFORE, the parties have signed this Agreement on the date first written above.

HORIZON PHARMA, INC.
HORIZON PHARMA USA, INC.

By:

Title: Chairman, President & CEO
Print Name: Timothy P. Walbert

/s/ Timothy P. Walbert
Signature:

As authorized agent of the Company

EXECUTIVE:

SHAO-LEE LIN

/s/ Shao-Lee Lin
Shao-Lee Lin, individually

Exhibit 10.68

EXECUTIVE EMPLOYMENT AGREEMENT BY AND BETWEEN HORIZON PHARMA, INC., HORIZON PHARMA USA, INC. AND MICHAEL DESJARDIN

This Executive Employment Agreement (hereinafter referred to as the ***"Agreement"***), is entered into by and between Horizon Pharma, Inc., a Delaware corporation, and its wholly owned subsidiary, Horizon Pharma USA, Inc., a Delaware corporation, each having a principal place of business at 150 S. Saunders Road, Lake Forest, IL 60045 (hereinafter referred to together as the ***"Company"***) and Michael DesJardin (hereinafter referred as to the ***"Executive"***). The terms of this Agreement shall be effective commencing February 16, 2017 (the "***Effective Date***"). Certain capitalized terms used in this Agreement have the meanings as set forth in Section 4.5.

RECITALS

WHEREAS, the Executive previously entered into: (i) an employment offer letter agreement with Raptor Pharmaceuticals Corp. ("***Raptor***") on February 17, 2015, (ii) a Change in Control Severance Agreement with Raptor, and (iii) a Retention Agreement with the Company dated January 13, 2017 (the "***Retention Agreement***") (collectively, the "***Prior Agreement"***);

WHEREAS, the Company's parent entity, Horizon Pharma Public Limited Company ("***Horizon plc***") acquired Raptor on October 25, 2016, and Raptor became a wholly owned subsidiary of Horizon plc;

WHEREAS, on December 12, 2016, Executive's employment was transferred from Raptor to the Company;

WHEREAS, the Company desires assurance of the continued association and services of the Executive in order to continue to retain the Executive's experience, skills, abilities, background and knowledge, and is willing to continue to engage the Executive's services on the terms and conditions set forth in this Agreement, which as of the Effective Date shall replace and supersede in its entirety the terms of the Prior Agreement; and

WHEREAS, Executive desires to be in the continued employ of the Company, and is willing to accept such continued employment on the terms and conditions set forth in (i) this Agreement, and (ii) the letter agreement by and between the Executive and Raptor dated October 13, 2016 (the "***Transition Services Agreement***") which will continue in full force and effect following the Effective Date.

AGREEMENT

1. Employment.

1.1 Term. The Company hereby agrees to continue to employ the Executive, and the Executive hereby accepts continued employment by the Company, upon the terms and

conditions set forth in this Agreement. Executive's employment shall be governed under the terms set forth in this Agreement beginning on the Effective Date and shall continue until it is terminated pursuant to Section 4 herein (hereinafter referred to as the ***"Term"***).

1.2 Title. From and after the Effective Date the Executive will have the title of Executive Vice President, Technical Operations (such position held by Executive during such period is hereinafter referred to as ***"EVP TO")*** and Executive shall continue to serve in such other capacity or capacities commensurate with his position as EVP TO as the President and CEO of the Company may from time to time prescribe.

1.3 Duties. The Executive shall do and perform all services, acts or things necessary or advisable to manage and conduct the business of the Company and shall have the authority and responsibilities which are generally associated with the position of EVP TO including being responsible for the Company's technical operations. The Executive shall report to the President and CEO.

1.4 Policies and Practices. The employment relationship between the parties shall be governed by this Agreement and the policies and practices established by the Company and the Board of Directors (hereinafter referred to as the ***"Board"***). In the event that the terms of this Agreement differ from or are in conflict with the Company's policies or practices or the Company's Employee Handbook, this Agreement shall control.

1.5 Location. The Executive shall perform the services the Executive is required to perform pursuant to this Agreement in Novato California. The Company may from time to time require the Executive to travel temporarily to other locations outside of the Novato California area in connection with the Company's business.

2. Loyalty of Executive.

2.1 Loyalty. During the Executive's employment by the Company, the Executive shall devote the Executive's business energies, interest, abilities and productive time to the proper and efficient performance of Executive's duties under this Agreement. Subject to the prior written consent of the President and CEO, the Executive is permitted to serve on the board of directors of one other company, so long as the other company does not compete with the Company.

2.2 Exclusive Employment. Except with the prior written consent of the Chief Executive Officer, Executive shall not, during the term of this Agreement, undertake or engage in any other employment, occupation or business enterprise, other than ones in which Executive is a passive investor. Executive may engage in any civic and not-for-profit activities so long as such activities do not materially interfere with the performance of his duties hereunder or present a conflict of interest with the Company.

2.3 Agreement not to Participate in Company's Competitors. During the Term of this Agreement, the Executive agrees not to acquire, assume or participate in, directly or indirectly, any position, investment or interest known by Executive to be adverse or antagonistic to the Company, its business or prospects, financial or otherwise or in any company, person or entity that is, directly or indirectly, in competition with the business of the Company or any of its

affiliates. Notwithstanding the foregoing, Executive may invest and/or maintain investments in any public or private entity up to an amount of 2% of an entity's fully diluted shares and on a passive basis.

3. Compensation to Executive.

3.1 Base Salary. The Company shall pay the Executive a base salary at the initial annualized rate of four hundred twenty five thousand dollars ($425,000) per year, subject to standard deductions and withholdings, or such higher rate as may be determined from time to time by the Board or the compensation committee thereof (hereinafter referred to as the ***"Base Salary"***). Such Base Salary shall be paid in accordance with the Company's standard payroll practice. Payments of salary installments shall be made no less frequently than once per month. Executive's Base Salary will be reviewed annually and Executive shall be eligible to receive a salary increase (but not decrease) annually in an amount to be determined by the Board or the compensation committee thereof in its sole and exclusive discretion. Once increased, the new salary shall become the Base Salary for purposes of this Agreement and shall not be reduced without the Executive's written consent. Any material reduction in the Base Salary of the Executive, without his written consent, may be deemed Good Reason as set forth in and subject to Section 4.5.2 of this Agreement.

3.2 Discretionary Bonus. Executive's eligibility to receive a bonus for the 2016 calendar year will continue to be governed by the terms of Transition Services Agreement. Provided the Executive meets the conditions stated in this Section 3.2, commencing with the 2017 calendar year the Executive shall be eligible for an annual discretionary bonus (hereinafter referred to as the ***"Bonus"***) with a target amount of fifty percent (50%) of the Executive's Base Salary, subject to standard deductions and withholdings, based on the Board's determination, in good faith, and based upon the Executive's individual achievement and company performance objectives as set by the Board or the compensation committee thereof, of whether the Executive has met such performance milestones as are established for the Executive by the Board or the compensation committee thereof, in good faith, in consultation with the Executive (hereinafter referred to as the ***"Performance Milestones"***). The Performance Milestones will be based on certain factors including, but not limited to, the Executive's performance and the Company's financial performance. The Executive's Bonus target will be reviewed annually and may be adjusted by the Board or the compensation committee thereof in its discretion, provided however, that the Bonus target may only be materially reduced upon Executive's written consent. The Executive must be employed on the date the Bonus is awarded to be eligible for the Bonus, subject to the termination provisions thereof. The Bonus shall be paid during the calendar year following the performance calendar year.

3.3 Retention Bonuses.

3.3.1 Transition Service Agreement Retention Bonus. Executive shall continue to be eligible to earn a retention bonus on the terms set forth in the Transition Services Agreement.

3.3.2 Additional Retention Bonus. Executive is eligible to earn an additional one-time retention bonus in the aggregate amount of $630,000 (the "***Additional Retention***

Bonus"), less applicable taxes and withholdings. In order to earn the Additional Retention Bonus, Executive must remain employed by the Company or any other Affiliate (together, the "***Horizon Employer***") regularly working at least 30 hours per week and in good performance standing for the period from March 31, 2017 through and including November 1, 2017 (the "***Earn Date***"). The period from March 31, 2017 through and including the Earn Date is the "***Additional Retention Bonus Period***." If earned, the Additional Retention Bonus will be paid in a lump sum by the Company or its Affiliate, less applicable taxes and withholdings, on the first administratively practicable payroll pay date after the Earn Date.

3.3.3 Effect of Qualifying Termination. If during the Additional Retention Bonus Period, the Horizon Employer terminates Executive's employment without Cause, or Executive's employment with the Horizon Employer is terminated due to Executive's death or Complete Disability, Executive will be eligible for the following benefits, subject to Executive's satisfaction of the additional conditions specified below:

(i) If the Horizon Employer terminates Executive's employment without Cause during the Additional Retention Bonus Period, Executive will be eligible for the full amount of the Additional Retention Bonus.

(ii) If Executive's employment with the Horizon Employer is terminated due to Executive's death or Complete Disability during the Additional Retention Bonus Period, Executive will be eligible for a pro-rata portion of the Additional Retention Bonus, with such pro-rata portion determined by dividing the number of days Executive was actually employed by the Horizon Employer during the Additional Retention Bonus Period by the total number of days in the Additional Retention Bonus Period (the "***Pro-Rata Additional Retention Bonus***").

For the avoidance of doubt, if prior to expiration of the Additional Retention Bonus Period: (i) Executive provides notice of employment resignation, or actually severs the employment relationship by resignation (for any reason, including due to retirement or resignation for Good Reason), or (ii) the Horizon Employer terminates Executive's employment for Cause; then Executive will not be eligible for and will not earn the full Additional Retention Bonus or any Pro-Rata Additional Retention Bonus. Under no circumstances will Executive be eligible to receive both the full Additional Retention Bonus and a Pro-Rata Additional Retention Bonus.

3.3.4 Additional Conditions to Earn Additional Retention Bonus. Notwithstanding the foregoing, in order to earn the full Additional Retention Bonus or Pro-Rata Additional Retention Bonus in connection with any employment termination, Executive (or Executive's estate or legal guardian, if applicable) must execute and deliver to Horizon the Release, and such Release must become effective in accordance with its terms, but in no event later than sixty (60) days following the employment termination date. If earned, such bonus payment will be paid in a lump sum by the Horizon Employer or its Affiliate, less applicable taxes and withholdings, on the first administratively practicable payroll pay date after the Release becomes effective.

3.4 Equity Awards.

3.4.1 Prior Equity Grants. All Company equity awards granted to Executive prior to the Effective Date shall continue in effect from and following the Effective Date in accordance with their existing terms.

3.4.2 New Equity Grants. Subject to Executive's timely acceptance and execution of this Agreement, on February 21, 2017 Executive was granted the following equity awards pursuant to and subject to the terms of the Horizon Pharma plc 2014 Equity Incentive Plan ("***2014 Equity Incentive Plan***") and its form of stock option and restricted stock unit award agreements, in the forms provided to Executive concurrently with this Agreement (collectively the "***Equity Plan Documents***") and compliance with applicable securities laws:

(i) Option. A stock option to purchase up to 17,824 ordinary shares of Horizon plc (the "***Option***"). The Option has an exercise price equal to the fair market value of Horizon plc's ordinary shares on the applicable date of grant, which is February 21, 2017. The Option will be an incentive stock option to the maximum extent permitted by applicable tax laws. Any portion of the Option that does not qualify as an incentive stock option will be a nonstatutory stock option. Subject to Executive's continued provision of services to the Company through the applicable vesting dates, the Option shall vest as follows: 25% of the total number of shares subject to the Option shall vest on the first anniversary of the date of grant (the "***Vesting Commencement Date***") and 1/36 of the remaining number of shares subject to the Option shall vest on each monthly anniversary thereafter so that the Option would fully vest on the four (4) year anniversary of the Vesting Commencement Date subject to Executive's continued services with the Company through such date.

(ii) Restricted Stock Unit Award. A restricted stock unit award in respect of 8,726 ordinary shares of Horizon plc (the "***RSU Award***"). Subject to Executive's continued provision of services to the Company through the applicable vesting dates, the RSU Award shall vest as follows: 25% of the total number of units subject to the RSU Award shall vest on the first anniversary of the Vesting Commencement Date, and thereafter 25% of the total number of units subject to the RSU Award shall vest on each anniversary thereafter, so that the RSU Award would fully vest on the fourth anniversary of the Vesting Commencement Date, subject to Executive's continued services with the Company through such date.

3.5 Legal Review. Upon the Executive's submission of appropriate itemized proof and verification of reasonable and customary legal fees incurred by the Executive in obtaining legal advice associated with the review, preparation, approval, and execution of this Agreement, the Company shall pay for up to $10,000.00 of such legal fees subject to receipt of appropriate proof and verification of such legal fees no later than sixty (60) days of receipt of an invoice for legal services from the Executive and/or his attorneys. To be eligible for reimbursement, the invoice must be submitted no later than ninety (90) days after the legal fees are incurred.

3.6 Changes to Compensation. The Executive's compensation may be changed from time to time by mutual agreement of the Executive and the Company. In the event that the Executive's base salary is materially decreased without his written consent, said decrease will be Good Reason for the Executive to terminate the Agreement as set forth in and subject to Section 4.5.2 of this Agreement.

3.7 Taxes. All amounts paid under this Agreement to the Executive by the Company will be paid less applicable tax withholdings and any other withholdings required by law or authorized by the Executive.

3.8 Benefits. The Executive shall, in accordance with Company policy and the terms of the applicable plan documents, be eligible to participate in benefits under any executive benefit plan or arrangement which may be in effect from time to time and made available to the Company's executives or key management employees, provided, however, that the Executive shall be entitled to at least four (4) weeks of paid vacation annually.

4. Termination.

4.1 Termination by the Company. The Executive's employment with the Company may be terminated only under the following conditions:

4.1.1 Termination for Death or Disability. The Executive's employment with the Company shall terminate effective upon the date of the Executive's death or "Complete Disability" (as defined in Section 4.5.1), provided, however, that this Section 4.1.1 shall in no way limit the Company's obligations to provide such reasonable accommodations to the Executive and/or his heirs as may be required by law.

4.1.2 Termination by the Company For Cause. The Company may terminate the Executive's employment under this Agreement for "Cause" (as defined in Section 4.5.3) by delivery of written notice to the Executive specifying the Cause or Causes relied upon for such termination, provided that such notice is delivered within two (2) months following the occurrence or discovery of any event or events constituting "Cause". Any notice of termination given pursuant to this Section 4.1.2 shall effect termination as of the date of the notice or such date as specified in the notice. The Executive shall have the right to appear before the CEO before any termination for Cause becomes effective and binding upon the Executive.

4.1.3 Termination by the Company Without Cause. The Company may terminate the Executive's employment under this Agreement at any time and for any reason or no reason subject to the requirements set out in Section 4.4 of this Agreement. Such termination shall be effective on the date the Executive is so informed or as otherwise specified by the Company, pursuant to notice requirements set forth in Section 6 of this Agreement.

4.2 Termination By The Executive. The Executive may terminate his employment with the Company at any time and for any reason or no reason, including, but not limited, to the following conditions:

4.2.1 Good Reason. The Executive may terminate his employment under this Agreement for "Good Reason" (as defined below in Section 4.5.2) by delivery of written notice to the Company specifying the Good Reason relied upon by the Executive for such termination in accordance with the requirements of such section.

4.2.2 Without Good Reason. The Executive may terminate the Executive's employment hereunder for other than Good Reason upon thirty (30) days written notice to the Company.

4.3 Termination by Mutual Agreement of the Parties. The Executive's employment pursuant to this Agreement may be terminated at any time upon a mutual agreement in writing of the parties. Any such termination of employment shall have the consequences specified in such mutual agreement.

4.4 Compensation to Executive Upon Termination. In connection with any termination of the Executive's employment for any reason, the Executive or the Executive's estate, as applicable, shall be entitled to any amounts payable to the Executive or the Executive's beneficiaries subject to and accordance with the terms of the Company's employee welfare benefit plans or policies (excluding any severance pay).

4.4.1 Death or Complete Disability. If the Executive's employment shall be terminated by death or Complete Disability as provided in Section 4.1.1, the Company shall pay to Executive, and/or Executive's heirs, all earned but unpaid Base Salary, any earned but unpaid discretionary bonuses for any prior period at such time as bonuses would have been paid if the Executive remained employed, all accrued but unpaid business expenses, and all accrued but unused vacation time earned through the date of termination at the rate in effect at the time of termination (hereinafter referred to as the ***"Accrued Amounts"***), less standard deductions and withholdings. The Executive shall also be eligible to receive a pro-rated bonus for the year of termination, as determined by the Board or the Compensation Committee of the Board based on actual performance and the period of the year he was employed (hereinafter referred to as the ***"Pro-rata Bonus"***), less standard deductions and withholdings, to be paid as a lump sum within thirty (30) days after the date of termination.

4.4.2 With Cause or Without Good Reason. If the Executive's employment shall be terminated by the Company for Cause, or if the Executive terminates employment hereunder without Good Reason, the Company shall pay the Executive's Base Salary, accrued but unpaid business expenses and accrued and unused vacation benefits earned through the date of termination at the rate in effect at the time of termination, less standard deductions and withholdings.

4.4.3 Without Cause or For Good Reason.

(i) Not in Connection With a Change in Control. If the Company terminates the Executive's employment without Cause or the Executive terminates his employment for Good Reason, and Section 4.4.3(ii) below does not apply, the Company shall pay the Accrued Amounts subject to standard deductions and withholdings, to be paid as a lump sum no later than thirty (30) days after the date of termination. In addition, subject to the limitations stated in this Agreement and upon the Executive's furnishing to the Company an executed (the "***Release***") within the applicable time period set forth therein, but in no event later than forty-five days following termination of employment and permitting such Release to become effective in accordance with its terms (the "***Release Effective Date***"), and subject to Executive entering into no later than the Release Effective Date a non-competition agreement to be effective during the Severance Period (as defined below), substantially similar to Section 2.3, and continuing to abide by its terms during the Severance Period, the Executive shall be entitled to:

(a) the equivalent of the Executive's Base Salary in effect at the time of termination will continue to be paid for a period of twelve (12) months following the date of termination (hereinafter referred to as the "***Severance Period***"), less standard deductions and withholdings, to be paid during the Severance Period according to the Company's regular payroll practices, subject to any delay in payment required by Section 4.6 in connection with the Release Effective Date; and

(b) in the event the Executive timely elects continued coverage under COBRA, the Company will continue to pay the same portion of Executive's COBRA health insurance premium as the percentage of health insurance premiums that it paid during the Executive's employment, including any amounts that Company paid for benefits to the qualifying family members of the Executive, following the date of termination up until the earlier of either (i) the last day of the Severance Period or, (ii) the date on which the Executive begins full-time employment with another company or business entity which offers comparable health insurance coverage to the Executive (such period, the "***COBRA Payment Period***"). Notwithstanding the foregoing, if the Company determines, in its sole discretion, that the Company cannot provide the COBRA premium benefits without potentially incurring financial costs or penalties under applicable law (including, without limitation, Section 2716 of the Public Health Service Act), the Company shall in lieu thereof pay Executive a taxable cash amount, which payment shall be made regardless of whether the Executive or his qualifying family members elect COBRA continuation coverage (the "***Health Care Benefit Payment***"). The Health Care Benefit Payment shall be paid in monthly or bi-weekly installments on the same schedule that the COBRA premiums would otherwise have been paid to the insurer. The Health Care Benefit Payment shall be equal to the amount that the Company otherwise would have paid for COBRA insurance premiums (which amount shall be calculated based on the premium for the first month of coverage), and shall be paid until the expiration of the COBRA Payment Period.

(ii) In Connection With a Change in Control. If the Company (or its successor) terminates the Executive's employment without Cause or the Executive terminates his employment for Good Reason within the period commencing ninety (90) days immediately prior to a Change in Control of the Company and ending eighteen (18) months immediately following a Change in Control of the Company (as defined in Section 4.5.4 of this Agreement), the Executive shall receive the Accrued Amounts subject to standard deductions and withholdings, to be paid as a lump sum no later than thirty (30) days after the date of termination. In addition, subject to the limitations stated in this Agreement and upon the Executive's furnishing to the Company (or its successor) an executed Release within the applicable time period set forth therein, but in no event later than forty-five days following termination of employment and permitting such Release to become effective in accordance with its terms, and subject to Executive entering into no later than the Release Effective Date a non-competition agreement to be effective during the Severance Period, substantially similar to Section 2.3, and continuing to abide by its terms during the Severance Period, then in lieu of (and not additional to) the benefits provided pursuant to Section 4.4.3(i) above, the Executive shall be entitled to:

(a) the equivalent of the Executive's Base Salary in effect at the time of termination will continue to be paid during the Severance Period, less standard deductions and withholdings, to be paid during the Severance Period according to the Company's regular payroll practices, subject to any delay in payment required by Section 4.6 in connection with the Release Effective Date;

(b) Executive's target Bonus in effect at the time of termination, or if none, the last target Bonus in effect for Executive, less standard deductions and withholdings, to be paid in a lump sum within ten (10) days following the later of (i) the Release Effective Date, or (ii) the effective date of the Change in Control; and

(c) in the event the Executive timely elects continued coverage under COBRA, the Company will continue to pay the same portion of Executive's COBRA health insurance premium as the percentage of health insurance premiums that it paid during the Executive's employment, including any amounts that Company paid for benefits to the qualifying family members of the Executive, following the date of termination until the expiration of the COBRA Payment Period. Notwithstanding the foregoing, if the Company determines, in its sole discretion, that the Company cannot provide the COBRA premium benefits without potentially incurring financial costs or penalties under applicable law (including, without limitation, Section 2716 of the Public Health Service Act), the Company shall in lieu thereof pay Executive the Health Care Benefit Payment, which payment shall be made regardless of whether the Executive or his qualifying family members elect COBRA continuation coverage. The Health Care Benefit Payment shall be paid in monthly or bi-weekly installments on the same schedule that the COBRA premiums would otherwise have been paid to the insurer. The Health Care Benefit Payment shall be equal to the amount that the Company otherwise would have paid for COBRA insurance premiums (which amount shall be calculated based on the premium for the first month of coverage), and shall be paid until the expiration of the COBRA Payment Period.

(iii) No Duplication of Benefits. For the avoidance of doubt, in no event will Executive be entitled to benefits under Section 4.4.3(i) and Section 4.4.3(ii). If Executive commences to receive benefits under Section 4.4.3(i) due to a qualifying termination prior to a Change in Control and thereafter becomes entitled to benefits under Section 4.4.3(ii), any benefits previously provided to Executive under Section 4.4.3(i) shall offset the benefits to be provided to Executive under Section 4.4.3(ii) and shall be deemed to have been provided to Executive pursuant to Section 4.4.3(ii).

4.4.4 Equity Award Acceleration.

(i) In Connection With a Change in Control. In the event that the Executive's employment is terminated without Cause or for Good Reason within the ninety (90) days immediately preceding or during the eighteen (18) months immediately following a Change in Control of the Company (as defined in Section 4.5.4 of this Agreement), the vesting of the Option, the RSU Award and any other time-based vesting Company equity awards granted to Executive shall be fully accelerated such that on the effective date of such termination (or, if later, the date of the Change in Control) one hundred percent (100%) of the equity award shares granted to Executive prior to such termination shall be fully vested and immediately exercisable, if applicable, by the Executive.

(ii) Release and Waiver. Any equity vesting acceleration pursuant to this Section 4.4.4 shall be conditioned upon and subject to the Executive's delivery to the Company of a fully effective Release in accordance with the terms specified by Section 4.4.3 hereof and such vesting acceleration benefit shall be in addition to the benefits provided by Section 4.4.3 hereof.

4.5 Definitions. For purposes of this Agreement, the following terms shall have the following meanings:

4.5.1 Affiliate. ***"Affiliates"*** means Horizon Pharma plc and each of its majority owned subsidiaries and ***"Affiliate"*** means any of the Affiliates.

4.5.2 Cause. ***"Cause"*** for the Company to terminate Executive's employment hereunder shall mean the occurrence of any of the following events, as determined reasonably and in good faith by the Board or a committee designated by the Board:

(i) the Executive's gross negligence or willful failure to substantially perform his duties and responsibilities to the Company or willful and deliberate violation of a Company policy;

(ii) the Executive's conviction of a felony or the Executive's commission of any act of fraud, embezzlement or dishonesty against the Company or involving moral turpitude that is likely to inflict or has inflicted material injury on the business of the Company, to be determined by the sole discretion of the Company;

(iii) the Executive's unauthorized use or disclosure of any proprietary information or trade secrets of the Company or any other party that the Executive owes an obligation of nondisclosure as a result of the Executive's relationship with the Company; and

(iv) the Executive's willful and deliberate breach of the obligations under this Agreement that causes material injury to the business of the Company.

4.5.3 Change in Control. For purposes of this Agreement, ***"Change in Control"*** means: (i) a sale of all or substantially all of the assets of the Company; (ii) a merger or consolidation in which the Company is not the surviving entity and in which the holders of the Company's outstanding voting stock immediately prior to such transaction own, immediately after such transaction, securities representing less than fifty percent (50%) of the voting power of the entity surviving such transaction or, where the surviving entity is a wholly-owned subsidiary of another entity, the surviving entity's parent; (iii) a reverse merger in which the Company is the surviving entity but the shares of Common Stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities of the surviving entity's parent, cash or otherwise, and in which the holders of the Company's outstanding voting stock immediately prior to such transaction own, immediately after such transaction, securities representing less than fifty percent (50%) of the voting power of the Company or, where the Company is a wholly-owned subsidiary of another entity, the Company's parent; or (iv) an acquisition by any person, entity or group (excluding any employee benefit plan, or related trust, sponsored or maintained by the Company or subsidiary of the Company or other entity controlled by the Company) of the beneficial ownership of securities of

the Company representing at least seventy-five percent (75%) of the combined voting power entitled to vote in the election of Directors; provided, however, that nothing in this paragraph shall apply to a sale of assets, merger or other transaction effected exclusively for the purpose of changing the domicile of the Company.

4.5.4 Complete Disability. ***"Complete Disability"*** shall mean the inability of the Executive to perform the Executive's duties under this Agreement, whether with or without reasonable accommodation, because the Executive has become permanently disabled within the meaning of any policy of disability income insurance covering employees of the Company then in force. In the event the Company has no policy of disability income insurance covering employees of the Company in force when the Executive becomes disabled, the term "Complete Disability" shall mean the inability of the Executive to perform the Executive's duties under this Agreement, whether with or without reasonable accommodation, by reason of any incapacity, physical or mental, which the Board, based upon medical advice or an opinion provided by a licensed physician, determines to have incapacitated the Executive from satisfactorily performing all of the Executive's usual services for the Company, with or without reasonable accommodation, for a period of at least one hundred eighty (180) days during any twelve (12) month period that need not be consecutive.

4.5.5 Good Reason. ***"Good Reason"*** for the Executive to terminate the Executive's employment hereunder shall mean the occurrence of any of the following events without the Executive's consent:

(i) a material reduction in the Executive's duties, authority, or responsibilities relative to the duties, authority, or responsibilities in effect immediately prior to such reduction, including by way of example, having the same title, duties, authority and responsibilities at a subsidiary level following a Change in Control;

(ii) the relocation of the Executive's primary work location to a point more than fifty (50) miles from the Executive's current work location set forth in Section 1.5 that requires a material increase in Executive's one-way driving distance;

(iii) a material reduction by the Company of the Executive's base salary or annual target Bonus opportunity, without the written consent of the Executive, as initially set forth herein or as the same may be increased from time to time pursuant to this Agreement; and

(iv) a material breach by the Company of Section 1.2 of this Agreement.

Provided, however that, such termination by the Executive shall only be deemed for Good Reason pursuant to the foregoing definition if (i) the Company is given written notice from the Executive within sixty (60) days following the first occurrence of the condition that he considers to constitute Good Reason describing the condition and the Company fails to satisfactorily remedy such condition within thirty (30) days following such written notice, and (ii) the Executive terminates employment within thirty (30) days following the end of the period within which the Company was entitled to remedy the condition constituting Good Reason but failed to do so.

4.5.6 Release. ***"Release"*** means a waiver and release of claims in a form acceptable to the Company and substantially as attached hereto as **EXHIBIT A**.

4.6 Application of Internal Revenue Code Section 409A. Notwithstanding anything to the contrary set forth herein, any payments and benefits provided under this Agreement (the ***"Severance Benefits"***) that constitute "deferred compensation" within the meaning of Section 409A of the Internal Revenue Code of 1986, as amended (the ***"Code"***) and the regulations and other guidance thereunder and any state law of similar effect (collectively ***"Section 409A"***) shall not commence in connection with Executive's termination of employment unless and until Executive has also incurred a "separation from service" (as such term is defined in Treasury Regulation Section 1.409A-1(h) (***"Separation From Service"***), unless the Company reasonably determines that such amounts may be provided to Executive without causing Executive to incur the additional 20% tax under Section 409A.

It is intended that each installment of the Severance Benefits payments provided for in this Agreement is a separate "payment" for purposes of Treasury Regulation Section 1.409A-2(b)(2)(i). For the avoidance of doubt, it is intended that payments of the Severance Benefits set forth in this Agreement satisfy, to the greatest extent possible, the exemptions from the application of Section 409A provided under Treasury Regulation Sections 1.409A-1(b)(4), 1.409A-1(b)(5) and 1.409A-1(b)(9). However, if the Company (or, if applicable, the successor entity thereto) determines that the Severance Benefits constitute "deferred compensation" under Section 409A and Executive is, on the termination of service, a "specified employee" of the Company or any successor entity thereto, as such term is defined in Section 409A(a)(2)(B)(i) of the Code, then, solely to the extent necessary to avoid the incurrence of the adverse personal tax consequences under Section 409A, the timing of the Severance Benefit payments shall be delayed until the earlier to occur of: (i) the date that is six months and one day after Executive's Separation From Service, or (ii) the date of Executive's death (such applicable date, the ***"Specified Employee Initial Payment Date"***), the Company (or the successor entity thereto, as applicable) shall (A) pay to Executive a lump sum amount equal to the sum of the Severance Benefit payments that Executive would otherwise have received through the Specified Employee Initial Payment Date if the commencement of the payment of the Severance Benefits had not been so delayed pursuant to this Section and (B) commence paying the balance of the Severance Benefits in accordance with the applicable payment schedules set forth in this Agreement.

Notwithstanding anything to the contrary set forth herein, Executive shall receive the Severance Benefits described above, if and only if Executive duly executes and returns to the Company within the applicable time period set forth therein, but in no event more than forty-five days following Separation From Service, the Company's standard form of release of claims in favor of the Company (attached to this Agreement as Exhibit A) (the "***Release***") and permits the release of claims contained therein to become effective in accordance with its terms (such latest permitted date, the **"*Release Deadline*"**). If the severance benefits are not covered by one or more exemptions from the application of Section 409A and the Release could become effective in the calendar year following the calendar year in which Executive separates from service, the Release will not be deemed effective any earlier than the Release Deadline. Notwithstanding any

other payment schedule set forth in this Agreement, none of the Severance Benefits will be paid or otherwise delivered prior to the effective date (or deemed effective date) of the Release. Except to the extent that payments may be delayed until the Specified Employee Initial Payment Date pursuant to the preceding paragraph, on the first regular payroll pay day following the effective date of the Release, the Company will pay Executive the Severance Benefits Executive would otherwise have received under the Agreement on or prior to such date but for the delay in payment related to the effectiveness of the Release, with the balance of the Severance Benefits being paid as originally scheduled.

The severance benefits are intended to qualify for an exemption from application of Section 409A or comply with its requirements to the extent necessary to avoid adverse personal tax consequences under Section 409A, and any ambiguities herein shall be interpreted accordingly.

4.7 Application of Internal Revenue Code Section 280G. If any payment or benefit Executive would receive pursuant to a Change in Control from the Company or otherwise (***"Payment"***) would (i) constitute a "parachute payment" within the meaning of Section 280G of the Code, and (ii) but for this sentence, be subject to the excise tax imposed by Section 4999 of the Code (the ***"Excise Tax"***), then such Payment shall be equal to the Reduced Amount. The "Reduced Amount" shall be either (x) the largest portion of the Payment that would result in no portion of the Payment being subject to the Excise Tax or (y) the largest portion, up to and including the total, of the Payment, whichever amount, after taking into account all applicable federal, state and local employment taxes, income taxes, and the Excise Tax (all computed at the highest applicable marginal rate), results in Executive's receipt, on an after-tax basis, of the greater economic benefit notwithstanding that all or some portion of the Payment may be subject to the Excise Tax. If a reduction in payments or benefits constituting "parachute payments" is necessary so that the Payment equals the Reduced Amount, reduction shall occur in the manner that results in the greatest economic benefit for Executive. If more than one method of reduction will result in the same economic benefit, the items so reduced will be reduced pro rata.

In the event it is subsequently determined by the Internal Revenue Service that some portion of the Reduced Amount as determined pursuant to clause (x) in the preceding paragraph is subject to the Excise Tax, Executive agrees to promptly return to the Company a sufficient amount of the Payment so that no portion of the Reduced Amount is subject to the Excise Tax. For the avoidance of doubt, if the Reduced Amount is determined pursuant to clause (y) in the preceding paragraph, Executive will have no obligation to return any portion of the Payment pursuant to the preceding sentence.

Unless Executive and the Company agree on an alternative accounting firm, the accounting firm engaged by the Company for general tax compliance purposes as of the day prior to the effective date of the Change in Control shall perform the foregoing calculations. If the accounting firm so engaged by the Company is serving as accountant or auditor for the individual, entity or group effecting the Change in Control, the Company shall appoint a nationally recognized accounting firm to make the determinations required hereunder. The Company shall bear all expenses with respect to the determinations by such accounting firm required to be made hereunder.

The Company shall use commercially reasonable efforts to cause the accounting firm engaged to make the determinations hereunder to provide its calculations, together with detailed supporting documentation, to Executive and the Company within fifteen (15) calendar days after the date on which Executive's right to a Payment is triggered (if requested at that time by Executive or the Company) or such other time as requested by Executive or the Company.

4.8 Indemnification Agreements. Concurrently with the execution of this Agreement, the Company and the Executive shall enter into indemnification agreements, copies of which are attached hereto as Exhibit B-1 and Exhibit B-2.

4.9 Confidential Information and Invention Assignment Agreement. Concurrently with the execution of this Agreement, Executive shall enter into Company's Confidential Information and Invention Assignment Agreement, a copy of which is attached as Exhibit C.

4.10 Arbitration Agreement. Concurrently with the execution of this Agreement and in consideration for the benefits provided hereunder, Executive shall enter into Company's Arbitration Agreement, a copy of which is attached as Exhibit D.

4.11 Insider Trading Policy; Window Period Policy. Executive hereby acknowledges that Executive has received and read a copy of the Horizon Pharma plc Insider Trading Policy and Horizon Pharma plc Window Period Policy (the "***Trading and Window Period Policies***"). Executive agrees to comply with the specific requirements of the Trading and Window Period Policies in all respects during Executive's employment or other service relationship with the Company and/or an Affiliate. Executive understands that the Trading and Window Period Policies constitutes a material term of Executive's employment or other service relationship with the Company and/or an Affiliate and that Executive's failure to comply in all respects with the Trading and Window Period Policies is a basis for termination for Cause.

4.12 No Mitigation or Offset. The Executive shall not be required to seek or accept other employment, or otherwise to mitigate damages, as a condition to receipt of the Severance Benefits, and the Severance Benefits shall not be offset by any amounts received by the Executive from any other source, except to the extent that the Executive's rights to the benefits described in Sections 4.4.3(i)(b) or 4.4.3(ii)(c), as applicable, are terminated by reason of the Executive obtaining full-time employment with another company or business entity which offers comparable health insurance coverage.

5. Assignment and Binding Effect.

This Agreement shall be binding upon the Executive and the Company and inure to the benefit of the Executive and the Executive's heirs, executors, personal representatives, assigns, administrators and legal representatives. Because of the unique and personal nature of the Executive's duties under this Agreement, neither this Agreement nor obligations under this Agreement shall be assignable by the Executive. This Agreement shall be binding upon and inure to the benefit of the Company and its successors, assigns and legal representatives, provided that the Agreement may only be assigned to an acquirer of all or substantially all of the Company's assets. Any such successor of the Company will be deemed substituted for the

Company under the terms of this Agreement for all purposes. For this purpose, "successor" means any person, firm, corporation or other business entity which at any time, whether by purchase, merger or otherwise, directly or indirectly acquires all or substantially all of the assets or business of the Company.

6. Notice.

For the purposes of this Agreement, notices, demands, and all other forms of communication provided for in this Agreement shall be in writing and shall be deemed to have been duly given when delivered or (unless otherwise specified) mailed by registered mail, return receipt requested, postage prepaid, or by confirmed facsimile, addressed as set forth below, or to such other address as any party may have furnished to the other in writing in accordance herewith, except that notices of address shall be effective only upon receipt, as follows:

If to the Company:

Horizon Pharma, Inc.
150 S. Saunders Road
Lake Forest, IL 60045
Attention: Timothy P. Walbert, Chairman, President & CEO
Fax: 847-572-1372

If to the Executive:

Michael DesJardin
1520 Valencia Road
Aptos, CA 95003

Any such written notice shall be deemed given on the earlier of the date on which such notice is personally delivered or five (5) days after its deposit in the United States mail as specified above. Either party may change its address for notices by giving written notice to the other party in the manner specified in this section.

7. Choice of Law.

This Agreement shall be governed by the laws of the State of California, without regard to any conflicts of law principals thereof that would call for the application of the laws of any other jurisdiction.

8. Integration.

This Agreement, including Exhibit A, Exhibit B-1, Exhibit B-2, Exhibit C, Exhibit D, the Trading and Window Period Policies, the Equity Plan Documents, and the Transition Services Agreement contains the complete, final and exclusive agreement of the parties relating to the terms and conditions of the Executive's employment and the termination of Executive's employment, and supersedes all prior and contemporaneous oral and written employment agreements or arrangements between the parties, including but not limited to the Prior Agreement. By executing this Agreement, Executive hereby agrees that Executive's Prior

Agreement is terminated and superseded in its entirety by this Agreement as of the Effective Date and that Executive waives any right that Executive may have and/or is not entitled to severance benefits under the Prior Agreement.

9. Amendment.

This Agreement cannot be amended or modified except by a written agreement signed by the Executive and the Company.

10. Waiver.

No term, covenant or condition of this Agreement or any breach thereof shall be deemed waived, except with the written consent of the party against whom the wavier is claimed, and any waiver or any such term, covenant, condition or breach shall not be deemed to be a waiver of any preceding or succeeding breach of the same or any other term, covenant, condition or breach.

11. Severability.

The finding by a court of competent jurisdiction of the unenforceability, invalidity or illegality of any provision of this Agreement shall not render any other provision of this Agreement unenforceable, invalid or illegal. Such court shall have the authority to modify or replace the invalid or unenforceable term or provision with a valid and enforceable term or provision, which most accurately represents the parties' intention with respect to the invalid, unenforceable, or illegal term or provision.

12. Interpretation; Construction.

The headings set forth in this Agreement are for convenience of reference only and shall not be used in interpreting this Agreement. This Agreement has been drafted and negotiated by legal counsel representing the Company and the Executive. The parties acknowledge that each party and its counsel has reviewed and revised, or had an opportunity to review and revise, this Agreement, and any rule of construction to the effect that any ambiguities are to be resolved against the drafting party shall not be employed in the interpretation of this Agreement.

13. Execution by Facsimile Signatures and in Counterparts.

The parties agree that facsimile signatures shall have the same force and effect as original signatures. This Agreement may be executed in one or more counterparts, each of which shall be deemed an original but all of which together shall constitute one and the same instrument.

14. Survival.

The provisions of this Agreement, and of all other agreements referenced herein, shall survive the termination of this Agreement, and of the Executive's employment by the Company for any reason, to the extent necessary to enable the parties to enforce their respective rights hereunder.

[Remainder of Page Intentionally Left Blank]

IN WITNESS WHEREFORE, the parties have signed this Agreement on the date first written above.

COMPANY:

HORIZON PHARMA, INC.
HORIZON PHARMA USA, INC.

By:

Title: Chairman, President & CEO

Print Name: Timothy P. Walbert

/s/ Timothy Walbert
Signature:

As authorized agent of the Company

March 16, 2017
Date

EXECUTIVE:

Michael DesJardin

/s/ Michael DesJardin
Michael DesJardin, individually

March 16, 2017
Date

EXHIBIT A

RELEASE AND WAIVER OF CLAIMS

In consideration of the payments and other benefits set forth in Section 3 of the Executive Employment Agreement dated February 16, 2017, (the ***"Employment Agreement"***), to which this form is attached, I, Michael DesJardin, hereby furnish Horizon Pharma, Inc. and Horizon Pharma USA, Inc. (together the ***"Company"***), with the following release and waiver (***"Release and Waiver"***).

In exchange for the consideration provided to me by the Employment Agreement that I am not otherwise entitled to receive, I hereby generally and completely release the Company and its directors, officers, employees, shareholders, partners, agents, attorneys, predecessors, successors, parent and subsidiary entities, insurers, Affiliates, and assigns from any and all claims, liabilities and obligations, both known and unknown, that arise out of or are in any way related to events, acts, conduct, or omissions occurring relating to my employment or the termination thereof prior to my signing this Release and Waiver. This general release includes, but is not limited to: (1) all claims arising out of or in any way related to my employment with the Company or the termination of that employment; (2) all claims related to my compensation or benefits from the Company, including, but not limited to, salary, bonuses, commissions, vacation pay, expense reimbursements, severance pay, fringe benefits, stock, stock options, or any other ownership interests in the Company; (3) all claims for breach of contract, wrongful termination, and breach of the implied covenant of good faith and fair dealing; (4) all tort claims, including, but not limited to, claims for fraud, defamation, emotional distress, and discharge in violation of public policy; and (5) all federal, state, and local statutory claims, including, but not limited to, claims for discrimination, harassment, retaliation, attorneys' fees, or other claims arising under the federal Civil Rights Act of 1964 (as amended), the federal Americans with Disabilities Act of 1990, the federal Age Discrimination in Employment Act of 1967 (as amended) (***"ADEA"***), the California Labor Code (as amended), the California Family Rights Act, and the California Fair Employment and Housing Act (as amended). Notwithstanding the foregoing, this Release and Waiver, shall not release or waive my rights: to indemnification under the articles and bylaws of the Company, any and all indemnification agreements, or applicable law; to payments under Section 4 of the Employment Agreement; under any provision of the Employment Agreement that survives the termination of that agreement; under any applicable workers' compensation statute; under any option, restricted share or other agreement concerning any equity interest in the Company; as a shareholder of the Company or any other right that is not waivable under applicable law.

I acknowledge that, among other rights, I am waiving and releasing any rights I may have under ADEA, that this Release and Waiver is knowing and voluntary, and that the consideration given for this Release and Waiver is in addition to anything of value to which I was already entitled as an executive of the Company. If I am 40 years of age or older upon execution of this Release and Waiver, I further acknowledge that I have been advised, as required by the Older Workers Benefit Protection Act, that: (a) the release

and waiver granted herein does not relate to claims under the ADEA which may arise after this Release and Waiver is executed; (b) I should consult with an attorney prior to executing this Release and Waiver; and (c) I have twenty-one (21) days from the date of termination of my employment with the Company in which to consider this Release and Waiver (although I may choose voluntarily to execute this Release and Waiver earlier); (d) I have seven (7) days following the execution of this Release and Waiver to revoke my consent to this Release and Waiver; and (e) this Release and Waiver shall not be effective until the seven (7) day revocation period has expired unexercised. If I am less than 40 years of age upon execution of this Release and Waiver, I acknowledge that I have the right to consult with an attorney prior to executing this Release and Waiver (although I may choose voluntarily not to do so); and (c) I have five (5) days from the date of termination of my employment with the Company in which to consider this Release and Waiver (although I may choose voluntarily to execute this Release and Waiver earlier).

I acknowledge my continuing obligations under my Confidential Information and Inventions Agreement dated March 15, 2017. Pursuant to the Confidential Information and Inventions Agreement I understand that among other things, I must not use or disclose any confidential or proprietary information of the Company and I must immediately return all Company property and documents (including all embodiments of proprietary information) and all copies thereof in my possession or control. I understand and agree that my right to the payments and other benefits I am receiving in exchange for my agreement to the terms of this Release and Waiver is contingent upon my continued compliance with my Confidential Information and Inventions Agreement.

This Release and Waiver, including my Confidential Information and Inventions Agreement dated March 15, 2017, constitutes the complete, final and exclusive embodiment of the entire agreement between the Company and me with regard to the subject matter hereof. I am not relying on any promise or representation by the Company that is not expressly stated herein. This Release and Waiver may only be modified by a writing signed by both me and a duly authorized officer of the Company.

Date: March 16, 2017

By: /s/ Michael DesJardin
Michael DesJardin

Exhibit 10.69

HORIZON PHARMA, INC.

FIRST AMENDMENT TO
EXECUTIVE EMPLOYMENT AGREEMENT

This First Amendment to Executive Employment Agreement (this "***Amendment***"), amending that certain Executive Employment Agreement dated February 16, 2017 (the "***Employment Agreement***"), by and among Horizon Pharma, Inc., a Delaware corporation, and its wholly owned subsidiary, Horizon Pharma USA, Inc., a Delaware corporation (hereinafter referred to together as the "***Company***"), and Michael DesJardin (the "***Executive***"), is entered into as of May 4, 2017 by and among the Company and the Executive. Capitalized terms used herein which are not defined herein shall have the definition ascribed to them in the Employment Agreement.

RECITALS

WHEREAS, the Company and the Executive have previously entered into the Employment Agreement;

WHEREAS, Section 9 of the Employment Agreement provides that the Employment Agreement may be amended with the written agreement of the Company and the Executive; and

WHEREAS, the Company and the Executive desire to amend the Employment Agreement as set forth herein.

AGREEMENT

NOW, THEREFORE, in consideration of the foregoing and the promises and covenants contained herein and in the Employment Agreement, and for other good and valuable consideration, the receipt of which is hereby acknowledged, the parties hereto agree as follows:

1. Section 4.4.3 of the Employment Agreement. Section 4.4.3 of the Employment Agreement is hereby amended and restated in its entirety to read as follows:

"**4.4.3 Without Cause or For Good Reason.**

(i) Not in Connection With a Change in Control. If the Company terminates the Executive's employment without Cause or the Executive terminates his employment for Good Reason, and Section 4.4.3(ii) below does not apply, the Company shall pay the Accrued Amounts subject to standard deductions and withholdings, to be paid as a lump sum no later than thirty (30) days after the date of termination. In addition, subject to the limitations stated in this Agreement and upon the Executive's furnishing to the Company an executed waiver and release of claims (the form of which is attached hereto as Exhibit A) (the "***Release***") within the applicable time period set forth therein, but in no event later than forty-five days following termination of employment and permitting such Release to become effective in accordance with its terms (the "***Release***

Effective Date"), and subject to Executive entering into no later than the Release Effective Date a non-competition agreement to be effective during the Severance Period (as defined below), substantially similar to Section 2.3, and continuing to abide by its terms during the Severance Period, the Executive shall be entitled to:

(a) the equivalent of the Executive's Base Salary in effect at the time of termination will continue to be paid for a period of twelve (12) months following the date of termination (hereinafter referred to as the "***Non Change in Control Severance Period***"), less standard deductions and withholdings, to be paid during the Non Change in Control Severance Period according to the Company's regular payroll practices, subject to any delay in payment required by Section 4.6 in connection with the Release Effective Date; and

(b) in the event the Executive timely elects continued coverage under COBRA, the Company will continue to pay the same portion of Executive's COBRA health insurance premium as the percentage of health insurance premiums that it paid during the Executive's employment, including any amounts that Company paid for benefits to the qualifying family members of the Executive, following the date of termination up until the earlier of either (i) the last day of the Non Change in Control Severance Period or, (ii) the date on which the Executive begins full-time employment with another company or business entity which offers comparable health insurance coverage to the Executive (such period, the "***Non Change in Control COBRA Payment Period***"). Notwithstanding the foregoing, if the Company determines, in its sole discretion, that the Company cannot provide the COBRA premium benefits without potentially incurring financial costs or penalties under applicable law (including, without limitation, Section 2716 of the Public Health Service Act), the Company shall in lieu thereof pay Executive a taxable cash amount, which payment shall be made regardless of whether the Executive or his qualifying family members elect COBRA continuation coverage (the "***Health Care Benefit Payment***"). The Health Care Benefit Payment shall be paid in monthly or bi-weekly installments on the same schedule that the COBRA premiums would otherwise have been paid to the insurer. The Health Care Benefit Payment shall be equal to the amount that the Company otherwise would have paid for COBRA insurance premiums (which amount shall be calculated based on the premium for the first month of coverage), and shall be paid until the expiration of the Non Change in Control COBRA Payment Period.

(ii) In Connection With a Change in Control. If the Company (or its successor) terminates the Executive's employment without Cause or the Executive terminates his employment for Good Reason within the period commencing three (3) months immediately prior to a Change in Control of the Company and ending eighteen (18) months immediately following a Change in Control of the Company (as defined in Section 4.5.4 of this Agreement), the Executive shall receive the Accrued Amounts subject to standard deductions and withholdings, to be paid as a lump sum no later than thirty (30) days after the date of termination. In addition, subject to the limitations stated in this Agreement and upon the Executive's furnishing to the Company (or its successor) an executed Release within the applicable time period set forth therein, but in no event later than forty-five days following termination of employment and permitting such

Release to become effective in accordance with its terms, and subject to Executive entering into no later than the Release Effective Date a non-competition agreement to be effective during the Severance Period, substantially similar to Section 2.3, and continuing to abide by its terms during the Severance Period, then in lieu of (and not additional to) the benefits provided pursuant to Section 4.4.3(i) above, the Executive shall be entitled to:

(a) the equivalent of the Executive's Base Salary in effect at the time of termination will continue to be paid for a period of eighteen (18) months following the date of termination (hereinafter referred to as the "***Change in Control Severance Period***"), less standard deductions and withholdings, to be paid during the Change in Control Severance Period according to the Company's regular payroll practices, subject to any delay in payment required by Section 4.6 in connection with the Release Effective Date;

(b) one and half (1.5) times Executive's target Bonus in effect at the time of termination, or if none, one and half (1.5) times the last target Bonus in effect for Executive, less standard deductions and withholdings, to be paid in a lump sum within ten (10) days following the later of (i) the Release Effective Date, or (ii) the effective date of the Change in Control; and

(c) in the event the Executive timely elects continued coverage under COBRA, the Company will continue to pay the same portion of Executive's COBRA health insurance premium as the percentage of health insurance premiums that it paid during the Executive's employment, including any amounts that Company paid for benefits to the qualifying family members of the Executive, following the date of termination until the expiration of the Change in Control Severance Period. Notwithstanding the foregoing, if the Company determines, in its sole discretion, that the Company cannot provide the COBRA premium benefits without potentially incurring financial costs or penalties under applicable law (including, without limitation, Section 2716 of the Public Health Service Act), the Company shall in lieu thereof pay Executive the Health Care Benefit Payment, which payment shall be made regardless of whether the Executive or his qualifying family members elect COBRA continuation coverage. The Health Care Benefit Payment shall be paid in monthly or bi-weekly installments on the same schedule that the COBRA premiums would otherwise have been paid to the insurer. The Health Care Benefit Payment shall be equal to the amount that the Company otherwise would have paid for COBRA insurance premiums (which amount shall be calculated based on the premium for the first month of coverage), and shall be paid until the expiration of the Change in Control Severance Period.

(iii) No Duplication of Benefits. For the avoidance of doubt, in no event will Executive be entitled to benefits under Section 4.4.3(i) and Section 4.4.3(ii). If Executive commences to receive benefits under Section 4.4.3(i) due to a qualifying termination prior to a Change in Control and thereafter becomes entitled to benefits under Section 4.4.3(ii), any benefits previously provided to Executive under Section 4.4.3(i) shall offset the benefits to be provided to Executive under Section 4.4.3(ii) and shall be deemed to have been provided to Executive pursuant to Section 4.4.3(ii)."

2. Section 4.4.4 of the Employment Agreement. Section 4.4.4 of the Employment Agreement is hereby amended and restated in its entirety to read as follows:

"4.4.4 Equity Award Acceleration.

(i) Not in Connection With a Change in Control. In the event that the Executive's employment is terminated without Cause or for Good Reason and Section 4.4.4 (ii) below does not apply, the vesting of any equity awards granted to Executive that vest solely subject to Executive's continued services to the Company (the "***Time-Based Vesting Equity Awards***") shall be deemed vested and immediately exercisable (if applicable) by the Executive with respect to such number of shares as determined in accordance with their applicable vesting schedules as if Executive had provided an additional twelve (12) months of services as of the date of termination. Treatment of any performance based vesting equity awards will be governed solely by the terms of the agreements under which such awards were granted and will not be eligible to accelerate vesting pursuant to the foregoing provision.

(ii) In Connection With a Change in Control. In the event that the Executive's employment is terminated without Cause or for Good Reason within the three (3) months immediately preceding or during the eighteen (18) months immediately following a Change in Control of the Company (as defined in Section 4.5.4 of this Agreement), the vesting of any Time-Based Vesting Equity Awards granted to Executive shall be fully accelerated such that on the effective date of such termination (or if later, the date of the Change in Control) one hundred percent (100%) of any Time-Based Vesting Equity Awards granted to Executive prior to such termination shall be fully vested and immediately exercisable, if applicable, by the Executive. Treatment of any performance based vesting equity awards will be governed solely by the terms of the agreements under which such awards were granted and will not be eligible to accelerate vesting pursuant to the foregoing provision.

(iii) Release and Waiver. Any equity vesting acceleration pursuant to this Section 4.4.4 shall be conditioned upon and subject to the Executive's delivery to the Company of a fully effective Release in accordance with the terms specified by Section 4.4.3 hereof and such vesting acceleration benefit shall be in addition to the benefits provided by Section 4.4.3 hereof."

3. Effect of Amendment. Except as expressly modified by this Amendment, the Employment Agreement shall remain unmodified and in full force and effect.

4. Governing Law. This Amendment shall be governed by the laws of the State of Illinois, without regard to any conflicts of law principals thereof that would call for the application of the laws of any other jurisdiction.

5. Counterparts. This Amendment may be executed via facsimile or electronic (i.e., PDF) transmission and in any number of counterparts, each of which shall be deemed an original, but all of which together shall constitute one instrument.

[Remainder of Page Intentionally Left Blank]

IN WITNESS WHEREOF, the parties have executed this First Amendment to Executive Employment Agreement as of the date first written above.

COMPANY:

HORIZON PHARMA, INC.
HORIZON PHARMA USA, INC.

By: /s/ Timothy P. Walbert
TIMOTHY P. WALBERT, CHAIRMAN, PRESIDENT AND CHIEF EXECUTIVE OFFICER

EXECUTIVE:

/s/ Michael DesJardin
MICHAEL DESJARDIN

Exhibit 10.70

CONSULTING AGREEMENT

THIS CONSULTING AGREEMENT is made by and between Horizon Pharma USA, Inc. with its principal place of business at 150 South Saunders Road, Lake Forest, Illinois 60045 ("**Company**"), and **DAVID HAPPEL**, an individual residing at PO Box 203, 2362 Caballo Ranchero Drive, Diablo, CA 94528 ("**Consultant**"), effective February 1, 2018 (the "**Effective Date**"), for the purpose of setting forth the exclusive terms and conditions by which Company will acquire Consultant's services on a limited and temporary basis. Company and Consultant may be referred to herein individually as a "Party," or collectively as the "Parties."

In consideration of the mutual obligations specified in this Agreement, and any compensation paid to Consultant for his or her services, the Parties agree to the following:

1. Work, Payment and Term. Attached to this Agreement as **EXHIBIT A** hereto is a statement of the work performed or to be performed by Consultant, the payment terms for such work, the types of any expenses to be paid in connection with such work, any Background Technology (as defined in Section 3) to be used by Consultant in performing the work, and such other terms and conditions as the Parties deem appropriate or necessary for the performance of the work. Consultant shall perform all such work himself or herself, engaging the assistance of other individuals only with the prior written consent of Company.

2. Nondisclosure and Trade Secrets.

(a) During the term of this Agreement and in the course of Consultant's performance hereunder, Consultant may receive and otherwise be exposed to confidential and proprietary information owned by Company or its parent, subsidiaries or group affiliates (collectively, with Company, the "**Company Group**") or received by Company Group from third parties pursuant to an obligation of confidentiality with respect thereto, relating to the Company Group's business practices, strategies and technologies. Such confidential and proprietary information may include, but not be limited to, any compound, chemical, peptide, protein, complex, conjugate, virus, extract, media, vector, cell, cell component, cell line, formulation or sample; any procedure, discovery, invention, formula, data, result, idea or technique; any trade secret, trade dress, copyright, patent or other intellectual property right, or any registration or application therefor, or materials relating thereto; and any information relating to any of the foregoing or to any research, development, manufacturing, engineering, marketing, servicing, sales, financing, legal or other business activities or to any present or future products, prices, plans, forecasts, suppliers, clients, customers, employees, consultants or investors; whether in oral, written, graphic or electronic form (collectively referred to as "**Information**").

(b) Consultant acknowledges the confidential and secret nature of the Information, and agrees that the Information is the extremely valuable property of the Company Group or of the third party from which the Company Group received such Information. Accordingly, Consultant agrees not to reproduce any of the Information in any format, not to use the Information except in the performance of the work described in this Agreement, and not to disclose all or any part of the Information in any form to any third party, such obligations shall apply in each case during the term of this Agreement and for a period of ten (10) years thereafter, except with the prior written consent of Company. Upon termination of this Agreement for any reason, including expiration of the term of this Agreement, Consultant agrees to cease using and to return to Company all whole and partial copies and derivatives of the Information, whether in Consultant's possession or under Consultant's direct or indirect control.

(c) Consultant shall not disclose or otherwise make available to Company in any manner any confidential information of Consultant or any information received by Consultant from third parties, unless Company first agrees in writing to receive such information.

3. Ownership of Work Product.

(a) Consultant shall specifically describe and identify in EXHIBIT A to this Agreement any and all technology, including without limitation information, materials and related intellectual property rights, which (i) Consultant intends to use in performing the work under this Agreement, (ii) is either owned solely by Consultant or controlled by Consultant such that Consultant possesses the right to grant a license or sublicense thereunder and (iii) is in existence prior to the Effective Date ("**Background Technology**").

(b) Consultant agrees that any and all ideas, developments, discoveries, improvements, inventions and works of authorship conceived, written, created, tested, or first reduced to practice in the performance of work under this Agreement, including but not limited to any and all ideas, developments, discoveries, improvements, inventions and works of authorship that are in any way conceived, written, created, improved, tested or first reduced to practice by use of any of the Company Group's supplies, equipment, facilities, resources, or trade secret information, together with all intellectual property rights relating thereto ("**Work Product**") shall be the sole and exclusive property of Company. Consultant hereby assigns and transfers to Company all its right, title and interest in and to any and all such Work Product. If Consultant has any rights to Work Product that cannot, under applicable law, be assigned to Company, Consultant unconditionally and irrevocably waives the enforcement of such rights and all claims and causes of action of any kind against Company with respect to such rights. Consultant agrees, at the Company's request and expense, to consent to and join in any action to enforce such rights. If Consultant has any right to Work Product that can neither be assigned to Company nor waived by Consultant, Consultant hereby grants to Company an exclusive, irrevocable, perpetual, worldwide, fully paid and royalty free license, with rights to sublicense through multiple levels of sublicensees, to develop, make, have made, use, sell, have sold, offer for sale and import such Work Product. Consultant agrees to maintain written records of all Work Product and to promptly make full written disclosure to Company of all Work Product.

(c) Company acknowledges that Consultant shall retain all of Consultant's rights in any Background Technology. Consultant hereby grants to Company a non-exclusive, irrevocable, perpetual, worldwide, fully paid and royalty free license, with rights to sublicense through multiple levels of sublicensees, under the Background Technology to develop, make, have made, use, sell, have sold, offer for sale and import Company products, including Work Product.

(d) Consultant further agrees to execute all papers, including without limitation all patent applications, invention assignments and copyright assignments, and otherwise assist Company as reasonably required to perfect Company's right, title and interest in Work Product as expressly granted to Company under this Agreement. Such assistance shall include but not be limited to providing affidavits or testimony in connection with patent interference, validity or infringement proceedings and participating in other legal proceedings. Reasonable costs related to such assistance, if required, shall be paid by Company. Consultant's obligation to assist Company as described above in this paragraph shall continue beyond the termination of this Agreement. If Company is unable, after reasonable effort, to secure Consultant's signature on any document as provided in this Section 3, Consultant hereby designates and appoints Company and its duly authorized officers and agents as its agent and

attorney in fact to execute, verify and file applications, and to do all other lawfully permitted acts necessary to achieve the intent of this Section 3 with the same legal force and effect as if executed by Consultant.

4. Conflicting Engagements. Consultant will notify Company in writing prior to entering into any employment or consulting arrangement with one or more third parties which involves either subject matter substantially similar to services that Consultant is to provide hereunder, services which Consultant is to provide for the benefit of third parties who are competitors of Company or services that Company might reasonably determine would impair Consultant's ability to provide the services described in Exhibit A or otherwise fulfill his responsibilities or obligations provided for in this Agreement. During the term of this Agreement, Consultant shall not accept any employment or consulting work which conflicts with Consultant's obligations to Company hereunder or which may involve use or disclosure of Information other than as permitted hereunder. Company expressly acknowledges that Consultant's employment with Chrono Therapeutics (www.chronothera.com) is not a conflicting engagement under this Section 4.

5. Term; Termination. The term of this Agreement shall be for a period beginning on February 1, 2018 and ending on January 31, 2019 (the "**Term**"), unless previously terminated pursuant to this Section 5. During the Term, Company may terminate this Agreement upon ten (10) days prior written notice to Consultant, with no further obligations or liability owed to Consultant, if Company reasonably determines that Consultant: (1) materially breaches this Agreement in any manner, including, inter alia, a breach of Section 4, or (2) commits any acts, or engages in any activities, that Company reasonably determines are unlawful, dishonest or detrimental to the best interests of Company.

In the event this Agreement is terminated or expires, for whatever reason, Consultant shall cease work immediately after receiving notice from Company, return all Information (including all copies thereof) as provided in Section 2, deliver all Work Product and related documentation to Company, and provide Company with an invoice for any work for which compensation has not already been paid. If compensation has been advanced to Consultant, Consultant shall reimburse any amounts for which work has not been performed prior to the date of the notice of termination. Sections 2, 3, 5, 6, 7, 10, 11, 12, 13, 14, 15, 16 and 17 shall survive the termination of this Agreement for any reason, including expiration of the term of this Agreement.

6. Compliance with Applicable Laws. Consultant warrants that all materials supplied and work performed under this Agreement shall be in compliance with all applicable laws and regulations.

7. Independent Contractor. Consultant is an independent contractor, is not an agent or employee of Company and is not authorized to act on behalf of Company. Consultant will not be eligible for any employee benefits, nor will Company make deductions from any amounts payable to Consultant for taxes or social securities. Payment of all taxes and social securities due on any amounts paid to Consultant hereunder shall be the sole responsibility of Consultant.

8. Non-Solicitation. For the period of this Agreement and for one (1) year thereafter, Consultant will not, either directly or indirectly, solicit or attempt to solicit any employee, independent contractor, or consultant of Company to terminate his, her, or its relationship with, Company in order to become an employee, consultant, or independent contractor to or for any other person or entity.

9. Assignment. The Parties' rights and obligations under this Agreement will bind and inure to the benefit of their respective successors and assigns, except that Consultant may not delegate or assign any of his or her obligations or rights under this Agreement without Company's prior written consent.

10. Complete Agreement. This Agreement and **EXHIBIT A** attached hereto and hereby incorporated herein, constitute the Parties' final, exclusive and complete understanding and agreement with respect to the subject matter hereof, and supersede all prior and contemporaneous understandings and agreements relating to its subject matter.

11. Waiver; Amendment; Severability. This Agreement may not be waived, modified or amended unless mutually agreed upon in writing by both Parties. In the event any provision of this Agreement is found to be legally unenforceable, such unenforceability shall not prevent enforcement of any other provision of the Agreement.

12. Choice of Law. This Agreement shall be governed by the laws of the State of Illinois, without regard to any conflicts of law principals thereof that would call for the application of the laws of any other jurisdiction. The Parties consent to the exclusive jurisdiction and venue of the federal court in the Northern District of Illinois, and state courts located in the state of Illinois, county of Lake.

13. Notice. For the purposes of this Agreement, notices, demands, and all other forms of communication provided for in this Agreement shall be in writing and shall be deemed to have been duly given when delivered or (unless otherwise specified) mailed by registered mail, return receipt requested, postage prepaid, or by confirmed facsimile, addressed as set forth below, or to such other address as any party may have furnished to the other in writing in accordance herewith, except that notices of address shall be effective only upon receipt, as follows:

If to Company:

Horizon Pharma USA, Inc.
150 South Saunders Road
Lake Forest, IL 60045
Attention: Human Resources, Irina Konstantinovsky
Executive Vice President, Chief Human Resources Officer
ikonstantinovsky@horizonpharma.com
Fax: 224-383-3001

A copy to:

Horizon Pharma USA, Inc.
150 South Saunders Road
Lake Forest, IL 60045
Attention: Legal Department, Nelson Alexander
nalexander@horizonpharma.com
Fax: 224-383-3001

Horizon Pharma plc
150 South Saunders Road
Lake Forest, IL 60045
Attention: Chairman, President and CEO, Timothy P Walbert
twalbert@horizonpharma.com
Fax: 847.572.1372

If to the Consultant:

David Happel
PO Box 203
2362 Caballo Ranchero Drive
Diablo, CA 94528

Any such written notice shall be deemed given on the earlier of the date on which such notice is personally delivered, sent by telefax with a confirmatory copy sent by first class mail, upon confirmation of receipt in case of registered mail, or electronic mail. Either party may change its address for notices by giving written notice to the other party in the manner specified in this section.

14. Execution in Facsimile and Electronic Signatures. Facsimile and electronically transmitted signatures shall have the same force and effect as original signatures.

15. Execution in Counterparts. This Agreement may be executed in one or more counterparts, each of which shall be deemed an original and all of which together shall constitute a single instrument.

16. Legal and Equitable Remedies. Consultant hereby acknowledges and agrees that in the event of any breach of this Agreement by Consultant, including, without limitation, the actual or threatened disclosure of Information without the prior express written consent of Company, Company will suffer an irreparable injury, such that no remedy at law will afford it adequate protection against, or appropriate compensation for, such injury. Accordingly, Consultant agrees that Company shall have the right to enforce this Agreement and any of its provisions by injunction, specific performance or other equitable relief, without bond and without prejudice to any other rights and remedies that Company may have for a breach of this Agreement.

17. Warranty; Indemnification. Consultant warrants that he or she has good and marketable title to all Work Product. Consultant further warrants that the Work Product shall be free and clear of all liens, claims, encumbrances or demands of third parties, including any claims by any such third parties with respect to such third parties' intellectual property rights in the Work Product. Consultant warrants that Consultant has not been debarred under any applicable law, rule or regulation including, without limitation, Section 306 (a) or 306 (b) of the Federal Food, Drug and Cosmetic Act (codified at 21 U.S.C. 335(a) and 335(b)). Consultant covenants that should Consultant be convicted in the future of any act for which a person can be debarred as described in any applicable law, rule or regulation including, without limitation, Section 306 (a) or 306 (b) of the Federal Food, Drug and Cosmetic Act, Consultant shall immediately notify Company of such conviction in writing. Consultant shall indemnify, defend and hold harmless Company and its officers, agents, directors, employees, and customers from and against any claim, liability, loss, judgment or expense (including reasonable attorneys' and expert witnesses' fees and costs)

resulting from or arising out of any such claims by any third parties which are based upon or are the result of any breach of such warranties. Should Company permit Consultant to use any of Company's equipment, tools or facilities (the "**Company Equipment**") in the performance of the services during the term of this Agreement, such permission will be gratuitous and Consultant shall indemnify, defend and hold harmless Company and its officers, directors, agents and employees from and against any claim, loss, expense or judgment of injury to person or property (including death) arising out of Consultant's willful misconduct or negligent use of any such Company Equipment.

IN WITNESS WHEREFORE, the Parties have signed this Agreement on the date first written below.

TIMOTHY P. WALBERT **HORIZON PHARMA USA, INC.**	**DAVID HAPPEL**
/s/ Timothy P. Walbert	/s/ David Happel
By:	
Chairman, President and CEO	Consultant
Title	Title:
January 23, 2018	February 19, 2018
Date:	Date:

[signature page to Consulting Agreement]

EXHIBIT A

Work to be performed: Consultant will provide services supporting the Company's orphan drug development programs and commercialization strategies. Consultant's activities will be directed by Timothy P. Walbert ("**Walbert**"), or any Company representative designated by Walbert, and Consultant will report to Walbert, or any Company representative designated by Walbert.

Type or rate of payment: Payment for work performed during the Term will be in an amount equal to $5,000.00 a month, payable on approximately the 15th day of each month during the Term.

Travel expenses: Company will pay Consultant's reasonable traveling expenses, incurred at Company's written request and with its advance approval, in accordance with the procedures that the Company establishes from time to time.

Other terms (if any):

Exhibit 10.71

*****Text Omitted and Filed Separately with the Securities and Exchange Commission. Confidential Treatment Requested Under 17 C.F.R. Sections 200.80(b)(4) and 240.24b-2.**

SECOND AMENDMENT TO THE SUPPLY AGREEMENT BETWEEN HORIZON PHARMA IRELAND LIMITED AND NUVO PHARMACEUTICALS INC

This AMENDMENT NO. 2 TO SUPPLY AGREEMENT (this "Amendment") is made and entered into as of January 1, 2017 by and between Nuvo Pharmaceuticals .Inc., formerly known as Nuvo Research Inc., a company incorporated under the laws of the province of Ontario, Canada ("NUVO"), having offices at 7560 Airport Road, Unit 10, Mississauga, Ontario, L4T 4114, and Horizon Pharma Ireland Limited, a Irish limited company ("Horizon"), and amends that certain Supply Agreement, dated as of October 17, 2014, as amended by Amendment No. 1 to Supply Agreement, dated as of February 4, 2016 (the "Agreement"), by and between NUVO and Horizon. Capitalized terms used herein and not otherwise defined herein shall have the meanings assigned to such terms in the Agreement.

AGREEMENT

1. Exhibit A Transfer Prices (formerly Schedule 5) of the Agreement is hereby amended and replaced with Revised Exhibit A attached hereto.

2. EFFECT OF THIS AMENDMENT. Except as expressly provided herein, this Amendment shall not constitute an amendment, modification or waiver of any provision of the Agreement or any rights or obligations of any party under or in respect of the Agreement. Except as modified by this Amendment, the Agreement shall continue in full force and effect. Upon the execution of this Amendment by each of the parties hereto, each reference in the Agreement to "this Agreement" or the words "hereunder," "hereof," "herein" or words of similar effect referring to the Agreement shall mean and be a reference to the Agreement as amended by this Amendment, and a reference to the Agreement in any other instrument or document shall be deemed a reference to the Agreement as amended by this Amendment. This Amendment shall be subject to, shall form a part of, and shall be governed by, the terms and conditions set forth in the Agreement, as amended by this Amendment.

3. GENERAL. This Amendment may be executed in multiple counterparts, each of which may be delivered via facsimile or other electronic means, which taken together shall constitute the original agreement.

[*Signature Page to Follow.*]

IN WITNESS WHEREOF, the parties to this Amendment indicate their agreement effective as of the date set forth at the beginning of this Amendment by signing below.

HORIZON PHARMA IRELAND LIMITED	NUVO PHARMACEUTICALS INC.
By: /s/ David G. Kelly	By: /s/ Katina Loucaides
(Signed)	(Signed)
Name: David G Kelly	Name: Katina Loucaides
(Typed)	(Typed)
Title: EVP and Company Sec.	Title: VP, General Counsel

REVISED EXHIBIT A

Transfer Prices

Supplied Product:

[…***…]

*** **Confidential Treatment Requested**

Exhibit 10.72

*****Text Omitted and Filed Separately with the Securities and Exchange Commission. Confidential Treatment Requested Under 17 C.F.R. Sections 200.80(b)(4) and 240.24b-2.**

THIRD AMENDMENT TO THE SUPPLY AGREEMENT BETWEEN HORIZON PHARMA IRELAND LIMITED AND NUVO PHARMACEUTICALS INC

This AMENDMENT NO. 3 TO SUPPLY AGREEMENT (this "**Amendment**") is made and entered into as of February 16, 2018 by and between Nuvo Pharmaceuticals Inc., formerly known as Nuvo Research Inc., a company incorporated under the laws of the province of Ontario, Canada ("**NUVO**"), having offices at 6733 Mississauga Road, Suite 610, Mississauga, ON L5N 6J5, Canada, and Horizon Pharma Ireland Limited, a Irish limited company ("**Horizon Pharma**"), and amends that certain Supply Agreement, dated as of October 17, 2014, as amended by Amendment No. 1 to Supply Agreement, dated as of February 4, 2016 and Amendment No. 2 to Supply Agreement, dated as of January 1, 2017 (collectively, the "**Agreement**"), by and between NUVO and Horizon Pharma. Capitalized terms used herein and not otherwise defined herein shall have the meanings assigned to such terms in the Agreement.

AGREEMENT

1. Section 7.6 of the Supply Agreement is hereby repealed and replaced with the following:

7.6 **Safety Stock Reserve**. NUVO agrees to hold and maintain (a) […***…] of stock reserve of all Raw Materials (other than API and […***…] bottles) and primary Packaging supplies for the Supplied Product, (b) […***…] stock reserve of […***…] bottles for the Supplied Product and (c)(i) […***…] stock reserve of API until such time as the Alternate API Manufacturer is approved by the relevant Regulatory Authorities in the Horizon Pharma Territory and (ii) […***…] stock reserve of API after the Alternate API Manufacturer is approved by the relevant Regulatory Authorities in the Horizon Pharma Territory, in each case, based on Horizon Pharma's most recent Forecast; provided, notwithstanding anything contained in this Agreement, NUVO shall as soon as practicable obtain a stock reserve of DMSO, equal to the amount necessary to supply […***…] of Supplied Product, based on Horizon Pharma's Initial Forecast. Thereafter, NUVO shall maintain, at all times during the Term, a stock reserve of DMSO equal to […***…] of Supplied Product, based on Horizon Pharma's most current Forecast. If NUVO obtains any Raw Materials, primary Packaging supplies, other components or DMSO for its stock reserve pursuant to this Section 7.6 and, as a result of changes in the Forecast, is unable to use such materials either to supply Supplied Product to Horizon Pharma or to a Third Party, the Parties will share the cost of such excess materials equally and Horizon Pharma will reimburse NUVO for its share of such costs within […***…] following receipt of an invoice therefor.

2. EFFECT OF THIS AMENDMENT. Except as expressly provided herein, this Amendment shall not constitute an amendment, modification or waiver of any provision of the Agreement or any rights or obligations of any party under or in respect of the Agreement. Except as modified by this Amendment, the Agreement shall continue in full force and effect. Upon the execution of this Amendment by each of the parties hereto,

*** **Confidential Treatment Requested**

each reference in the Agreement to "this Agreement" or the words "hereunder," "hereof," "herein" or words of similar effect referring to the Agreement shall mean and be a reference to the Agreement as amended by this Amendment, and a reference to the Agreement in any other instrument or document shall be deemed a reference to the Agreement as amended by this Amendment. This Amendment shall be subject to, shall form a part of, and shall be governed by, the terms and conditions set forth in the Agreement, as amended by this Amendment.

3. GENERAL. This Amendment may be executed in multiple counterparts, each of which may be delivered via facsimile or other electronic means, which taken together shall constitute the original agreement.

IN WITNESS WHEREOF, the parties to this Amendment indicate their agreement effective as of the date set forth at the beginning of this Amendment by signing below.

HORIZON PHARMA IRELAND LIMITED	NUVO PHARMACEUTICALS INC.
By: /s/ Paul Condon	By: /s/ Jesse Ledger
(Signed)	(Signed)
Name: Paul Condon	Name: Jesse Ledger
(Typed)	(Typed)
Title: Director	Title: President and CEO

Exhibit 21.1

Subsidiaries of Horizon Pharma Public Limited Company:

NAME:	JURISDICTION OF INCORPORATION:
Andromeda Biotech Limited	Israel
Horizon European Products, LLC	Delaware
Horizon Orphan LLC	Delaware
Horizon Pharma Aon Limited	Ireland
Horizon Pharma Capital Limited	Ireland
Horizon Pharma Dó Limited	Ireland
Horizon Pharma Finance Limited	Ireland
Horizon Pharma Finance S.à.r.l	Luxembourg
Horizon Pharma GmbH	Germany
Horizon Pharma Holdings 2 Limited	Ireland
Horizon Pharma Holdings Limited	Ireland
Horizon Pharma Investment Limited	Bermuda
Horizon Pharma Ireland Limited	Ireland
Horizon Pharma Israel Holding Corp. Ltd	Israel
Horizon Pharma Rheumatology LLC	Delaware
Horizon Pharma Services Limited	Ireland
Horizon Pharma Switzerland GmbH	Switzerland
Horizon Pharma Treasury Limited	Ireland
Horizon Pharma Trí Limited	Ireland
Horizon Pharma USA, Inc.	Delaware
Horizon Pharma, Inc.	Delaware
Horizon Pharmaceutical LLC	Delaware
Horizon Therapeutics, LLC	Delaware
Horizon Pharma Services LLC	Delaware
Hyperion Therapeutics Ireland Holding Limited	Ireland
Hyperion Therapeutics Ireland Operating Limited	Ireland
HZNP Canada Limited	Canada
HZNP European Holdings, C.V.	Netherlands
HZNP Limited	Ireland
HZNP USA LLC	Delaware
Misneach Europe LLC	Delaware
Horizon Pharma Tepro, Inc	Delaware

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-8 (No. 333-198865, 333-203933, 333-211118, 333-220316 and 333-222516) of Horizon Pharma plc of our report dated February 28, 2018 relating to the financial statements, financial statement schedule and the effectiveness of internal control over financial reporting, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP
Chicago, Illinois
February 28, 2018

Exhibit 31.1

Certification of Principal Executive Officer

I, Timothy P. Walbert, certify that:

1. I have reviewed this annual report on Form 10-K of Horizon Pharma PLC (the "registrant");

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

    a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

    b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

    c. Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

    d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

    a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

    b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 28, 2018

/s/ Timothy P. Walbert
Timothy P. Walbert
Chairman, President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

Certification of Principal Financial Officer

I, Paul W. Hoelscher, certify that:

1. I have reviewed this annual report on Form 10-K of Horizon Pharma PLC (the "registrant");

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

    a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

    b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

    c. Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

    d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

    a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

    b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 28, 2018

/s/ Paul W. Hoelscher
Paul W. Hoelscher
Executive Vice President, Chief Financial Officer
(Principal Financial Officer)

Exhibit 32.1

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and 18 U.S.C. Section 1350, I, Timothy P. Walbert, President, Chief Executive Officer and Chairman of the Board of Horizon Pharma PLC (the "Company"), certify to the best of my knowledge that:

1. the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2017 (the "Report"), to which this Certification is attached as Exhibit 32.1, fully complies with the requirements of Section 13(a) or 15(d) of the Exchange Act; and
2. the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 28, 2018

/s/ Timothy P. Walbert
Timothy P. Walbert
Chairman, President and Chief Executive Officer
(Principal Executive Officer)

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of the Company under the Securities Act of 1933, as amended, or the Exchange Act (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.

Exhibit 32.2

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and 18 U.S.C. Section 1350, I, Paul W. Hoelscher, Executive Vice President and Chief Financial Officer of Horizon Pharma PLC (the "Company"), certify to the best of my knowledge that:

1. the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2017 (the "Report"), to which this Certification is attached as Exhibit 32.2, fully complies with the requirements of Section 13(a) or 15(d) of the Exchange Act; and
2. the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 28, 2018

/s/ Paul W. Hoelscher
Paul W. Hoelscher
Executive Vice President, Chief Financial Officer
(Principal Financial Officer)

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of the Company under the Securities Act of 1933, as amended, or the Exchange Act (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2018

or

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to

Commission File Number 001-35238

HORIZON PHARMA PUBLIC LIMITED COMPANY

(Exact name of Registrant as specified in its charter)

Ireland	**Not Applicable**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
Connaught House, 1st Floor **1 Burlington Road, Dublin 4, D04 C5Y6, Ireland**	**Not Applicable**
(Address of principal executive offices)	**(zip code)**

011 353 1 772 2100

(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	Name of Each Exchange on Which Registered
Ordinary shares, nominal value $0.0001 per share	**The Nasdaq Global Select Market**

Securities registered pursuant to Section 12(g) of the Act:

None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐.

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒.

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	☒	Accelerated filer	☐
Non-accelerated filer	☐	Smaller reporting company	☐
Emerging growth company	☐		

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined by Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

The aggregate market value of the registrant's voting ordinary shares held by non-affiliates of the registrant, based upon the $16.56 per share closing sale price of the registrant's ordinary shares on June 30, 2018 (the last business day of the registrant's most recently completed second quarter), was approximately $2.7 billion. Solely for purposes of this calculation, the registrant's directors and executive officers and holders of 10% or more of the registrant's outstanding ordinary shares have been assumed to be affiliates and an aggregate of 928,584 ordinary shares held by such persons on June 30, 2018 are not included in this calculation.

As of February 20, 2019, the registrant had outstanding 169,619,321 ordinary shares.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement for the registrant's 2019 Annual General Meeting of Shareholders are incorporated by reference into Part III of this Annual Report on Form 10-K.

HORIZON PHARMA PLC
FORM 10-K — ANNUAL REPORT
For the Fiscal Year Ended December 31, 2018

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PART I

Special Note Regarding Forward-Looking Statements

This Annual Report on Form 10-K contains "forward-looking statements" — that is, statements related to future, not past, events — as defined in Section 21E of the Securities Exchange Act of 1934, as amended, that reflect our current expectations regarding our future growth, results of operations, business strategy and plans, financial condition, cash flows, performance, business prospects, and opportunities, as well as assumptions made by, and information currently available to, our management. Forward-looking statements include any statement that does not directly relate to a current or historical fact. Forward-looking statements generally can be identified by words such as "believe," "may," "could," "will," "estimate," "continue," "anticipate," "intend," "seek," "plan," "expect," "should," "would", or similar expressions. These statements are based on current expectations and assumptions that are subject to risks and uncertainties inherent in our business, which could cause our actual results to differ materially from those indicated in the forward-looking statements. Factors that could cause actual results to differ materially from those indicated in the forward-looking statements include, without limitation: our ability to successfully execute our sales and marketing strategy, including continuing to successfully recruit and retain sales and marketing personnel and to successfully build the market for our medicines; our ability to continue our transition to a rare and rheumatic disease company and build a sustainable pipeline of new medicine candidates; whether we will be able to realize the expected benefits of strategic transactions, including whether and when such transactions will be accretive to our net income; the rate and degree of market acceptance of, and our ability and our distribution and marketing partners' ability to obtain coverage and adequate reimbursement and pricing for, our medicines from government and third-party payers and risks relating to the success of our patient access programs; our ability to maintain regulatory approvals for our medicines; our ability to conduct clinical development and obtain regulatory approvals for our medicine candidates, including potential delays in initiating and completing studies and filing for and obtaining regulatory approvals and whether data from clinical studies will support regulatory approval; our need for and ability to obtain additional financing; the accuracy of our estimates regarding future financial results; our ability to successfully execute our strategy to develop or acquire additional medicines or companies, including disruption from any future acquisition or whether any acquired development programs will be successful; our ability to manage our anticipated future growth; the ability of our medicines to compete with generic medicines, especially those representing the active pharmaceutical ingredients in our medicines as well as new medicines that may be developed by our competitors; our ability and our distribution and marketing partners' ability to comply with regulatory requirements regarding the sales, marketing and manufacturing of our medicines and medicine candidates; the performance of our third-party distribution partners, licensees and manufacturers over which we have limited control; our ability to obtain and maintain intellectual property protection for our medicines; our ability to defend our intellectual property rights with respect to our medicines; our ability to operate our business without infringing the intellectual property rights of others; the loss of key commercial or management personnel; regulatory developments in the United States and other countries, including potential changes in healthcare laws and regulations; and other risks detailed below in Part I — Item 1A. "Risk Factors".

Although we believe that the expectations reflected in our forward-looking statements are reasonable, we cannot guarantee future results, events, levels of activity, performance or achievement. We undertake no obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, unless required by law.

Item 1. Business

Unless otherwise indicated or the context otherwise requires, references to the "Company", "we", "us" and "our" refer to Horizon Pharma plc and its consolidated subsidiaries.

Overview

Horizon Pharma plc is focused on researching, developing and commercializing innovative medicines that address unmet treatment needs for rare and rheumatic diseases. By expanding our growing pipeline of medicines in development and exploring all potential uses for currently marketed medicines, we strive to make a powerful difference for patients, their caregivers and physicians.

Our Strategy

We aspire to be a leading rare disease biopharma company that delivers innovative therapies to patients and generates high returns for our shareholders.

Our approach has been different from typical biopharma companies. Instead of starting with a pipeline and raising capital to finance development opportunities, we first developed a successful commercial business, generating cash flows and significant growth. We then deployed our cash flows and access to capital to the development and acquisition of leading-edge therapeutic products for rare diseases.

Today we have a growing pipeline of development programs, eleven on-market medicines and total annual net sales of $1.2 billion in 2018 – a transformation from our beginnings as a public company in 2011, with two medicines and total annual net sales of $6.9 million.

Our highest strategic priority is to build a robust and differentiated pipeline of rare disease medicines. We are also focused on maximizing the growth of our rare-disease medicines – in particular, of KRYSTEXXA®, our biologic for the treatment of chronic gout refractory to conventional therapy, or uncontrolled gout.

We have two operating segments, the orphan and rheumatology segment and the primary care segment. The orphan and rheumatology operating segment, our strategic growth segment, has generated a four-year compound annual growth rate from 2014 to 2018 of 101.2 percent, underscoring the value of our strategy, with its focus on rare disease medicines. We expect the segment to drive future growth as well, supported by our durable base of rare disease medicines; our growth driver, KRYSTEXXA; and if approved, teprotumumab, our late-stage development biologic candidate, which we believe offers significant growth potential. Teprotumumab, which successfully completed a Phase 2 clinical trial and is currently undergoing a Phase 3 confirmatory trial, targets the treatment of thyroid eye disease, a debilitating rare autoimmune condition for which there is no approved treatment.

Three components support our strategic efforts:

Clinical development – In support of our expanding pipeline and the value-maximization of our on-market medicines, we have augmented our scientific expertise and capabilities with the addition of a new research and development leadership team in 2018. Members of the team are overseeing our two internal clinical studies – the Phase 3 confirmatory clinical trial for teprotumumab and our KRYSTEXXA immunomodulation trial, with another trial – a KRYSTEXXA trial for kidney transplant patients with uncontrolled gout – expected to launch in the second half of 2019. Research and development is also integrally partnered with our business development organization, adding scientific acumen to the process as we continue to look at opportunities to augment our rare disease pipeline through development-stage acquisitions, licensing and collaboration agreements.

Business development – We have a disciplined and robust business development strategy that has resulted in nine acquisitions and three divestitures over the past seven years, including our first acquisition of a development-stage medicine candidate – teprotumumab – in 2017, as well as two transformative transactions in 2016 that brought us three rare disease medicines. In 2018, we announced the addition of two collaborative programs to our rheumatology program for next-generation gout biologics.

Commercial execution – We have a strong record of successfully commercializing our medicines and rapidly increasing the value and improving the performance of medicines we acquire. We attribute our successful results to deep expertise and knowledge of our commercial teams, coupled with the holistic approach we employ supporting our patient and physician communities. KRYSTEXXA is a prime example of the value of our approach: an underperforming asset when we acquired it in 2016 and in two short years we transformed it to be the flagship growth driver for our company.

Our Company

We are a public limited company formed under the laws of Ireland. We operate through a number of international and U.S. subsidiaries with principal business purposes to perform research and development or manufacturing operations, serve as distributors of our medicines, hold intellectual property assets or provide us with services and financial support.

Our principal executive offices are located at Connaught House, 1st Floor, 1 Burlington Road, Dublin 4, D04 C5Y6, Ireland and our telephone number is 011 353 1 772 2100. Our website address is www.horizonpharma.com. Information found on, or accessible through, our website is not a part of, and is not incorporated into, this Annual Report on Form 10-K.

Acquisitions and Divestitures

Since January 1, 2016, we completed the following acquisitions and divestitures:

- Effective January 1, 2019, we amended our license and supply agreements with Jagotec AG and Skyepharma AG, which are affiliates of Vectura Group plc, or Vectura. Under these amendments, we agreed to transfer all economic benefits of LODOTRA® in Europe to Vectura during an initial transition period, with full rights transferring to Vectura when certain transfer activities have been completed. We will no longer record LODOTRA revenue from January 1, 2019. See the "Manufacturing, Commercial, Supply and License Agreements" section, included in Item 1 of this Annual Report on Form 10-K, for further details of the amendments.
- On December 28, 2018, we sold our rights to RAVICTI® and AMMONAPS® (known as BUPHENYL® in the United States) outside of North America and Japan to Medical Need Europe AB, part of the Immedica Group, or Immedica. We previously distributed RAVICTI and AMMONAPS through a commercial partner in Europe and other non-U.S. markets. We have retained rights to RAVICTI and BUPHENYL in North America and Japan.
- On June 30, 2017, we completed our acquisition of certain rights to interferon gamma-1b from Boehringer Ingelheim International GmbH, or Boehringer Ingelheim International, in all territories outside of the United States, Canada and Japan. Interferon gamma-1b is known as IMUKIN® outside of the United States, Canada and Japan. On July 24, 2018, we sold the rights to IMUKIN in all territories outside of the United States, Canada and Japan to Clinigen Group plc, or Clinigen, for an upfront payment and a potential additional contingent consideration payment, or the IMUKIN sale.
- On June 23, 2017, we sold our European subsidiary that owned the marketing rights to PROCYSBI® (cysteamine bitartrate) delayed-release capsules and QUINSAIR™ (levofloxacin inhalation solution) in Europe, the Middle East and Africa, or EMEA, regions, to Chiesi Farmaceutici S.p.A., or Chiesi.
- On May 8, 2017, we completed our acquisition of River Vision Development Corp., or River Vision, which added the late development-stage rare disease biologic medicine candidate teprotumumab to our research and development pipeline.
- On October 25, 2016, we completed our acquisition of Raptor Pharmaceutical Corp., or Raptor, which added the rare disease medicines PROCYSBI and QUINSAIR to our medicine portfolio, or the Raptor acquisition.
- On January 13, 2016, we completed our acquisition of Crealta Holdings LLC, or Crealta, which added the rare disease medicine KRYSTEXXA and the primary care medicine MIGERGOT® to our medicine portfolio, or the Crealta acquisition.

The consolidated financial statements presented herein include the results of operations of the acquired businesses from the applicable dates of acquisition. See Note 4 of the Notes to consolidated financial statements, included in Item 15 of this Annual Report on Form 10-K, for further details of our acquisitions and divestitures.

Our Medicines

We believe our medicines address unmet therapeutic needs in orphan diseases, arthritis, pain and inflammation and inflammatory diseases and provide significant advantages over existing therapies.

Our current marketed medicine portfolio consists of the following:

Medicine	Disease	2018 Net Sales (in millions)	Marketing Rights
ORPHAN AND RHEUMATOLOGY MEDICINES:			
KRYSTEXXA	Chronic refractory gout ("uncontrolled gout")	$258.9	Worldwide
RAVICTI	Urea cycle disorders	$226.7	North America and Japan (1)
PROCYSBI	Nephropathic cystinosis	$154.9	United States and certain other countries (2)
ACTIMMUNE®	Chronic granulomatous disease and severe, malignant osteopetrosis	$105.6	United States, Canada and Japan (3)
RAYOS®	Rheumatoid arthritis, polymyalgia rheumatic, systemic lupus erythematosus and multiple other indications	$61.1	North America (4)
BUPHENYL	Urea cycle disorders	$21.8	North America and Japan (5)
QUINSAIR	Treatment of chronic pulmonary infections due to *Pseudomonas aeruginosa* in cystic fibrosis patients	$0.5	Canada and certain other countries (6)
PRIMARY CARE MEDICINES:			
PENNSAID 2%®	Pain of osteoarthritis of the knee(s)	$190.2	United States
DUEXIS®	Signs and symptoms of osteoarthritis and rheumatoid arthritis	$114.7	Worldwide (7)
VIMOVO®	Signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis	$67.6	United States
MIGERGOT	Vascular headache	$3.6	United States

(1) On December 28, 2018, we sold our rights to RAVICTI outside of North America and Japan to Immedica. The amount shown in the table above includes net sales outside of North America and Japan of $4.1 million for 2018. RAVICTI is also available in Canada through an exclusive distribution agreement with Innomar Strategies Inc., or Innomar.

(2) We market PROCYSBI in the United States and Canada. Innomar is our exclusive distributor for PROCYSBI in Canada. We also have marketing rights to PROCYSBI in Asia. PROCYSBI is also available in Latin America through a managed access program through our partner Uno Healthcare Inc.

(3) ACTIMMUNE is known as IMUKIN outside the United States, Canada and Japan. On July 24, 2018, we sold the rights to IMUKIN in all territories outside of the United States, Canada and Japan to Clinigen. The amount shown in the table above includes net sales for IMUKIN of $1.3 million for 2018.

(4) Outside the United States, RAYOS is sold and marketed as LODOTRA. We recorded $2.1 million of LODOTRA net sales in 2018. Effective January 1, 2019, we amended our license and supply agreements with Jagotec AG and Skyepharma AG, which are affiliates of Vectura. Under these amendments, we agreed to transfer all economic benefits of LODOTRA in Europe to Vectura during an initial transition period, with full rights transferring to Vectura when certain transfer activities have been completed. We will no longer record LODOTRA revenue from January 1, 2019. See the "Manufacturing, Commercial, Supply and License Agreements" section, included in Item 1 of this Annual Report on Form 10-K, for further details of the amendments.

(5) BUPHENYL is known as AMMONAPS outside of North America and Japan. On December 28, 2018, we sold our rights to AMMONAPS outside of North America and Japan to Immedica. The amount shown in the table above includes net sales for AMMONAPS of $5.6 million for 2018. Orphan Pacific, Inc. holds an exclusive distribution agreement for the distribution of BUPHENYL in Japan.

(6) We market QUINSAIR in Canada and Latin America. Innomar is our exclusive distributor for QUINSAIR in Canada. We also have marketing rights for QUINSAIR in the United States and Asia. We have not received regulatory approval to market QUINSAIR in the United States.

(7) DUEXIS rights in Mexico and Chile have been licensed to Grünenthal S.A., or Grünenthal.

Information on our total revenues by product in each of the years ended December 31, 2018, 2017 and 2016 is included in the section titled "Management's Discussion and Analysis of Financial Condition and Results of Operations" in this Annual Report on Form 10-K.

ORPHAN AND RHEUMATOLOGY

Our orphan and rheumatology segment includes our marketed medicines KRYSTEXXA, RAVICTI, PROCYSBI, ACTIMMUNE, RAYOS, BUPHENYL and QUINSAIR.

KRYSTEXXA

A PEGylated uric acid specific enzyme (uricase), KRYSTEXXA is the first and only U.S. Food and Drug Administration, or FDA, approved medicine for the treatment of uncontrolled gout. Uncontrolled gout occurs in patients who have failed to normalize serum uric acid, or sUA, and whose signs and symptoms are inadequately controlled with conventional therapies, such as xanthine oxidase inhibitors, or XOIs, at the maximum medically appropriate dose, or for whom these drugs are contraindicated.

KRYSTEXXA has a unique mechanism of action that rapidly reverses disease progression. Unlike conventional XOI therapies, which address the over-production or under-excretion of uric acid, KRYSTEXXA converts uric acid into allantoin, a water-soluble molecule, which the body can easily eliminate through the urine. Renal excretion of allantoin is ten times more efficient than uric acid excretion. Additionally, many chronic kidney disease, or CKD, patients have gout, and the disease tends to be more prevalent as CKD advances. While conventional XOI gout therapies can place additional burden on the kidneys and have dosing limitations, KRYSTEXXA has been proven effective and safe for uncontrolled gout patients with CKD without the need to adjust dosing.

Gout is one of the most common forms of inflammatory arthritis and can be assessed by a simple blood test for the amounts of uric acid in the blood (sUA levels). Typically in gout, when uric acid levels are greater than 6.8 milligrams per deciliter, urate will crystallize and deposit. These hard deposits are known as tophi and may occur anywhere in the body, including joints, as well as organs, such as the kidney and heart. When under-treated medically, tophi often lead to bone erosions and loss of functional ability. Gout flares, a common characteristic of uncontrolled gout, are intensely painful. They may or may not be accompanied by tophi. A systemic disease, uncontrolled gout frequently causes crippling disabilities and significant joint damage. Of the 8.3 million gout sufferers in the United States, we estimate that greater than 100,000 patients have uncontrolled gout.

KRYSTEXXA was approved by the FDA in 2010 following the results of two replicate clinical trials six months in duration involving eighty-five patients treated with KRYSTEXXA. The mean baseline sUA levels for patients in the trial were greater than 10 mg/dL, and seventy-one percent of patients had visible tophi. The primary endpoint for the trials was the ability to maintain a low sUA for eighty percent of the samples taken at months three and six. As a result of the every-other-week dosing of KRYSTEXXA at 8 mg, forty-two percent of KRYSTEXXA patients achieved complete response versus zero percent for the placebo group; and forty-five percent of KRYSTEXXA patients achieved complete resolution of tophi versus eight percent for the placebo group over six months.

We are focused on optimizing and maximizing the peak sales potential of KRYSTEXXA by expanding our commercialization efforts, as well as investing in education, patient and physician outreach, activities related to label expansion and investigation programs that demonstrate KRYSTEXXA as an effective treatment for uncontrolled gout. We believe that KRYSTEXXA represents a significant opportunity and potential growth driver for our orphan and rheumatology segment.

We doubled our KRYSTEXXA commercial team in 2018, we increased our promotional efforts to further penetrate rheumatology and initiate marketing to nephrology and we are growing our customer base from both new and existing prescribers. In addition to selling and marketing to a larger number of rheumatologists, we are also expanding our outreach to include nephrologists, as we believe KRYSTEXXA offers a solution to a clinical need experienced by many nephrologists in dealing with uncontrolled gout patients with CKD.

As the only FDA-approved medication for the treatment of uncontrolled gout, KRYSTEXXA faces limited direct competition. We believe that the complexity of manufacturing KRYSTEXXA provides a barrier to potential generic competition. However, a number of competitors have medicines in Phase 1 or Phase 2 trials, including Selecta Biosciences, Inc., who have presented phase 2 clinical data and have indicated their plans to initiate a six-month head-to-head trial comparing their candidate to KRYSTEXXA in 2019. Though KRYSTEXXA does not have any direct competitors, because there is no other medication approved for uncontrolled gout, other therapies could be used prior to use of KRYSTEXXA, and if effective, could reduce the treatable patient population for KRYSTEXXA.

RAVICTI

RAVICTI is indicated for use as a nitrogen-binding agent for chronic management of adult and pediatric patients two months of age and older with urea cycle disorders, or UCDs, that cannot be managed by dietary protein restriction and/or amino acid supplementation alone. UCDs are rare, life-threatening genetic disorders. RAVICTI must be used with dietary protein restriction and, in some cases, dietary supplements (for example, essential amino acids, arginine, citrulline or protein-free calorie supplements).

UCDs are inherited metabolic diseases caused by a deficiency of one of the enzymes or transporters that constitute the urea cycle. The urea cycle involves a series of biochemical steps in which ammonia, a potent neurotoxin, is converted to urea, which is excreted in the urine. UCD patients may experience episodes during which the ammonia levels in their blood become excessively high, called hyperammonemic crises, which may result in irreversible brain damage, coma or death. We estimate that there are approximately 2,600 patients with UCDs living in the United States, including approximately 1,000 diagnosed patients.

UCD symptoms may first occur at any age depending on the severity of the disorder, with more severe defects presenting earlier in life. However, a prompt diagnosis and careful management of the disease can lead to good clinical outcomes. In December 2018, we received FDA approval to expand the age range for the use of RAVICTI in the chronic management of UCDs in patients from birth to two months.

RAVICTI competes with older-generation nitrogen scavenger medicines. In the United States, RAVICTI competes with generic forms of sodium phenylbutyrate, including BUPHENYL. RAVICTI has advantages over older-generation medicines leading to better patient adherence and compliance rates, such as its better tolerability for patients. It is ingested by mouth and therefore requires little preparation and it has little taste and lower sodium content than its competitors.

Our strategy for RAVICTI is to drive growth through increased awareness and diagnosis of UCDs, to drive conversion from older-generation nitrogen scavengers, such as generic forms of sodium phenylbutyrate, to RAVICTI, based on the medicine's differentiated benefits and to increase awareness of label expansion to position RAVICTI as first line of therapy.

On December 28, 2018, we sold our rights to RAVICTI outside of North America and Japan to Immedica. We previously distributed RAVICTI through a commercial partner in Europe and other non-U.S. markets. We have retained rights to RAVICTI in North America and Japan.

PROCYSBI

PROCYSBI is indicated for nephropathic cystinosis, or NC, a rare and life-threatening metabolic disorder. PROCYSBI capsules contain cysteamine bitartrate in the form of innovative microspheronized beads that are individually coated to create delayed and extended-release properties, allowing patients to maintain consistent therapeutic systemic drug levels over a twelve-hour dosing period. The enteric-coated beads are pH sensitive and bypass the stomach for dissolution and absorption in the more alkaline environment of the proximal small intestine. Randomized controlled clinical trials and extended treatment with PROCYSBI therapy have demonstrated consistent cystine depletion as monitored by levels of the biomarker (and surrogate marker), white blood cell cystine.

PROCYSBI is differentiated by its ability to control cystine concentration continuously over twelve hours. Older therapies require administration of medicine every six hours. By taking PROCYSBI, patients have to dose only twice a day, leaving them greater control over their medication schedule and lifestyle. Additionally, because PROCYSBI can be administered through a feeding tube or mixed with approved food and beverages, the patient can choose a more flexible dosing regimen. PROCYSBI also has fewer known side effects, such as less severe body odor, than older-generation therapies.

We estimate that there are approximately 500 patients diagnosed with cystinosis living in the United States. NC comprises ninety-five percent of known cases of cystinosis. In these patients, elevated cystine can lead to cellular dysfunction and death; without treatment, the disease is usually fatal by the end of the first decade of life. Cystinosis is progressive, eventually causing irreversible tissue damage and multi-organ failure, including kidney failure, blindness, muscle wasting and premature death. NC is usually diagnosed in infancy after children display symptoms to physicians, including markedly increased urination, thirst, dehydration, gastrointestinal distress, failure to thrive, rickets, photophobia and kidney symptoms specific to Fanconi syndrome. Management of cystinosis requires lifelong therapy.

In addition to patients who have already been identified, we believe that a number of patients with atypical phenotypic presentation and end-stage renal disease have their condition as a result of undiagnosed late-onset NC and would benefit from treatment with PROCYSBI.

Other than PROCYSBI, we are aware of two pharmaceutical products currently approved to treat cystinosis, Cystagon® and Cystaran®. Cystagon, an immediate-release cysteamine bitartrate capsule, is an older-generation systemic cystine-depleting therapy for cystinosis in the United States marketed by Mylan N.V., and by Orphan Europe SARL in markets outside of the United States. Cystagon is PROCYSBI's primary competitor. Cystaran, a cysteamine ophthalmic solution, is approved in the United States for treatment of corneal crystal accumulation in patients with cystinosis and is marketed by Leadiant Biosciences, Inc.

We believe that PROCYSBI will continue to be well received in the market and continue to expect Cystagon to be the primary competitor for PROCYSBI for the foreseeable future.

Our strategy for PROCYSBI is to drive conversion of patients from Cystagon to PROCYSBI, increase the uptake of diagnosed but untreated patients, identify previously undiagnosed patients who are suitable for treatment and increase awareness of label expansion to position PROCYSBI as first line of therapy.

ACTIMMUNE

ACTIMMUNE is indicated for chronic granulomatous disease, or CGD, and severe, malignant osteopetrosis, or SMO. It is a biologically manufactured protein called interferon gamma-1b that is similar to a protein the human body makes naturally. Interferon gamma helps prevent infection in CGD patients and enhances osteoclast function in SMO patients. ACTIMMUNE is the only medicine approved by the FDA to reduce the frequency and severity of serious infections associated with CGD and for delaying disease progression in patients with SMO. ACTIMMUNE is believed to work by modifying the cellular function of various cells, including those in the immune system and those that help form bones.

CGD is a genetic disorder of the immune system. It is described as a primary immunodeficiency disorder, which means it is not caused by another disease or disorder. In people who have CGD, a type of white blood cell called a phagocyte is defective. These defective phagocytes cannot generate superoxide, leading to an inability to kill harmful microorganisms such as bacteria and fungi. As a result, the immune system is weakened. People with CGD are more likely to have certain problems, such as recurrent severe bacterial and fungal infections and chronic inflammatory conditions. These patients are prone to developing masses called granulomas, which can occur repeatedly in organs throughout the body and cause a variety of problems. We estimate that there are approximately 1,600 patients with CGD in the United States.

SMO is a form of osteopetrosis and is sometimes referred to as marble bone disease or malignant infantile osteopetrosis because it occurs in very young children. While exact numbers are not known, it has been estimated that one out of 250,000 children is born with SMO.

ACTIMMUNE currently faces limited competition. There are additional or alternative approaches used to treat patients with CGD and SMO, including the increasing trend towards the use of bone marrow transplants in patients with CGD, however, there are currently no medicines on the market that compete directly with ACTIMMUNE.

Our strategy for ACTIMMUNE includes driving growth by increasing awareness and diagnosis of CGD and increasing the persistence of and adherence to treatment.

RAYOS

RAYOS is indicated for the treatment of multiple conditions: rheumatoid arthritis, or RA; ankylosing spondylitis, or AS; polymyalgia rheumatica, or PMR; primary systemic amyloidosis; asthma; chronic obstructive pulmonary disease; systemic lupus erythematosus, or SLE; and a number of other conditions. We focus our promotion of RAYOS on rheumatology indications, including RA and PMR.

RAYOS is composed of an active core containing prednisone that is encapsulated by an inactive porous shell, and acts as a barrier between the medicine's active core and the patient's gastrointestinal, or GI, fluids. RAYOS was developed using Vectura's proprietary GeoClock™ and GeoMatrix™ technologies, for which we hold an exclusive worldwide license for the delivery of glucocorticoid, a class of corticosteroid. The delivery system enables a delayed release, synchronizing the prednisone delivery time with the patient's elevated cytokine levels, thereby taking effect at a physiologically optimal point to inhibit cytokine production, and thus significantly reducing the signs and symptoms of RA and PMR.

RA is a chronic disease that causes pain, stiffness and swelling, primarily in the joints; PMR is an inflammatory disorder that causes significant muscle pain and stiffness; SLE is a chronic autoimmune disease that primarily affects women and causes inflammation and pain in the joints and muscles as well as overall fatigue.

RAYOS competes with a number of medicines in the market to treat RA, including corticosteroids, such as prednisone; traditional disease-modifying anti-rheumatic drugs, or DMARDs, such as methotrexate; and biologic agents, such as Humira and Enbrel. The majority of RA patients are treated with DMARDs, which are typically used as initial therapy in patients with RA. Biologic agents are typically added to DMARDs as combination therapy. It is common for an RA patient to take a combination of a DMARD, an oral corticosteroid, a non-steroidal anti-inflammatory drug, or NSAID, and/or a biologic agent.

Outside the United States, RAYOS is sold and marketed as LODOTRA. Effective January 1, 2019, we amended our license and supply agreements with Jagotec AG and Skyepharma AG, which are affiliates of Vectura. Under these amendments, we agreed to transfer all economic benefits of LODOTRA in Europe to Vectura during an initial transition period, with full rights transferring to Vectura when certain transfer activities have been completed. We will no longer record LODOTRA revenue from January 1, 2019. See the "Manufacturing, Commercial, Supply and License Agreements" section, included in Item 1 of this Annual Report on Form 10-K, for further details of the amendments.

BUPHENYL

BUPHENYL tablets for oral administration and BUPHENYL powder for oral, nasogastric, or gastrostomy tube administration are indicated as adjunctive therapy in the chronic management of patients with UCDs involving deficiencies of carbamoyl phosphate synthetase, ornithine transcarbamylase or argininosuccinic acid synthetase.

BUPHENYL is indicated in all patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first twenty-eight days of life). It is also indicated in patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy. It is important that the diagnosis be made early and treatment initiated immediately to improve chances of survival. BUPHENYL must be combined with dietary protein restriction and, in some cases, essential amino acid supplementation. We distribute BUPHENYL in the United States.

On December 28, 2018, we sold our rights to AMMONAPS outside of North America and Japan to Immedica. We previously distributed AMMONAPS through a commercial partner in Europe and other non-U.S. markets. We have retained rights to BUPHENYL in North America and Japan.

QUINSAIR

QUINSAIR is a formulation of the antibiotic drug levofloxacin, suitable for inhalation via a nebulizer, indicated for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adult patients with cystic fibrosis, or CF. CF is a rare, life-threatening genetic disease affecting approximately 70,000 people worldwide, and results in buildup of abnormally thick secretions that can cause chronic lung infections and progressive lung damage in many patients that eventually leads to death.

QUINSAIR's route of delivery allows higher concentrations of drug in the lung sputum than can be achieved via systemic (for example, oral) administration. QUINSAIR, as approved in Canada and Latin America, is administered twice daily in twenty-eight-day cycles, using a hand-held nebulizer with a disposable handset known as the Zirela® device, manufactured by our partner PARI Pharma GmbH, or PARI, and configured specifically for use with QUINSAIR. QUINSAIR is not approved in the United States.

Chronic pulmonary infections due to *Pseudomonas aeruginosa* are currently treated primarily with inhaled antibiotics, including tobramycin, an aminoglycoside-class antibiotic sold by Novartis Pharmaceuticals Corporation as TOBI® or in dry-powder-inhalation format as TOBI Podhaler® and sold by others in generic form, aztreonam, a monobacter-class antibiotic which is marketed in an inhaled formulation by Gilead Sciences, Inc. under the tradename Cayston®, and colistimethate sodium, a polymixin-class antibiotic which is approved and marketed in inhaled formulations in Europe. Tobramycin, aztreonam and colistimethane are primarily effective against gram-negative bacteria such as *Pseudomonas aeruginosa*. However, the prevalence of multi-drug-resistant *Pseudomonas aeruginosa* is growing. Thus, we believe there is an unmet need that might be addressed with a new class of inhaled antibiotic such as the fluoruquinolone class that levofloxacin represents.

PRIMARY CARE

Our primary care segment includes our marketed medicines PENNSAID 2%, DUEXIS, VIMOVO and MIGERGOT.

PENNSAID 2%

PENNSAID 2% is indicated for the treatment of pain of osteoarthritis, or OA, of the knee(s). OA is a type of arthritis that is caused by the breakdown and eventual loss of the cartilage of one or more joints.

An analgesic that is easy-to-apply topically directly to the knee, PENNSAID 2% contains diclofenac sodium, a commonly prescribed NSAID to treat OA pain, and dimethyl sulfoxide, or DMSO, a penetrating agent that helps ensure that diclofenac sodium is absorbed through the skin to the site of inflammation and pain. Topical NSAIDs such as PENNSAID 2% are generally viewed as safer alternatives to oral NSAID treatment because they reduce systemic exposure to a fraction of that of an oral NSAID. PENNSAID 2% is the only topical NSAID offered with the convenience of a metered-dose pump, which ensures that the patient receives the correct amount of PENNSAID 2% solution with each use. PENNSAID 2% competes primarily with the generic version of Voltaren Gel, a market leader in the topical NSAID category.

DUEXIS

DUEXIS is indicated for the relief of signs and symptoms of RA and OA and to decrease the risk of developing upper-GI ulcers in patients who are taking ibuprofen for these indications. RA is a chronic disease that causes pain, stiffness and swelling, primarily in the joints.

DUEXIS provides a fixed-dose combination in tablet form of ibuprofen, the most widely prescribed NSAID, and famotidine, a well-established GI agent used to treat dyspepsia, gastroesophageal reflux disease and active ulcers.

Fixed-dose combination therapy provides significant advantages over multiple-pill regimens: fixed-dose combinations can reduce the number of pills taken; ensure that the correct dosage of each component is taken at the correct time, improving compliance; and is often associated with better treatment outcomes.

In general, DUEXIS faces competition from the separate use of NSAIDs for pain relief and GI medications to address the risk of NSAID-induced ulcers. However, the prescribing information for DUEXIS states that DUEXIS should not be substituted with the single-ingredient products of ibuprofen and famotidine. DUEXIS competes with other NSAIDs, including Celebrex®, manufactured by Pfizer Inc., and celecoxib, a generic form of the medicine supplied by other pharmaceutical companies. DUEXIS also competes with TIVORBEX™ (indomethacin) capsules, VIVLODEX® (meloxicam) capsules and ZORVOLEX ® (diclofenac) capsules marketed by Iroko Pharmaceuticals, LLC.

VIMOVO

VIMOVO is indicated for the relief of signs and symptoms of OA, RA and AS and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers. It is a proprietary, fixed-dose, delayed-release tablet that combines enteric-coated naproxen, an NSAID, surrounded by a layer of immediate-release esomeprazole magnesium. Naproxen has proven anti-inflammatory and analgesic properties, and esomeprazole magnesium reduces the stomach acid secretions that can cause upper-GI ulcers. Both naproxen and esomeprazole magnesium have well-documented and excellent long-term safety profiles, and both medicines have been used by millions of patients worldwide. VIMOVO has been shown to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID associated gastric ulcers.

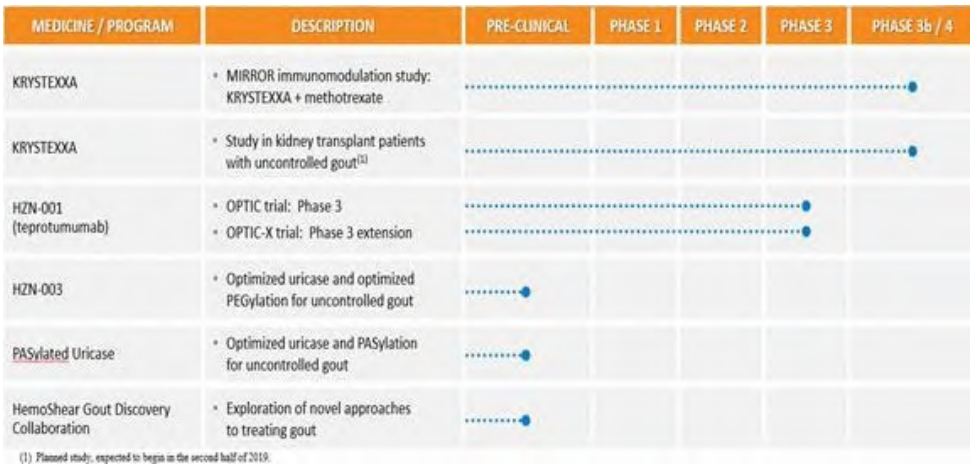
Similar to DUEXIS, VIMOVO faces competition from the separate use of NSAIDs for pain relief and GI medications to address the risk of NSAID-induced ulcers. However, the prescribing information for VIMOVO states that VIMOVO should not be substituted with the single-ingredient products of naproxen and esomeprazole magnesium. VIMOVO also competes with other NSAIDs, including Celebrex, TIVORBEX, VIVLODEX and ZORVOLEX.

MIGERGOT

MIGERGOT is indicated as therapy to abort or prevent vascular headaches, such as migraines, migraine variants or so- called “histaminic cephalalgia”.

Research and Development

Our research and development programs currently include pre-clinical and clinical development of new medicine candidates and activities related to label expansions for existing medicines. We devote significant resources to research and development activities associated with our medicines and medicine candidates, and in 2017 added the first development-stage candidate, teprotumumab, to our pipeline. The graphic below summarizes our significant research and development activities in order of the program stage, from post-market to pre-clinical:



KRYSTEXXA MIRROR trial

KRYSTEXXA is a recombinant protein of uricase, an enzyme not found in humans, and PEGylation. As with many biologic medicines, some people treated with KRYSTEXXA develop antidrug antibodies as part of an immune response to the medicine and lose response to therapy.

We are evaluating ways to maximize KRYSTEXXA benefit to patients by improving its response rate. In the KRYSTEXXA pivotal trials, forty-two percent of patients achieved complete response. While this is impressive relative to the response rate of biologic medicines used for other types of inflammatory arthritis, we are investigating ways to increase the number of patients who can achieve a complete response with KRYSTEXXA by pairing KRYSTEXXA with immunomodulator medicines. There is well-documented evidence that the addition of immunomodulators to biological therapies can decrease rates of immunogenicity, as the immunomodulators work to reduce the formation of anti-drug antibodies to the medicine, allowing it to maintain appropriate blood levels over a longer period of time. Our clinical trial, MIRROR, is currently underway in which we are evaluating the administration of KRYSTEXXA with methotrexate, the most commonly used immunomodulator by rheumatologists. Additionally, we are adapting the MIRROR trial to support the potential for registration and modification of our KRYSTEXXA FDA label.

KRYSTEXXA Study in Kidney Transplant Patients with Uncontrolled Gout

We plan to initiate a clinical trial in the second half of 2019 to evaluate the effect of KRYSTEXXA, our medicine for uncontrolled gout, on serum uric acid levels in kidney transplant patients with uncontrolled gout. Kidney transplant patients have more than a tenfold increase in the prevalence of gout when compared to the general population, and literature suggests that high serum uric acid levels are associated with organ rejection. Managing uncontrolled gout is one of the most common and significant unmet needs of kidney transplant patients.

HZN-001: Teprotumumab

Teprotumumab is a fully human monoclonal antibody inhibitor of insulin-like growth factor type 1 receptor being studied in a confirmatory Phase 3 clinical trial for the treatment of thyroid eye disease, or TED, which is a rare eye disease. There are no FDA-approved therapies for TED; therefore, there is a significant unmet need for an effective and safe treatment.

TED can be associated with Graves' disease, but it is a separate and distinct disease. TED is an eye condition in which the body attacks its own orbital cells. This leads to inflammation and expansion of tissue, muscle, and fat cells behind the eye, which causes the eye to bulge outward, known as proptosis. Proptosis can cause corneal ulcers, double vision and misaligned eyes. In rare instances, it can result in compression of the optic nerve that can lead to blindness. We estimate that 15,000 to 20,000 patients would be eligible for treatment annually in the United States. Teprotumumab received orphan drug, fast track and breakthrough therapy designations from the FDA in 2016 and would receive twelve years of biologic exclusivity upon approval.

The Phase 2 clinical trial results for teprotumumab were published in *The New England Journal of Medicine* in May 2017 and demonstrated clinically meaningful and statistically significant results in patients with active moderate-to-severe TED. The primary endpoint of the Phase 2 clinical trial was the responder rate at week twenty-four, defined as a reduction of proptosis of at least 2mm and a reduction in the clinical activity score of at least two points: Sixty-nine percent of teprotumumab patients achieved the primary endpoint versus twenty percent of the placebo patients ($p < 0.001$). In the secondary endpoint of proptosis alone, seventy-one patients achieved a reduction of at least 2mm.

In October 2018, we presented data at week seventy-two that demonstrated that these results were durable – with more than 50 percent of patients maintaining a response approximately one year off therapy. These results support our belief that teprotumumab offers patients a potential disease-modifying medicine.

In September 2018, we completed the enrollment of patients in the confirmatory Phase 3 clinical trial titled "Treatment of Graves' Orbitopathy (Thyroid Eye Disease) to Reduce Proptosis with Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study", or OPTIC. OPTIC enrolled eighty-three patients who met OPTIC Phase 3 eligibility criteria across thirteen centers in the United States, Germany and Italy, and those patients were randomized to receive eight infusions of either teprotumumab or placebo every three weeks for twenty-one weeks, the same regimen as was studied in the Phase 2 clinical trial. The primary endpoint measures the proptosis responder rate of at least 2 mm reduction of proptosis in the study eye (without deterioration in the fellow eye) at week twenty-four. In addition, the OPTIC trial measures several secondary endpoints at week twenty-four. Safety will also be evaluated. We expect data read-out by the end of the first quarter of 2019, and, if successful, we anticipate submitting a biologics license application, or BLA, in mid-2019, with the potential for approval in 2020.

Additionally, patients participating in the OPTIC trial have the option to participate in an extension study, or OPTIC-X, in which participants may receive an additional eight infusions of teprotumumab. OPTIC-X will provide additional data on whether non-responders from the initial twenty-four weeks of treatment during OPTIC would benefit from longer treatment, and if patients who lose response off drug after the initial twenty-four weeks of treatment would benefit from retreatment.

HZN-003: Potential Next-Generation Biologic for Uncontrolled Gout Using Optimized Uricase and Optimized PEGylation Technology

A potential biologic for uncontrolled gout, HZN-003 is a pre-clinical, genetically engineered uricase with optimized PEGylation technology that has the potential to improve the half-life and reduce immunogenicity of this molecule. In addition, it has the potential for subcutaneous dosing. We licensed HZN-003 from MedImmune LLC, the global biologics research and development arm of the AstraZeneca Group, late in 2017. HZN-003 is a rheumatology pipeline program with the objective of enhancing our leadership position in the uncontrolled gout market.

PASylated Uricase

We have entered into a PASylated uricase collaboration program to identify uncontrolled gout biologic candidates. This project involves PASylation technology as a biological alternative to synthetic PEGylation. PASylation is a new approach for extending the half-life of pharmaceutically active proteins and reducing immunogenicity. In addition, it has the potential for subcutaneous dosing.

HemoShear Gout Discovery Collaboration

We have entered into a collaboration agreement with HemoShear Therapeutics, LLC, a biotechnology company, to discover and develop novel therapeutics for gout. The collaboration provides us an opportunity to address unmet treatment needs for people with gout by evaluating new targets for the control of serum uric acid levels as well as new targets to address the inflammation associated with acute flares of gout.

Distribution

We use central third-party logistics, FDA-compliant warehouses for storage and distribution of our medicines into the supply chain. Our third-party logistics providers specialize in integrated operations that include warehousing and transportation services that can be scaled and customized to our needs based on market conditions and the demands and delivery service requirements for our medicines and materials. Their services eliminate the need to build dedicated internal infrastructures that would be difficult to scale without significant capital investment. Our third-party logistics providers warehouse all medicines in controlled FDA-registered facilities. Incoming orders are prepared and shipped through an order entry system to ensure just in time delivery of the medicines.

Sales and Marketing

As of December 31, 2018, our sales force was composed of approximately 420 sales representatives consisting of approximately 25 orphan disease sales representatives, 140 rheumatology sales specialists and 255 primary care sales representatives.

Our orphan and rheumatology sales representatives focus on marketing our orphan and rheumatology medicines to a limited number of healthcare practitioners who specialize in fields such as pediatric immunology, allergy, infectious diseases, metabolic disorders, rheumatology and nephrology to help them understand the potential benefits of our medicines. We have entered into, and may continue to enter into, agreements with third parties for commercialization of our medicines outside the United States.

Patients are able to fill prescriptions for our primary care medicines and RAYOS through pharmacies participating in our HorizonCares patient access program, as well as other pharmacies. In addition, we have business arrangements with pharmacy benefit managers and other payers to secure formulary status and reimbursement of our primary care medicines.

We have a comprehensive compliance program in place to address adherence with various laws and regulations relating to our sales, marketing, and manufacturing of our medicines, as well as certain third-party relationships, including pharmacies. Specifically with respect to pharmacies, the compliance program utilizes a variety of methods and tools to monitor and audit pharmacies, including those that participate in our patient access programs, to confirm their activities, adjudication and practices are consistent with our compliance policies and guidance.

Manufacturing, Commercial, Supply and License Agreements

We have agreements with third parties for active pharmaceutical ingredients, or APIs, and manufacturing of our medicines, formulation and development services, fill, finish and packaging services, transportation, and distribution and logistics services for certain medicines. In most cases, we retain certain levels of safety stock or maintain alternate supply relationships that we can utilize without undue disruption of our manufacturing processes if a third party fails to perform its contractual obligations.

KRYSTEXXA

KRYSTEXXA is produced by fermentation of a genetically engineered Escherichia coli bacterium containing the DNA which encodes for uricase. The complementary DNA coding for the uricase is based on mammalian sequences. Uricase is purified and is then PEGylated with a PEGylation agent to produce the bulk medicine, pegloticase. PEGylation and purification of the active drug substance is achieved by conventional column chromatography. The resulting highly purified sterile solution is filled in a single-use vial for intravenous infusion following dilution. In support of its manufacturing process, we store multiple vials of the Escherichia coli bacterium master cell bank and working cell bank at multiple locations in order to ensure adequate backup should any cell bank be lost in a catastrophic event.

NOF Supply Agreement

In August 2015, Crealta and NOF Corporation, or NOF, in Japan, entered into an exclusive supply agreement for the PEGylation agent used in the manufacture of KRYSTEXXA. We assumed this agreement as part of the Crealta acquisition. Under the terms of this agreement, we are required to issue NOF forecasts of our requirements for the PEGylation agent, a portion of which are binding. The agreement expires in August 2020. Either we or NOF may also terminate the agreement upon a material breach, if not cured within a specified period of time, or in the event of the other party's insolvency. While there are no minimum purchase obligations under the agreement, we are required to use NOF as our exclusive supplier for the PEGylation agent, subject to certain exceptions if NOF is unable to supply the PEGylation agent.

Bio-Technology General (Israel) Supply Agreement

In March 2007, Savient Pharmaceuticals, Inc. (as predecessor in interest to Crealta), or Savient, entered into a commercial supply agreement with Bio-Technology General (Israel) Ltd, or BTG Israel, for the production of the bulk KRYSTEXXA medicine, or bulk product. We assumed this agreement as part of the Crealta acquisition and amended the agreement in September 2016. Under this agreement, we have agreed to purchase certain minimum annual order quantities and are obligated to purchase at least eighty percent of our annual world-wide bulk product requirements from BTG Israel. The term of the agreement runs until December 31, 2030, and will automatically renew for successive three year periods unless earlier terminated by either party upon three years' prior written notice. The agreement may be terminated earlier by either party in the event of a force majeure, liquidation, dissolution, bankruptcy or insolvency of the other party, uncured material breach by the other party or after January 1, 2024, upon three years' prior written notice. Under this agreement, if the manufacture of the bulk product is moved out of Israel, we may be required to obtain the approval of the Israeli Office of the Chief Scientist, or OCS, because certain KRYSTEXXA intellectual property was initially developed with a grant funded by the OCS and we may be required to pay the OCS additional amounts as a repayment for the OCS grant funding. We issue eighteen-month forecasts of the volume of KRYSTEXXA that we expect to order. The first six months of the forecasts are considered binding firm orders.

Exelead PharmaSource Supply Agreement

In October 2008, Savient and Exelead, Inc. (formerly known as Sigma Tau PharmaSource, Inc. (as successor in interest to Enzon Pharmaceuticals, Inc.)), or Exelead, entered into a commercial supply agreement for the packaging and supply of the final drug medicine KRYSTEXXA, which we acquired as part of the Crealta acquisition. This agreement remains in effect until terminated, and either we or Exelead may terminate the agreement with three years notice, given thirty days prior to the agreement anniversary date. Either we or Exelead may also terminate the agreement upon a material default, if not cured within a specified period of time, or in the event of the other party's insolvency or bankruptcy.

Duke University and Mountain View Pharmaceutical License Agreement

In August 1998, Savient entered into an exclusive, worldwide license agreement with Duke University, or Duke, and Mountain View Pharmaceuticals Inc., or MVP, which we acquired as part of the Crealta acquisition. Duke developed the recombinant uricase enzyme used in KRYSTEXXA and MVP developed the PEGylation technology used in the manufacture of KRYSTEXXA. Duke and MVP may terminate the agreement if we commit fraud or for our willful misconduct or illegal conduct; upon our material breach of the agreement, if not cured within a specified period of time; upon written notice if we have committed two or more material breaches under the agreement; or in the event of our bankruptcy or insolvency. Under the terms of the agreement, we are obligated to pay Duke a mid-single digit percentage royalty on our global net sales of KRYSTEXXA and a royalty of between five percent and fifteen percent on any global sublicense revenue. We are also obligated to pay MVP a mid-single digit percentage royalty on our net sales of KRYSTEXXA outside of the United States and royalty of between five percent and fifteen percent on any sublicense revenue outside of the United States.

RAVICTI

We have clinical and commercial supplies of glycerol phenylbutyrate API manufactured for us by two alternate suppliers, Helsinn Advanced Synthesis SA (Switzerland) and DSM Fine Chemicals Austria (now Patheon Austria GmbH & Co KG) on a purchase-order basis. We have manufacturing agreements to manufacture finished RAVICTI drug medicine with Lyne Laboratories, Inc., Halo Pharmaceuticals, Inc. and PCI Pharma Services.

Bausch Health Asset Purchase Agreement

As a result of our acquisition of Hyperion Therapeutics, Inc., or Hyperion, in May 2015, we became subject to an asset purchase agreement with Bausch Health Companies, Inc. (formerly Ucyclyd Pharma, Inc.), or Bausch, pursuant to which we are obligated to pay to Bausch mid to high single-digit royalties on our global net sales of RAVICTI. The asset purchase agreement cannot be terminated for convenience by either party. We have a license to certain Bausch manufacturing technology, however Bausch is permitted to terminate the license if we fail to comply with any payment obligations relating to the license and do not cure such failure within a defined time period.

Brusilow License Agreement

As a result of the Hyperion acquisition, we became subject to a license agreement with Saul W. Brusilow, M.D. and Brusilow Enterprises, Inc., or Brusilow, pursuant to which we license patented technology related to RAVICTI from Brusilow. Under such agreement, we are obligated to pay low-single digit royalties to Brusilow on net sales of RAVICTI that are, or were, covered by a valid claim of a licensed patent. The license agreement may be terminated for any uncured breach as well as bankruptcy. We may also terminate the agreement at any time by giving Brusilow prior written notice, in which case all rights granted to us would revert to Brusilow.

PROCYSBI

PROCYSBI drug product is comprised of enteric-coated beads of cysteamine bitartrate encapsulated in gelatin capsules. PROCYSBI drug product and API, cysteamine bitartrate, are manufactured on a contract basis by third parties.

Patheon Manufacturing Services Agreement

As a result of the Raptor acquisition, we assumed a manufacturing services agreement, as amended, with Patheon Pharmaceuticals Inc., or Patheon, for the manufacture and supply of PROCYSBI. Pursuant to the agreement, we must provide a rolling, non-binding forecast of PROCYSBI, with a portion of the forecast being a firm written order. The agreement has a term that runs until December 31, 2021 and which automatically renews for successive two-year terms if not terminated at least eighteen months in advance.

Cambrex Profarmaco Milano Supply Agreement

As a result of the Raptor acquisition, we assumed an API supply agreement, as amended, with Cambrex Profarmaco Milano, or Cambrex. Pursuant to the agreement, we must provide rolling, non-binding forecasts, with a portion of the forecast being the minimum floor of the firm order that must be placed. The Cambrex supply agreement has an initial term that runs until November 30, 2020, and which automatically renews for successive two-year terms if not terminated at least one year in advance.

UCSD License Agreement

In May 2017, we entered into an amended and restated license agreement with The Regents of the University of California, San Diego, or UCSD, which was amended in September 2018. We must pay UCSD a royalty in the mid-single digits on net sales of PROCYSBI in countries where PROCYSBI is covered by a patent right, and a royalty in the low-single digits on net sales of PROCYSBI in countries where PROCYSBI is not covered by a patent right. Each such royalty is subject to reduction for sales of PROCYSBI in countries in the event a generic substitute for PROCYSBI is sold in such countries. We must pay UCSD a minimum annual royalty in an amount less than $0.1 million. Royalties terminate upon the later of (a) the expiration date of the longest-lived patent rights on a country-by-country basis; and (b) twenty years after first commercial sale of PROCYSBI. We must also pay UCSD a percentage in the mid-teens of any fees we receive from our sublicensees under the agreement that are not earned royalties. We may also be obligated to pay UCSD aggregate developmental milestone payments of $0.3 million and aggregate regulatory milestone payments of $1.8 million for each orphan indication and aggregate developmental milestone payments of $0.8 million and aggregate regulatory milestone payments of $3.5 million for each non-orphan indication. We are also subject to certain diligence obligations relating to performing activities for specified indications, including maintaining existing regulatory approvals for PROCYSBI and commercializing PROCYSBI in countries where regulatory approvals have been obtained and using commercially reasonable efforts to develop, obtain regulatory approval, and commercialize certain other licensed medicines in the United States and other countries. Under the terms of our agreement with Chiesi, royalties due to UCSD on sales of PROCYSBI in EMEA will be paid by Chiesi to us, which we will forward to UCSD unless we instruct Chiesi to make such payments directly to UCSD.

ACTIMMUNE

ACTIMMUNE is a recombinant protein that is produced by fermentation of a genetically engineered Escherichia coli bacterium containing the DNA which encodes for the human protein. Purification of the active drug substance is achieved by conventional column chromatography. The resulting active drug substance is then formulated as a highly purified sterile solution and filled in a single-use vial for subcutaneous injection, which is the ACTIMMUNE finished drug medicine. In support of its manufacturing process, we and Boehringer Ingelheim RCV GmbH & Co KG, or Boehringer Ingelheim, store multiple vials of the Escherichia coli bacterium master cell bank and working cell bank in order to ensure adequate backup should any cell bank be lost in a catastrophic event.

Boehringer Ingelheim Supply Agreement

In June 2017, we entered into an exclusive global supply agreement with Boehringer Ingelheim Biopharmaceuticals GmbH, or Boehringer Ingelheim Biopharmaceuticals, pursuant to which Boehringer Ingelheim Biopharmaceuticals is required to manufacture and supply ACTIMMUNE and IMUKIN active drug substance and commercial quantities of the ACTIMMUNE and IMUKIN finished drug medicine. Boehringer Ingelheim Biopharmaceuticals is our sole source supplier for ACTIMMUNE active drug substance and finished drug medicine. Pursuant to the agreement, we are required to purchase minimum quantities of finished drug medicine during the term of the agreement. Boehringer Ingelheim Biopharmaceuticals manufactures our commercial requirements of ACTIMMUNE based on our forecasts and the annual contractual minimum purchase quantity. The supply agreement continues for an indefinite period but can be terminated by either party upon three years notice (but, in such case, cannot be terminated sooner than June 30, 2024), for an uncured material breach by the other party, upon the other party's bankruptcy or insolvency, or upon certain changes of control of the other party. We can terminate the supply agreement in the event we are prevented by regulatory authorities from distributing the product on the market for all indications.

License Agreements

Under a license agreement, as amended, with Genentech who was the original developer of ACTIMMUNE, we are or were obligated to pay royalties to Genentech on our net sales of ACTIMMUNE as follows:

- For the period from November 26, 2014, through May 5, 2018, a royalty in the twenty percent to thirty percent range for the first $3.7 million in net sales achieved in any calendar year and in the one percent to nine percent range for all additional net sales in any year; and
- From May 6, 2018, an annual royalty in the low single digits as a percentage of annual net sales.

Either Genentech or we may terminate the agreement if the other party becomes bankrupt or defaults, however, in the case of a default, the defaulting party has thirty days to cure the default before the license agreement may be terminated.

Under the terms of an assignment and option agreement with Connetics Corporation (which was the predecessor parent company to InterMune Pharmaceuticals Inc. and is now part of GlaxoSmithKline), or Connetics, we are obligated to pay low single-digit royalties to Connetics on our net sales of ACTIMMUNE in the United States.

RAYOS and LODOTRA

We purchase the API for RAYOS from Tianjin Tianyao Pharmaceuticals Co., Ltd. in China and from Sanofi Chimie SA in France. We have contracted with Jagotec AG, which is an affiliate of Vectura, for the production of RAYOS tablets and we entered into an agreement with Patheon for the packaging and assembling of RAYOS.

During the years ended December 31, 2018, 2017 and 2016, we were obligated to pay Vectura a mid-single digit percentage royalty on our adjusted gross sales of RAYOS and LODOTRA and on any sub-licensing income, which includes any payments not calculated based on the adjusted gross sales of RAYOS and LODOTRA, such as license fees, and lump sum and milestone payments.

Effective January 1, 2019, we amended our license and supply agreements with Jagotec AG and Skyepharma AG, which is also an affiliate of Vectura. Under these amendments, we agreed to transfer all economic benefits of LODOTRA in Europe to Vectura during an initial transition period, with full rights transferring to Vectura when certain transfer activities have been completed. In exchange for transferring the LODOTRA economic benefits and rights, the royalty payable by us to Vectura in respect of RAYOS sales in North America was amended whereby, effective January 1, 2019, we are obliged to pay Vectura a mid-double-digit percentage royalty on our net sales, subject to a minimum royalty of $8.0 million per year, with the minimum royalty requirement expiring on December 31, 2022. Under the amendments, we will no longer record LODOTRA revenue and we are no longer required to pay a royalty in respect of LODOTRA. In addition, under the amendments, from the earlier of the completion of the transfer activities or January 1, 2020, we will no longer be subject to a minimum purchase commitment in respect of the supply agreement with Jagotec AG.

BUPHENYL

When Hyperion purchased BUPHENYL, Hyperion assumed all of Bausch's rights and obligations under its manufacturing agreements for the medicine. We assumed these agreements when we acquired Hyperion. We purchase API for BUPHENYL from CU Chemie Uetikon GmbH and final manufacturing, testing and packaging of the medicine is provided by Pharmaceutics International Inc.

Under the terms of an amended and restated collaboration agreement with Bausch, we are obligated to pay to Bausch mid single-digit royalties on our net sales in the United States of BUPHENYL to UCD patients.

QUINSAIR

QUINSAIR drug product, its API, levofloxacin hemihydrate, and the Zirela nebulizer device are all manufactured on a contract basis by third parties. The API is exclusively supplied by TEVA API Inc. QUINSAIR drug product is manufactured by Catalent Pharma Solutions, LLC. Nebulizers are supplied by PARI in Starnberg, Germany.

PENNSAID 2%

In October 2014, in connection with the acquisition of the U.S. rights to PENNSAID 2% from Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.), or Nuvo, we entered into an exclusive supply agreement with Nuvo, which was amended in February 2016, January 2017 and February 2018, under which Nuvo is obligated to manufacture and supply PENNSAID 2% to us. The term of our supply agreement is through December 31, 2029, but the agreement may be terminated earlier by either party for any uncured material breach by the other party of its obligations under the supply agreement or upon the bankruptcy or similar proceeding of the other party.

A key excipient used in PENNSAID 2% as a penetration enhancer is DMSO. We and Nuvo rely on a sole proprietary form of DMSO for which we maintain a substantial safety stock. However, should this supply become inadequate, damaged, destroyed or unusable, we and Nuvo may not be able to qualify a second source.

DUEXIS

We purchase DUEXIS in final, packaged form exclusively from Sanofi-Aventis U.S. LLC, or Sanofi, for our commercial requirements in North America. The first API in DUEXIS is ibuprofen in a direct compression blend called DC85 and is supplied to Sanofi by BASF Corporation, or BASF, in Bishop, Texas. The second API in DUEXIS is famotidine, which is available from a number of international suppliers. Famotidine is currently sourced from two manufacturers. We currently receive both APIs in powder form and each is blended with a number of U.S. Pharmacopeia inactive ingredients.

BASF Contract

In July 2010, we entered into a contract with BASF for the purchase of DC85, which was subsequently amended effective as of January 2016. Pursuant to the agreement, we were obligated to source a significant majority of our commercial demand for DC85 from BASF. Prior to the expiration of the agreement in December 2018, BASF notified customers that were being supplied by the Bishop manufacturing facility, including us, that it would not be renewing supply agreements for 2019 due to a technical issue at the facility that has prevented it from supplying these customers. BASF is currently working to resolve the technical issue and recently notified us of its intention to resume supply of DC85. We consider our DUEXIS inventory on hand to be sufficient to meet current and future commercial requirements during the resolution process.

Manufacturing and Supply Agreement with Sanofi

In May 2011, we entered into a manufacturing and supply agreement with Sanofi, which was amended in September 2013 and May 2018. Pursuant to the agreement, Sanofi is obligated to manufacture and supply DUEXIS to us in final, packaged form, and we are obligated to purchase DUEXIS exclusively from Sanofi for our commercial requirements in North America and certain countries and territories in Europe, including the EU member states and Scandinavia, and South America. Sanofi must acquire the components necessary to manufacture DUEXIS, including the APIs, and is obligated to acquire all DC85 under the terms of our agreements with suppliers. In order to allow Sanofi to perform its obligations under the agreement, we granted Sanofi a non-exclusive license to our related intellectual property. The agreement term extends until May 2019, and automatically extends for successive two-year terms unless terminated by either party upon two years' prior written notice. Either party may terminate the agreement upon thirty days' prior written notice to the other party in the event of breach by the other party that is not cured within thirty days of notice (which notice period may be longer in certain, limited situations) or in the event we lose regulatory approval to market DUEXIS in all countries worldwide, and either party may terminate the agreement without cause upon two years' prior written notice to the other party at any time after the third anniversary of the first commercial sale of DUEXIS in any country worldwide.

VIMOVO

We purchase VIMOVO in final, packaged form from Patheon for our commercial requirements in North America. The first API in VIMOVO is naproxen which is supplied to Patheon by Divis Laboratories Limited in India. The second API in VIMOVO is esomeprazole magnesium trihydrate, which we source from Minakem Holding SAS in France.

Under a license agreement with Nuvo (formerly Aralez Pharmaceuticals Inc.), we are required to pay Nuvo a ten percent royalty based on net sales of VIMOVO sold by us, our affiliates or sublicensees during the royalty term, subject to a minimum annual royalty obligation of $7.5 million, which minimum royalty obligations will continue for each year during which one of Nuvo's patents covers VIMOVO in the United States and there are no competing medicines in the United States. The royalty rate may be reduced to a mid-single digit royalty rate as a result of loss of market share to competing medicines.

MIGERGOT

MIGERGOT drug product is ergotamine tartrate and caffeine-containing suppositories. ACP Nimble Buyer Inc., or ACP, an affiliate of Avista Capital Partners, performs the sourcing and procurement of the APIs, ergotamine tartrate and caffeine. MIGERGOT drug product is manufactured by ACP in South Plainfield, New Jersey under a supply agreement that expires on December 31, 2023.

Intellectual Property

Our objective is to aggressively patent the technology, inventions and improvements that we consider important to the development of our business. We have a portfolio of patents and applications based on clinical and pharmacokinetic/pharmacodynamic modeling discoveries, and our novel formulations. We intend to continue filing patent applications seeking intellectual property protection as we generate anticipated formulation refinements, new methods of manufacturing and clinical trial results.

We will only be able to protect our technologies and medicines from unauthorized use by third parties to the extent that valid and enforceable patents or trade secrets cover them. As such, our commercial success will depend in part on receiving and maintaining patent protection and trade secret protection of our technologies and medicines as well as successfully defending these patents against third-party challenges.

The patent positions of life sciences companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in such companies' patents has emerged to date in the United States. The patent situation outside the United States is even more uncertain. Changes in either the patent laws or in interpretations of patent laws in the United States or other countries may diminish the value of our intellectual property. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in our patents or in third-party patents. For example:

- we or our licensors might not have been the first to make the inventions covered by each of our pending patent applications and issued patents;
- we or our licensors might not have been the first to file patent applications for these inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies;
- it is possible that none of our pending patent applications or the pending patent applications of our licensors will result in issued patents;
- our issued patents and the issued patents of our licensors may not provide a basis for commercially viable drugs, or may not provide us with any competitive advantages, or may be challenged and invalidated by third parties;
- we may not be successful in any patent litigation to enforce our patent rights, including our pending patent litigation regarding PENNSAID 2%, DUEXIS and/or VIMOVO;
- we may not develop additional proprietary technologies or medicine candidates that are patentable; or
- the patents of others may have an adverse effect on our business.

KRYSTEXXA

We have licenses to U.S. and foreign patents and applications covering KRYSTEXXA. If not otherwise invalidated, those patents expire between 2019 and 2030. We continue to prosecute and pursue patent protection to obtain additional patent coverage on KRYSTEXXA and its uses.

In the United States, KRYSTEXXA has received twelve years of biologic exclusivity, expiring in 2022.

RAVICTI

We have ownership of U.S. and foreign patents and patent applications covering RAVICTI. If not otherwise invalidated, those patents expire between 2030 and 2032. We license our rights to patents and patent applications outside of North America and Japan to Immedica. We continue to prosecute and pursue patent protection to obtain additional patent coverage on RAVICTI and its uses.

In the United States, RAVICTI has been granted seven years of orphan drug exclusivity, which will expire in 2020. Under our settlement and license agreement with Par Pharmaceutical, Inc., Par Pharmaceutical, Inc. may enter the market on July 1, 2025, or earlier in certain circumstances. We also have a settlement and license agreement with Lupin Limited and Lupin Pharmaceuticals, Inc., or collectively Lupin, pursuant to which Lupin may enter the market on July 1, 2026, or earlier under certain circumstances.

PROCYSBI

We have U.S. and foreign patents and patent applications covering PROCYSBI, as well as licenses from UCSD to U.S. and foreign patents and patent applications covering PROCYSBI. If not otherwise invalidated, those patents expire between 2027 and 2034. We continue to prosecute and pursue patent protection to obtain additional patent coverage on PROCYSBI and its uses.

PROCYSBI received marketing authorization in September 2013 from the European Commission, or the EC, for marketing in the EU as an orphan medicinal product for the management of proven NC.

PROCYSBI received seven years of market exclusivity, through 2020, for patients six years and older as an orphan drug in the United States, and ten years of market exclusivity, through 2023, as an orphan drug in Europe. PROCYSBI received seven years of market exclusivity, through 2022, for patients two years of age to less than six years of age, and seven years of market exclusivity, through 2024, for patients one year of age to less than two years of age, as an orphan drug in the United States. During December 2017, the FDA awarded pediatric exclusivity to PROCYSBI in the United States, which adds an additional six month exclusivity period to the end of each orphan exclusivity period and patent term covering PROCYSBI.

ACTIMMUNE

We have licenses to U.S. patents covering ACTIMMUNE. If not otherwise invalidated, those patents expire in 2022. We continue to prosecute and pursue patent protection to obtain additional patent coverage on ACTIMMUNE and its uses.

RAYOS/LODOTRA

We have an exclusive license to U.S. and foreign patents and patent applications from Vectura covering RAYOS/LODOTRA. If not otherwise invalidated, those in-licensed patents expire between 2020 and 2028. We continue to prosecute and pursue additional patent coverage on RAYOS/LODOTRA and its uses. Under our settlement agreement with Teva Pharmaceuticals Industries Limited (formerly known as Actavis Laboratories FL, Inc., which itself was formerly known as Watson Laboratories, Inc. – Florida), or Teva, Teva may enter the market on December 23, 2022, or earlier under certain circumstances. Effective January 1, 2019, we amended our license and supply agreements with Jagotec AG and Skyepharma AG, which is also an affiliate of Vectura. Under these amendments, we agreed to transfer all economic benefits of LODOTRA in Europe to Vectura during an initial transition period, with full rights transferring to Vectura when certain transfer activities have been completed.

QUINSAIR

We have U.S. and foreign patents and patent applications covering QUINSAIR, as well as licenses from PARI and Tripex Pharmaceuticals, LLC to U.S. and foreign patents and patent applications covering QUINSAIR. If not otherwise invalidated, those patents expire between 2020 and 2037. We continue to prosecute and pursue patent protection to obtain additional patent coverage on QUINSAIR and its uses.

QUINSAIR received ten years of market exclusivity in the EU, beginning with its March 2015 marketing authorization.

PENNSAID 2%

We have ownership of U.S. patents and patent applications covering PENNSAID 2% from Nuvo. We also co-own other U.S. patent applications with Mallinckrodt LLC. If not otherwise invalidated, those patents expire between 2027 and 2030. Under our settlement agreements with Amneal Pharmaceuticals, LLC., Teligent, Inc., Perrigo Company plc, Taro Pharmaceuticals Industries Ltd., and Lupin, such parties may enter the market on October 17, 2027, or earlier under certain circumstances. We continue to prosecute and pursue patent protection in the United States to obtain additional patent coverage on PENNSAID 2% and its uses.

DUEXIS

We have multiple patents and patent applications related to DUEXIS. Unless otherwise invalidated, those patents expire in 2026. Under a settlement agreement with Par Pharmaceutical, Inc. and Par Pharmaceutical Companies, Inc., or collectively Par, Par may enter the market on January 1, 2023, or earlier under certain circumstances.

VIMOVO

We have licenses to U.S. patents and patent applications and trademarks covering VIMOVO from Nuvo and AstraZeneca AB. We co-own other U.S. patents and patent applications with Nuvo. If not otherwise invalidated, those in-licensed patents expire between 2022 and 2031. We continue to prosecute and pursue patent protection in the United States to obtain additional patent coverage on VIMOVO and its uses. Under a settlement agreement with Actavis Pharma Inc., or Actavis, Actavis may enter the market on January 1, 2025, or earlier under certain circumstances.

For a description of our legal proceedings related to intellectual property matters, see Note 18 of the Notes to consolidated financial statements, included in Item 15 of this Annual Report on Form 10-K.

Third-Party Coverage and Reimbursement

In both U.S. and foreign markets, our ability to commercialize our medicines successfully depends in significant part on the availability of coverage and adequate reimbursement to healthcare providers from third-party payers, including, in the United States, government payers such as the Medicare and Medicaid programs, managed care organizations and private health insurers. Third-party payers are increasingly challenging the prices charged for medicines and examining their cost effectiveness, in addition to their safety and efficacy. This is especially true in markets where over-the-counter and generic options exist. Even if coverage is made available by a third-party payer, the reimbursement rates paid for covered medicines might not be adequate. For example, third-party payers may use tiered coverage and may adversely affect demand for our medicines by not covering our medicines or by placing them in a more expensive formulary tier relative to competitive medicines (where patients have to pay relatively more out of pocket than for medicines in a lower tier). We cannot be certain that our medicines will be covered by third-party payers or that such coverage, where available, will be adequate, or that our medicines will successfully be placed on the list of drugs covered by particular health plan formularies. Many states have also created preferred drug lists and include drugs on those lists only when the manufacturers agree to pay a supplemental rebate. The industry competition to be included on such formularies and preferred drug lists often leads to downward pricing pressures on pharmaceutical companies. Also, third-party payers may refuse to include a particular branded drug on their formularies or otherwise restrict patient access to a branded drug when a less costly generic equivalent or other therapeutic alternative is available. In addition, because each third-party payer individually approves coverage and reimbursement levels, obtaining coverage and adequate reimbursement is a time-consuming and costly process. We may be required to provide scientific and clinical support for the use of any medicine to each third-party payer separately with no assurance that approval would be obtained, and we may need to conduct pharmacoeconomic studies to demonstrate the cost effectiveness of our medicines for formulary coverage and reimbursement. Even with studies, our medicines may be considered less safe, less effective or less cost-effective than competitive medicines, and third-party payers may not provide coverage and adequate reimbursement for our medicines or our medicine candidates. These pricing and reimbursement pressures may create negative perceptions to any medicine price increases, or limit the amount we may be able to increase our medicine prices, which may adversely affect our medicine sales and results of operations. Where coverage and reimbursement are not adequate, physicians may limit how much or under what circumstances they will prescribe or administer such medicines, and patients may decline to purchase them. This, in turn, could affect our ability to successfully commercialize our medicines and impact our profitability, results of operations, financial condition, and future success.

The U.S. market has seen a trend in which retail pharmacies have become increasingly involved in determining which prescriptions will be filled with the requested medicine or a substitute medicine, based on a number of factors, including potentially perceived medicine costs and benefits, as well as payer medicine substitution policies. Many states have in place requirements for prescribers to indicate “dispense as written” on their prescriptions if they do not want pharmacies to make medicine substitutions; these requirements are varied and not consistent across states. We may need to increasingly spend time and resources to ensure the prescriptions written for our medicines are filled as written, where appropriate.

Coverage policies, third-party reimbursement rates and medicine pricing regulation have been subject to significant change, and may change further at any time, particularly given recent political focus on the pharmaceutical industry. Even if favorable coverage and adequate reimbursement status is attained for one or more medicines, less favorable coverage policies and reimbursement rates may be implemented in the future.

Government Regulation

The FDA and comparable regulatory agencies in state and local jurisdictions and in foreign countries impose extensive requirements upon the clinical development, pre-market approval, manufacture, labeling, marketing, promotion, pricing, import, export, storage and distribution of medicines. These agencies and other regulatory agencies regulate research and development activities and the testing, approval, manufacture, quality control, safety, effectiveness, labeling, storage, recordkeeping, advertising and promotion of drugs and biologics. Failure to comply with applicable FDA or foreign regulatory agency requirements may result in warning letters, fines, civil or criminal penalties, additional reporting obligations and/or agency oversight, suspension or delays in clinical development, recall or seizure of medicines, partial or total suspension of production or withdrawal of a medicine from the market.

In the United States, the FDA regulates drug products under the Federal Food, Drug, and Cosmetic Act and its implementing regulations and biologics additionally under the Public Health Service Act. The process required by the FDA before medicine candidates may be marketed in the United States generally involves the following:

- submission to the FDA of an investigational new drug, or IND, which must become effective before human clinical trials may begin and must be updated annually;
- completion of extensive pre-clinical laboratory tests and pre-clinical animal studies, all performed in accordance with the FDA's Good Laboratory Practice, or GLP, regulations;
- performance of adequate and well-controlled human clinical trials to establish the safety and efficacy of the medicine candidate for each proposed indication;
- submission to the FDA of a new drug application, or NDA, or BLA as appropriate, after completion of all pivotal clinical trials to demonstrate the safety, purity and potency of the medicine candidate for the indication for use;
- a determination by the FDA within sixty days of its receipt of an NDA or BLA to file the application for review;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facilities to assess compliance with the FDA's current good manufacturing practices, or cGMPs, regulations for pharmaceuticals; and
- FDA review and approval of an NDA or BLA prior to any commercial marketing or sale of the medicine in the United States.

The development and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our medicine candidates will be granted on a timely basis, if at all.

The results of pre-clinical tests (which include laboratory evaluation as well as GLP studies to evaluate toxicity in animals) for a particular medicine candidate, together with related manufacturing information and analytical data, are submitted as part of an IND to the FDA. The IND automatically becomes effective thirty days after receipt by the FDA, unless the FDA, within the thirty-day time period, raises concerns or questions about the conduct of the proposed clinical trial, including concerns that human research subjects will be exposed to unreasonable health risks. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. IND submissions may not result in FDA authorization to commence a clinical trial. A separate submission to an existing IND must also be made for each successive clinical trial conducted during medicine development. Further, an independent institutional review board, or IRB, for each medical center proposing to conduct the clinical trial must review and approve the plan for any clinical trial before it commences at that center and it must monitor the study until completed. The FDA, the IRB or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk. Clinical testing also must satisfy extensive good clinical practice regulations and regulations for informed consent and privacy of individually identifiable information. Similar requirements to the U.S. IND are required in the European Economic Area, or the EEA, and other jurisdictions in which we may conduct clinical trials.

Clinical Trials. For purposes of NDA or BLA submission and approval, clinical trials are typically conducted in the following sequential phases, which may overlap:

- *Phase 1*. Studies are initially conducted in a limited population to test the medicine candidate for safety, dose tolerance, absorption, distribution, metabolism, and excretion, typically in healthy humans, but in some cases in patients.
- *Phase 2*. Studies are generally conducted in a limited patient population to identify possible adverse effects and safety risks, explore the initial efficacy of the medicine for specific targeted indications and to determine dose range or pharmacodynamics. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more expensive Phase 3 clinical trials.

- *Phase 3*. These are commonly referred to as pivotal studies. When Phase 2 evaluations demonstrate that a dose range of the medicine is effective and has an acceptable safety profile, Phase 3 clinical trials are undertaken in large patient populations to further evaluate dosage, provide substantial evidence of clinical efficacy and further test for safety in an expanded and diverse patient population at multiple, geographically dispersed clinical trial centers.
- *Phase 4*. The FDA may approve an NDA or BLA for a medicine candidate, but require that the sponsor conduct additional clinical trials to further assess the medicine after approval under a post-marketing commitment or post- marketing requirement. In addition, a sponsor may decide to conduct additional clinical trials after the FDA has approved a medicine. Post-approval trials are typically referred to as Phase 4 clinical trials.

The results of drug development, pre-clinical studies and clinical trials are submitted to the FDA as part of an NDA or BLA, as appropriate. Applications also must contain extensive chemistry, manufacturing and control information. Applications must be accompanied by a significant user fee. Once the submission has been accepted for filing, the FDA's goal is to review applications within twelve months of submission or, if the application relates to an unmet medical need in a serious or life-threatening indication, eight months from submission. The review process is often significantly extended by FDA requests for additional information or clarification. The FDA will typically conduct a pre-approval inspection of the manufacturer to ensure that the medicine can be reliably produced in compliance with cGMPs and will typically inspect certain clinical trial sites for compliance with good clinical practice, or GCP. The FDA may refer the application to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it typically follows such recommendations. The FDA may deny approval of an application by issuing a Complete Response Letter if the applicable regulatory criteria are not satisfied. A Complete Response Letter may require additional clinical data and/or trial(s), and/or other significant, expensive and time- consuming requirements related to clinical trials, pre-clinical studies or manufacturing. Data from clinical trials are not always conclusive and the FDA may interpret data differently than we or our collaborators interpret data. Approval may occur with boxed warnings on medicine labeling or Risk Evaluation and Mitigation Strategies, or REMS, which limit the labeling, distribution or promotion of a medicine. Once issued, the FDA may withdraw medicine approval if ongoing regulatory requirements are not met or if safety problems occur after the medicine reaches the market. In addition, the FDA may require testing, including Phase 4 clinical trials, and surveillance programs to monitor the safety effects of approved medicines which have been commercialized and the FDA has the power to prevent or limit further marketing of a medicine based on the results of these post-marketing programs or other information.

Clinical Trials in the EU. Clinical trials of medicinal products in the EU must be conducted in accordance with EU and national regulations and the international council for harmonization, or ICH, guidelines on GCP. Additional GCP guidelines from the EC, focusing in particular on traceability, apply to clinical trials of advanced therapy medicinal products. The sponsor must take out a clinical trial insurance policy, and in most EU countries, the sponsor is liable to provide "no fault" compensation to any study subject injured in the clinical trial.

Prior to commencing a clinical trial, the sponsor must obtain a clinical trial authorization from the competent authority, and a positive opinion from an independent ethics committee. The application for a clinical trial authorization must include, among other things, a copy of the trial protocol and an investigational medicinal product dossier containing information about the manufacture and quality of the medicinal product under investigation. Currently, clinical trial authorization applications must be submitted to the competent authority in each EU Member State in which the trial will be conducted. Under the new Regulation on Clinical Trials, which is expected to take effect in 2019, there will be a centralized application procedure where one national authority takes the lead in reviewing the application and the other national authorities have only a limited involvement. Any substantial changes to the trial protocol or other information submitted with the clinical trial applications must be notified to or approved by the relevant competent authorities and ethics committees. Medicines used in clinical trials must be manufactured in accordance with cGMP. Other national and EU-wide regulatory requirements also apply.

During the development of a medicinal product, the European Medicines Agency, or EMA, and national medicines regulators within the EU provide the opportunity for dialogue and guidance on the development program. At the EMA level, this is usually done in the form of scientific advice, which is given by the Scientific Advice Working Party of the Committee for Medicinal Products for Human Use. A fee is incurred with each scientific advice procedure. Advice from the EMA is typically provided based on questions concerning, for example, quality (chemistry, manufacturing and controls testing), nonclinical testing and clinical studies, and pharmacovigilance plans and risk-management programs.

Orphan Medicines. Under the Orphan Drug Act, the FDA may designate a medicine as an "orphan drug" if it is intended to treat a rare disease or condition, meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a medicine available in the United States for treatment of the disease or condition will be recovered from sales of the medicine. A company must request orphan drug designation before submitting an NDA for the drug and rare disease or condition. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan drug designation does not shorten the Prescription Drug User Fee Act, or PDUFA, goal dates for the regulatory review and approval process, although it does convey certain advantages such as tax benefits and exemption from the PDUFA application fee.

If a medicine with orphan designation receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the medicine generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor's marketing application for the same drug for the same indication for seven years, except in certain limited circumstances. Orphan exclusivity does not block the approval of a different drug for the same rare disease or condition, nor does it block the approval of the same drug for different indications. If a drug designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity. Orphan exclusivity will not bar approval of another medicine under certain circumstances, including if a subsequent medicine with the same drug for the same indication is shown to be clinically superior to the approved medicine on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand.

In the EU, Regulation (EC) No 141/2000 and Regulation (EC) No. 847/2000 provide that a medicine can be designated as an orphan medicinal product by the EC if its sponsor can establish: that the medicine is intended for the diagnosis, prevention or treatment of (1) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the EU when the application is made, or (2) a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that the marketing of the medicinal product in the EU would generate sufficient return to justify the necessary investment. For either of these conditions, the applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the EU or, if such method exists, the medicinal product will be of significant benefit to those affected by that condition. Once authorized, orphan medicinal products are entitled to ten years of market exclusivity in all EU Member States (extendable to twelve years for medicines that have complied with an agreed pediatric investigation plan pursuant to Regulation 1901/2006) and in addition a range of other benefits during the development and regulatory review process including scientific assistance for study protocols, authorization through the centralized marketing authorization procedure covering all member countries and a reduction or elimination of registration and marketing authorization fees. However, marketing authorization may be granted to a similar medicinal product with the same orphan indication during the regulatory exclusivity period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if this medicine is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if, at the end of the fifth year, it can be demonstrated on the basis of available evidence that the criteria for its designation as an orphan medicine are no longer satisfied, for example if the original orphan medicinal product has become sufficiently profitable not to justify maintenance of market exclusivity.

Other Regulatory Requirements. Medicines manufactured or distributed pursuant to FDA approvals are subject to continuing regulation by the FDA, including recordkeeping, annual medicine quality review, payment of program fees and reporting requirements. Adverse event experience with the medicine must be reported to the FDA in a timely fashion and pharmacovigilance programs to proactively look for these adverse events are mandated by the FDA. Our medicines may be subject to REMS requirements that affect labeling, distribution or post market reporting. Drug manufacturers and their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMPs, which impose certain procedural and documentation requirements upon us and our third-party manufacturers. Following such inspections, the FDA may issue notices on Form 483 and untitled letters or warning letters that could cause us or our third-party manufacturers to modify certain activities. A Form 483 notice, if issued at the conclusion of an FDA inspection, can list conditions the FDA investigators believe may have violated cGMP or other FDA regulations or guidelines. In addition to Form 483 notices and untitled letters, failure to comply with the statutory and regulatory requirements can subject a manufacturer to possible legal or regulatory action, such as suspension of manufacturing, seizure of medicine, injunctive action, additional reporting requirements and/or oversight by the agency, import alert or possible civil penalties. The FDA may also require us to recall a drug from distribution or withdraw approval for that medicine.

The FDA closely regulates the post-approval marketing and promotion of pharmaceuticals, including standards and regulations for direct-to-consumer advertising, dissemination of off-label information, industry-sponsored scientific and educational activities and promotional activities involving the Internet, including certain social media activities. Medicines may be marketed only for the approved indications and in accordance with the provisions of the approved label. Further, if there are any modifications to the medicine, including changes in indications, labeling, or manufacturing processes or facilities, we may be required to submit and obtain FDA approval of a new or supplemental application, which may require us to develop additional data or conduct additional pre-clinical studies and clinical trials. Failure to comply with these requirements can result in adverse publicity, untitled letters, corrective advertising and potential administrative, civil and criminal penalties, as well as damages, fines, withdrawal of regulatory approval, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs, additional reporting requirements and/or oversight by the agency, and imprisonment, any of which could adversely affect our ability to sell our medicines or operate our business and also adversely affect our financial results.

Physicians may, in their independent medical judgment, prescribe legally available pharmaceuticals for uses that are not described in the medicine's labeling and that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, impose stringent restrictions on manufacturers' communications regarding off-label use. Additionally, a significant number of pharmaceutical companies have been the target of inquiries and investigations by various U.S. federal and state regulatory, investigative, prosecutorial and administrative entities in connection with the promotion of medicines for off-label uses and other sales practices. These investigations have alleged violations of various U.S. federal and state laws and regulations, including claims asserting antitrust violations, violations of the Food, Drug and Cosmetic Act, false claims laws, the Prescription Drug Marketing Act, or PDMA, anti-kickback laws, and other alleged violations in connection with the promotion of medicines for unapproved uses, pricing and Medicare and/or Medicaid reimbursement. If our promotional activities, including any promotional activities that a contracted sales force may perform on our behalf, fail to comply with these regulations or guidelines, we may be subject to warnings from, or enforcement action by, these authorities. In addition, our failure to follow FDA rules and guidelines relating to promotion and advertising may cause the FDA to issue warning letters or untitled letters, suspend or withdraw an approved medicine from the market, require corrective advertising or a recall or institute fines or civil fines, additional reporting requirements and/or oversight or could result in disgorgement of money, operating restrictions, injunctions or criminal prosecution, any of which could harm our business. In addition, the distribution of prescription medicines is subject to the PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription medicine samples and impose requirements to ensure accountability in distribution, including a drug pedigree which tracks the distribution of prescription drugs. Further, under the Drug Quality and Security Act, drug manufacturers are subject to a number of requirements, including, medicine identification, tracing and verification, among others, that are designed to detect and remove counterfeit, stolen, contaminated or otherwise potentially harmful drugs from the U.S. drug supply chain. These requirements will be phased in over several years and compliance will likely increase the costs of the manufacture and distribution of drug medicines.

Outside the United States, the ability of our partners and us to market a medicine is contingent upon obtaining marketing authorization from the appropriate regulatory authorities. The requirements governing marketing authorization, pricing and reimbursement vary widely from country to country and region to region.

The EU and the EEA consist, at the time of writing, of the twenty-eight Member States of the EU (for details on the impact the United Kingdom leaving the EU will have, see the section entitled 'The Impact of Brexit' below), plus Norway, Iceland and Liechtenstein which are Member States of the EEA. These Member States have all acceded to the single market rules governing the supervision of medicinal products. Under the prevailing rules, medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. There are three procedures for an MA to be obtained:

- the Centralized MA, which is issued by the EC through the Centralized Procedure, based on the scientific opinion of the Committee for Medicinal Products for Human Use of the EMA, and which is valid throughout the entire territory of the EU/EEA. When decisions on granting of a Centralized MA are taken by the EU, the EEA Member States will take corresponding decisions on the basis the relevant acts to permit marketing of medicinal products. The Centralized Procedure is mandatory for certain types of products, such as (i) biotechnology medicinal products such as genetic engineering, (ii) orphan medicinal products, (iii) medicinal products containing a new active substance indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune and viral diseases and (iv) advanced-therapy medicines, such as gene therapy, somatic cell therapy or tissue-engineered medicines. The Centralized Procedure is optional for products containing a new active substance not yet authorized in the EU/EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU.
- Decentralized Procedure MAs are available for products not falling within the mandatory scope of the Centralized Procedure. An identical dossier is submitted to the competent authorities of each of the Member States in which the MA is sought, one of which is selected by the applicant as the Reference Member State, or RMS, to lead the evaluation of the regulatory submission. The competent authority of the RMS prepares a draft assessment report, a draft summary of the product characteristics, or SmPC, and a draft of the labeling and package leaflet as distilled from the preliminary evaluation, which are sent to the other Member States (referred to as the Concerned Member States, or CMS) for their approval. If the CMS raise no objections, based on a potential serious risk to public health, to the assessment, SmPC, labeling, or packaging proposed by the RMS, the RMS records the agreement, closes the procedure and informs the applicant accordingly. Each Member State concerned by the procedure is required to adopt a national decision to grant a national MA in conformity with the approved assessment report, SmPC and the labeling and package leaflet as approved. Where a product has already been authorized for marketing in a Member State of the EEA, the granted national MA can be used for mutual recognition in other Member States through the Mutual Recognition Procedure, or MRP, resulting in progressive national approval of the product in the EU/EEA.
- National MAs, which are issued by a single competent authority of the Member States of the EEA and only covers their respective territory, are also available for products not falling within the mandatory scope of the Centralized Procedure. Once a product has been authorized for marketing in a Member State of the EEA through the National Procedure, this National MA can also be recognized in other Member States through the MRP.

Under the procedures described above, before granting the MA, the EMA or the competent authority(ies) of the Member State(s) of the EEA prepare an assessment of the risk-benefit balance of the product against the scientific criteria concerning its quality, safety and efficacy.

Under Regulation (EC) No 726/2004/EC and Directive 2001/83/EC (each as amended), the EU has adopted a harmonized approach to data and market protection or exclusivity (known as the 8 + 2 + 1 formula). The data exclusivity period begins to run on the date when the first MA is granted in the EU. It confers on the MA holder of the reference medicinal product eight years of data protection and ten years of market protection. A reference medicinal product is defined to mean a medicinal product authorized based on a full dossier consisting of pharmaceutical and pre-clinical testing results and clinical trial data, such as a medicinal product containing a new active substance. The ten-year market protection can be extended cumulatively to a maximum period of eleven years if during the first eight years of those ten years of protection period, the MA holder obtains an authorization for one or more new therapeutic indications that are deemed to bring a significant clinical benefit compared to existing therapies.

The protection period means that an applicant for a generic medicinal product is not permitted to rely on pre-clinical pharmacological, toxicological, and clinical data contained in the file of the reference medicinal product of the originator until the first eight years of data protection have expired. Thereafter, a generic product application may be submitted and generic companies may rely on the pre-clinical and clinical data relating to the reference medicinal product to support approval of the generic product. However, a generic cannot market until ten years have elapsed from the initial authorization of the reference medicinal product or eleven years if the protection period is extended, based on the formula of 8+2+1.

In addition to the above, where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication. Finally, where a change of classification of a medicinal product has been authorized on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorization for a change of classification of the same substance for one year after the initial change was authorized.

The 8 + 2 + 1 exclusivity scheme applies to products that have been authorized in the EU by either the EMA through the Centralized Procedure or the competent authorities of the Member States of the EEA nationally, including through the Decentralized and Mutual Recognition procedures.

For a medicinal product which has received orphan designation under Regulation 141/2000, it will, as set out in further detail in the section entitled 'Orphan Medicines' above, benefit from a period of ten years of orphan market exclusivity which essentially constitutes a period of market monopoly. During this period of orphan market exclusivity, no EU regulatory authority is permitted to accept or approve an application for marketing authorization for a similar medicinal product or an extension application for the same therapeutic indication. This period can be extended cumulatively to a total of twelve years if the marketing authorization holder or applicant complies with the requirements for an agreed pediatric investigation plan pursuant to Regulation 1901/2006.

The holder of a Centralized MA or National MA is subject to various obligations under the applicable EU laws, such as pharmacovigilance obligations, requiring it to, among other things, report and maintain detailed records of adverse reactions, and to submit periodic safety update reports, or PSURs, to the competent authorities. All new marketing authorization applications must include a risk management plan, or RMP, describing the risk management system that the company will put in place and documenting measures to prevent or minimize the risks associated with the product. The regulatory authorities may also impose specific obligations as a condition of the marketing authorization. Such risk-minimization measures or post-authorization obligations may include additional safety monitoring, more frequent submission of PSURs, or the conduct of additional clinical trials or post-authorization safety studies. RMPs and PSURs are routinely available to third parties requesting access, subject to limited redactions. All advertising and promotional activities for the product must be consistent with the approved summary of product characteristics, and therefore all off-label promotion is prohibited. Direct-to-consumer advertising of prescription medicines is also prohibited in the EU. The holder must also ensure that the manufacturing and batch release of its product is in compliance with the applicable requirements. The MA holder is further obligated to ensure that the advertising and promotion of its products complies with applicable EU laws and industry code of practice as implemented in the domestic laws of the Member States of the EU/EEA. The advertising and promotional rules are enforced nationally by the EU/EEA Member States.

The Impact of Brexit. On June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the EU (commonly referred to as ''Brexit''). Thereafter, on March 29, 2017, the country formally notified the EU of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. The withdrawal of the United Kingdom from the EU is expected to take effect on March 29, 2019. Since the regulatory framework for pharmaceutical products in the United Kingdom covering quality, safety and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from EU directives and regulations, immediately following Brexit, it is expected that the United Kingdom's regulatory regime will remain aligned to EU regulations. It remains to be seen how Brexit will impact regulatory requirements for product candidates and products in the United Kingdom. In the longer term, Brexit could materially impact the future regulatory regime which applies to products and the approval of product candidates in the United Kingdom. In the short term, there is a risk of disrupted import and export processes due to a lack of administrative processing capacity by the respective United Kingdom and EU/Irish customs agencies that may delay time-sensitive shipments and may negatively impact our product supply chain.

Healthcare Fraud and Abuse Laws. As a pharmaceutical company, certain federal and state healthcare laws and regulations pertaining to fraud and abuse and patients' rights are and will be applicable to our business. We may be subject to various federal and state laws targeting fraud and abuse in the healthcare industry. For example, in the United States, there are federal and state anti-kickback laws that prohibit the payment or receipt of kickbacks, bribes or other remuneration intended to induce the purchase or recommendation of healthcare products and services or reward past purchases or recommendations. Violations of these laws can lead to civil and criminal penalties, including fines, imprisonment, additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement, and exclusion from participation in federal healthcare programs. These laws are applicable to manufacturers of products regulated by the FDA, such as us, and pharmacies, hospitals, physicians and other potential purchasers of such products.

The federal Anti-Kickback Statute prohibits persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, to induce either the referral of an individual, or the furnishing, recommending, or arranging for a good or service, for which payment may be made under a federal healthcare program, such as the Medicare and Medicaid programs. The term "remuneration" is defined as any remuneration, direct or indirect, overt or covert, in cash or in kind, and has been broadly interpreted to include anything of value, including for example, gifts, discounts, the furnishing of supplies or equipment, credit arrangements, payments of cash, waivers of payment, ownership interests and providing anything at less than its fair market value. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute may have been violated, and enforcement will depend on the relevant facts and circumstances. The Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the ACA, among other things, amended the intent requirement of the federal Anti-Kickback Statute to state that a person or entity need not have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the ACA provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act (discussed below) or the civil monetary penalties statute, which imposes penalties against any person who is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent, or to have offered improper inducements to federal health care program beneficiaries to select a particular provider or supplier. The federal Anti-Kickback Statute is broad, and despite a series of narrow safe harbors, prohibits many arrangements and practices that are lawful in businesses outside of the healthcare industry. Many states have also adopted laws similar to the federal Anti-Kickback Statute, some of which apply to the referral of patients for healthcare items or services reimbursed by any source, not only the Medicare and Medicaid programs, and do not contain identical safe harbors. In addition, where such activities involve foreign government officials, they may also potentially be subject to the Foreign Corrupt Practices Act. Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities, including our activities with physician customers, pharmacies, and patients, as well as our activities pursuant to partnerships with other companies and pursuant to contracts with contract research organizations, could be subject to challenge under one or more of such laws.

The federal False Claims Act prohibits any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. A claim includes "any request or demand" for money or property presented to the U.S. government. In addition, the ACA specified that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act. The federal False Claims Act has been the basis for numerous enforcement actions and settlements by pharmaceutical and other healthcare companies in connection with various alleged financial relationships with customers. In addition, a number of pharmaceutical manufacturers have reached substantial financial settlements in connection with allegedly causing false claims to be submitted because of the companies' marketing of products for unapproved, and thus non-reimbursable, uses. Certain marketing practices, including off-label promotion, may also violate false claims laws, as might violations of the federal physician self-referral laws, such as the Stark laws, which prohibit a physician from making a referral to certain designated health services with which the physician or the physician's family member has a financial interest and prohibit submission of a claim for reimbursement pursuant to the prohibited referral. The "qui tam" provisions of the False Claims Act allow a private individual to bring civil actions on behalf of the federal government alleging that the defendant has submitted a false claim to the federal government, and to share in any monetary recovery. In addition, various states have enacted similar fraud and abuse statutes or regulations, including, without limitation, false claims laws analogous to the False Claims Act, and laws analogous to the federal Anti-Kickback Statute, that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payer, and there are also federal criminal false claims laws.

Separately, there are a number of other fraud and abuse laws that pharmaceutical manufacturers must be mindful of, particularly after a medicine candidate has been approved for marketing in the United States. For example, a federal criminal law enacted as part of, the Health Insurance Portability and Accountability Act of 1996, or HIPAA, prohibits knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payers. The false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. There are also federal civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payers that are false or fraudulent, as well as federal and state consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

Healthcare Privacy and Security Laws. We may be subject to, or our marketing activities may be limited by, HIPAA, as amended by the Health Information Technology and Clinical Health Act (HITECH) and their respective implementing regulations, which established uniform standards for certain "covered entities" (healthcare providers, health plans and healthcare clearinghouses) governing the conduct of certain electronic healthcare transactions and protecting the security and privacy of protected health information. Among other things, HIPAA's privacy and security standards are directly applicable to "business associates" — independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. In addition to possible civil and criminal penalties for violations, state attorneys general are authorized to file civil actions for damages or injunctions in federal courts to enforce HIPAA and seek attorney's fees and costs associated with pursuing federal civil actions. Accordingly, state attorneys general (along with private plaintiffs) have brought civil actions seeking injunctions and damages resulting from alleged violations of HIPAA's privacy and security rules. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

In the EU/EEA, the General Data Protection Regulation (2016/679), or GDPR, went into effect on May 25, 2018 and replaced Directive 95/46/EC (the EU Privacy Directive). The GDPR applies to identified or identifiable personal data processed by automated means (for example, a computer database of customers) and data contained in, or intended to be part of, non-automated filing systems (traditional paper files) as well as transfer of such data to a country outside of the EU/EEA. Under the GDPR, fines of up to €20.0 million or up to 4% of the annual global turnover of the infringer, whichever is greater, could be imposed for significant non-compliance. The GDPR includes more stringent operational requirements for processors and controllers of personal data and creates additional rights for data subjects. Additionally, in June 2016, United Kingdom voters approved an exit from the EU, commonly referred to as "Brexit," which could also lead to further legislative and regulatory changes. In March 2017, the United Kingdom began the process to leave the EU by April 2019. While the Data Protection Act of 2018, that "implements" and complements the GDPR has achieved Royal Assent on May 23, 2018 and is now effective in the United Kingdom, it is still unclear whether transfer of data from the EEA to the United Kingdom will remain lawful under GDPR. We may incur liabilities, expenses, costs, and other operational losses under GDPR and applicable EU Member States and the United Kingdom privacy laws in connection with any measures we take to comply with them.

Additionally, California recently enacted legislation that has been dubbed the first "GDPR-like" law in the United States. Known as the California Consumer Privacy Act, or CCPA, it creates new individual privacy rights for consumers (as that word is broadly defined in the law) and places increased privacy and security obligations on entities handling personal data of consumers or households. When it goes into effect on January 1, 2020, the CCPA will require covered companies to provide new disclosures to California consumers, provide such consumers new ways to opt-out of certain sales of personal information, and allow for a new cause of action for data breaches. Legislators have stated that amendments will be proposed to the CCPA before it goes into effect, but it remains unclear what, if any, modifications will be made to this legislation or how it will be interpreted. As currently written, the CCPA will likely impact our business activities and exemplifies the vulnerability of our business to not only cyber threats but also the evolving regulatory environment related to personal data and protected health information.

"Sunshine" and Marketing Disclosure Laws. There are an increasing number of federal and state "sunshine" laws that require pharmaceutical manufacturers to make reports to states on pricing and marketing information. Several states have enacted legislation requiring pharmaceutical companies to, among other things, establish marketing compliance programs, file periodic reports with the state, and make periodic public disclosures on sales and marketing activities, and prohibiting certain other sales and marketing practices. In addition, a similar federal requirement requires manufacturers, including pharmaceutical manufacturers, to track and report to the federal government certain payments and other transfers of value made to physicians and other healthcare professionals and teaching hospitals and ownership or investment interests held by physicians and their immediate family members. The federal government began disclosing the reported information on a publicly available website in 2014. Certain states, such as Massachusetts, also make the reported information publicly available. In addition, there are state and local laws that require pharmaceutical representatives to be licensed and comply with codes of conduct, transparency reporting, and other obligations. These laws may adversely affect our sales, marketing, and other activities with respect to our medicines in the United States by imposing administrative and compliance burdens on us. If we fail to track and report as required by these laws or otherwise comply with these laws, we could be subject to the penalty provisions of the pertinent state and federal authorities. In the EU/EEA, declaration of transfers of value to healthcare professionals is subject to the requirements under the voluntary industry code of practice. France however has a statutory regime similar to the U.S. Sunshine Act.

Government Price Reporting. For those marketed medicines which are covered in the United States by the Medicaid programs, we have various obligations, including government price reporting and rebate requirements, which generally require medicines be offered at substantial rebates/discounts to Medicaid and certain purchasers (including "covered entities" purchasing under the 340B Drug Discount Program). We are also required to discount such medicines to authorized users of the Federal Supply Schedule of the General Services Administration, under which additional laws and requirements apply. These programs require submission of pricing data and calculation of discounts and rebates pursuant to complex statutory formulas, as well as the entry into government procurement contracts governed by the Federal Acquisition Regulations, and the guidance governing such calculations is not always clear. Compliance with such requirements can require significant investment in personnel, systems and resources, but failure to properly calculate our prices, or offer required discounts or rebates could subject us to substantial penalties. One component of the rebate and discount calculations under the Medicaid and 340B programs, respectively, is the "additional rebate", a complex calculation which is based, in part, on the extent that a branded drug's price increases over time more than the rate of inflation (based on the Consumer Price Index for All Urban Consumers). This comparison is based on the baseline pricing data for the first full quarter of sales associated with a branded drug's NDA, and baseline data cannot generally be reset, even on transfer of the NDA to another manufacturer. This "additional rebate" calculation can, in some cases where price increase have been relatively high versus the first quarter of sales of the NDA, result in Medicaid rebates up to 100 percent of a drug's "average manufacturer price" and 340B prices of one penny. Governments influence the price of medicinal products in the EU through their pricing and reimbursement rules and control of national healthcare systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular product candidate to currently available therapies. Other EU Member States allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on healthcare costs in general, particularly prescription medicines, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products.

In General. Because of the breadth of these laws and the narrowness of available statutory and regulatory exemptions, it is possible that some of our business activities in the United States could be subject to challenge under one or more of such laws. Moreover, state governmental agencies may propose or enact laws and regulations that extend or contradict federal requirements. If we or our operations are found to be in violation of any of the state or federal laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including significant civil and criminal penalties, damages, fines, imprisonment, exclusion from participation in U.S. federal or state healthcare programs, additional reporting requirements and/or oversight and the curtailment or restructuring of our operations. To the extent that any medicine we make is sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals. Any penalties, damages, fines, curtailment or restructuring of our operations could materially adversely affect our ability to operate our business and our financial results. Although compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. Moreover, achieving and sustaining compliance with applicable federal, state and foreign privacy, security, sunshine, government price reporting, and fraud laws may prove costly.

Impact of Healthcare Reform and Recent Public Scrutiny of Specialty Drug Pricing on Coverage, Reimbursement, and Pricing. In the United States and other potentially significant markets for our medicines, federal and state authorities as well as third-party payers are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative medicines and therapies, which has resulted in lower average net selling prices. Further, there is increased scrutiny of prescription drug pricing practices by federal and state lawmakers and enforcement authorities. In addition, there is an emphasis on managed healthcare in the United States and on country-specific and regional pricing and reimbursement controls in the EU, both of which will put additional pressure on medicine pricing, reimbursement and usage, which may adversely affect our future medicine sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical reimbursement policies and pricing in general.

The U.S. and some foreign jurisdictions are considering or have enacted a number of additional legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our medicines profitably. Among policy makers and payers in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs (including a number of proposals pertaining to prescription drugs, specifically), improving quality and/or expanding access. At the federal level, the Trump administration's budget proposal for fiscal year 2019 contains further drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid and to eliminate cost sharing for generic drugs for low-income patients. For example, in November 2018, CMS issued a proposed regulation that would require Part D plans to include drug pricing information and lower cost therapeutic alternatives as well as allow "step therapy" in Medicare Advantage for Part B drugs. While these proposed measures will require additional rulemaking and action by Congress to pass legislation to become effective, these provisions reinforce the administration's focus on controlling drug prices. At the state level, in Massachusetts, the MassHealth program has requested permission from the federal government to use commercial tools, such as a closed formulary, to negotiate more favorable rebate agreements from drug manufacturers. There also has been particular and increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices in recent years, particularly with respect to drugs that have been subject to relatively large price increases over relatively short time periods. There have been several recent state and federal lawmaker inquiries and proposed legislation as was the case in California designed to, among other things, bring more transparency to drug pricing, by requiring drug companies to notify insurers and government regulators of price increases and provide an explanation of the reasons for the increase. There have also been actions to review the relationship between pricing and manufacturer patient access programs, and reform government program reimbursement methodologies for drugs. In the United States, the pharmaceutical industry has already been significantly affected by major legislative initiatives, including, for example, the ACA. The ACA, among other things, imposes a significant annual fee on companies that manufacture or import branded prescription drug medicines. It also contains substantial provisions intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, and impose additional health policy reforms, any or all of which may affect our business. Since its enactment, there have been judicial and Congressional challenges to numerous provisions of the ACA. In January 2017, the United States House of Representatives and Senate passed legislation, the concurrent budget resolution for fiscal year 2017, which initiates actions that would repeal certain aspects of the ACA. Further, on January 20, 2017, U.S. President Donald Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA, to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. In May 2017, following the passage of the budget resolution for fiscal year 2017, the U.S. House of Representatives passed legislation known as the American Health Care Act, which, if enacted, would have amended and repealed significant portions of the ACA. The U.S. Senate considered but did not adopt other legislation to amend and/or replace elements of the ACA and authority to act under the fiscal year 2017 budget resolution expired on September 30, 2017. However, on October 12, 2017, U.S. President Donald Trump signed another Executive Order directing certain federal agencies to propose regulations or guidelines to permit small businesses to form association health plans, expand the availability of short-term, limited duration insurance, and expand the use of health reimbursement arrangements, which may circumvent some of the requirements for health insurance mandated by the ACA. In addition, citing legal guidance from the U.S. Department of Justice and the U.S. Department of Health and Human Services, the Trump administration has concluded that cost-sharing reduction, or CSR, payments to insurance companies required under the ACA have not received necessary appropriations from Congress and announced that it will discontinue these payments immediately until such appropriations are made. The loss of the CSR payments is expected to increase premiums on certain policies issued by qualified health plans under the ACA. Finally, while Congress has not passed comprehensive ACA repeal or replace legislation, the federal income tax legislation signed into law on December 22, 2017 includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate". We continue to evaluate the effect that the ACA and additional actions by Congress to possibly repeal and replace it has on our business.

Other legislative changes have also been proposed and adopted since the ACA was enacted. For example, the Budget Control Act of 2011 resulted in aggregate reductions in Medicare payments to providers of up to two percent per fiscal year, starting in 2013, and the American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Such laws, and others that may affect our business that have been recently enacted or may in the future be enacted, may result in additional reductions in Medicare and other healthcare funding. In the future, there will likely continue to be additional proposals relating to the reform of the U.S. healthcare system, some of which could further limit coverage and reimbursement of medicines, including our medicine candidates. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payers. Further, the Bipartisan Budget Act of 2018, or the BBA, among other things, amends the ACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans (also known as the Medicare "Donut Hole"), and also increases in 2019 the percentage that a drug manufacturer must discount the cost of prescription drugs from 50 percent under current law to 70 percent. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our medicines.

Irish Law Matters

As we are an Irish-incorporated company, the following matters of Irish law are relevant to the holders of our ordinary shares.

Irish Restrictions on Import and Export of Capital. Except as indicated below, there are no restrictions imposed specifically on non-residents of Ireland dealing in Irish domestic securities, which includes ordinary shares of Irish companies. Dividends and redemption proceeds also continue to be freely transferable to non-resident holders of such securities. The Financial Transfers Act 1992 gives power to the Minister for Finance of Ireland to restrict financial transfers between Ireland and other countries and persons. Financial transfers are broadly defined and include all transfers that would be movements of capital or payments within the meaning of the treaties governing the member states of the EU. The acquisition or disposal of interests in shares issued by an Irish incorporated company and associated payments falls within this definition. In addition, dividends or payments on redemption or purchase of shares and payments on a liquidation of an Irish incorporated company would fall within this definition. The Criminal Justice (Terrorist Offences) Act 2005 (as amended) also gives the Minister of Finance of Ireland the power to take various measures, including the freezing or seizure of assets, in order to combat terrorism. At present the Financial Transfers Act 1992, certain EU regulations (as implemented into Irish law) and the Criminal Justice (Terrorist Offences) Act 2005 (as amended) prohibit financial transfers involving certain persons and entities associated with the ISIL (Da'esh) and Al-Qaida organizations, the late Slobodan Milosevic and associated persons, Republic of Guinea-Bissau, Myanmar/Burma, Belarus, certain persons indicted by the International Criminal Tribunal for the former Yugoslavia, the late Osama bin Laden, Al-Qaida, the Taliban of Afghanistan, Democratic Republic of Congo, Democratic People's Republic of Korea (North Korea), Iran, Iraq, Côte d'Ivoire, Lebanon, Liberia, Zimbabwe, South Sudan, Sudan, Somalia, Republic of Guinea, Afghanistan, Egypt, Eritrea, Libya, Syria, Tunisia, Burundi, the Central African Republic, Ukraine, Yemen, Bosnia and Herzegovina, certain known terrorists and terrorist groups, and countries that harbor certain terrorist groups, without the prior permission of the Central Bank of Ireland or the Minister of Finance (as applicable).

Any transfer of, or payment in respect of, a share or interest in a share involving the government of any country that is currently the subject of United Nations or EU sanctions, any person or body controlled by any of the foregoing, or by any person acting on behalf of the foregoing, may be subject to restrictions pursuant to such sanctions as implemented into Irish law.

Irish Taxes Applicable to U.S. Holders

Withholding Tax on Dividends. While we have no current plans to pay dividends, dividends on our ordinary shares would generally be subject to Irish Dividend Withholding Tax, or DWT, at the standard rate of income tax (currently twenty percent), unless an exemption applies.

Dividends on our ordinary shares that are owned by residents of the United States and held beneficially through the Depositary Trust Company, or DTC, will not be subject to DWT provided that the address of the beneficial owner of the ordinary shares in the records of the broker is in the United States.

Dividends on our ordinary shares that are owned by residents of the United States and held directly (outside of DTC) will not be subject to DWT provided that the shareholder has completed the appropriate Irish DWT form and this form remains valid. Such shareholders must provide the appropriate Irish DWT form to our transfer agent at least seven business days before the record date for the first dividend payment to which they are entitled.

If any shareholder who is resident in the United States receives a dividend subject to DWT, he or she should generally be able to make an application for a refund from the Irish Revenue Commissioners on the prescribed form (DWT Claim Form 1).

While the U.S./Ireland Double Tax Treaty contains provisions regarding withholding tax, due to the wide scope of the exemptions from DWT available under Irish domestic law, it would generally be unnecessary for a U.S. resident shareholder to rely on the treaty provisions.

Income Tax on Dividends. A shareholder who is neither resident nor ordinarily resident in Ireland and who is entitled to an exemption from DWT generally has no additional liability to Irish income tax or to the universal social charge on a dividend from us unless that shareholder holds our ordinary shares through a branch or agency in Ireland through which a trade is carried on.

A shareholder who is neither resident nor ordinarily resident in Ireland and who is not entitled to an exemption from DWT generally has no additional liability to Irish income tax or to the universal social charge on a dividend from us. The DWT deducted by us discharges the liability to Irish income tax and to the universal social charge. This however is not the case where the shareholder holds the ordinary shares through a branch or agency in Ireland through which a trade is carried on.

Irish Tax on Capital Gains. A shareholder who is neither resident nor ordinarily resident in Ireland and does not hold our ordinary shares in connection with a trade or business carried on by such shareholder in Ireland through a branch or agency should not be within the charge to Irish tax on capital gains on a disposal of our ordinary shares.

Capital Acquisitions Tax. Irish capital acquisitions tax, or CAT, is composed principally of gift tax and inheritance tax. CAT could apply to a gift or inheritance of our ordinary shares irrespective of the place of residence, ordinary residence or domicile of the parties. This is because our ordinary shares are regarded as property situated in Ireland as our share register must be held in Ireland. The person who receives the gift or inheritance has primary liability for CAT.

CAT is levied at a rate of 33 percent above certain tax-free thresholds. The appropriate tax-free threshold is dependent upon (i) the relationship between the donor and the donee and (ii) the aggregation of the values of previous gifts and inheritances received by the donee from persons within the same category of relationship for CAT purposes. Gifts and inheritances passing between spouses are exempt from CAT. Our shareholders should consult their own tax advisers as to whether CAT is creditable or deductible in computing any domestic tax liabilities.

Stamp Duty. Irish stamp duty (if any) may become payable in respect of ordinary share transfers. However, a transfer of our ordinary shares from a seller who holds shares through DTC to a buyer who holds the acquired shares through DTC will not be subject to Irish stamp duty. A transfer of our ordinary shares (i) by a seller who holds ordinary shares outside of DTC to any buyer, or (ii) by a seller who holds the ordinary shares through DTC to a buyer who holds the acquired ordinary shares outside of DTC, may be subject to Irish stamp duty (currently at the rate of one percent of the price paid or the market value of the ordinary shares acquired, if greater). The person accountable for payment of stamp duty is the buyer or, in the case of a transfer by way of a gift or for less than market value, all parties to the transfer.

A shareholder who holds ordinary shares outside of DTC may transfer those ordinary shares into DTC without giving rise to Irish stamp duty provided that the shareholder would be the beneficial owner of the related book-entry interest in those ordinary shares recorded in the systems of DTC (and in exactly the same proportions) as a result of the transfer and at the time of the transfer into DTC there is no sale of those book-entry interests to a third party being contemplated by the shareholder. Similarly, a shareholder who holds ordinary shares through DTC may transfer those ordinary shares out of DTC without giving rise to Irish stamp duty provided that the shareholder would be the beneficial owner of the ordinary shares (and in exactly the same proportions) as a result of the transfer, and at the time of the transfer out of DTC there is no sale of those ordinary shares to a third party being contemplated by the shareholder. In order for the share registrar to be satisfied as to the application of this Irish stamp duty treatment where relevant, the shareholder must confirm to us that the shareholder would be the beneficial owner of the related book-entry interest in those ordinary shares recorded in the systems of DTC (and in exactly the same proportions) (or vice-versa) as a result of the transfer and there is no agreement for the sale of the related book-entry interest or the ordinary shares or an interest in the ordinary shares, as the case may be, by the shareholder to a third party being contemplated.

Employees

As of December 31, 2018, we had approximately 1,000 full-time employees. Of our employees as of December 31, 2018, approximately 180 were engaged in development, regulatory and manufacturing activities, approximately 580 were engaged in sales and marketing and approximately 240 were engaged in administration, including business development, finance, legal, information systems, facilities and human resources. None of our employees is subject to a collective bargaining agreement. We consider our employee relations to be satisfactory.

Available Information

We make available free of charge on or through our internet website our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and all amendments to those reports as soon as reasonably practicable after such material is electronically filed with or furnished to the Securities and Exchange Commission. We also regularly post copies of our press releases as well as copies of presentations and other updates about our business on our website. Our website address is www.horizonpharma.com. The information contained in or that can be accessed through our website is not part of this Annual Report on Form 10-K. Information is also available through the Securities and Exchange Commission's website at www.sec.gov.

Item 1A. Risk Factors

Certain factors may have a material adverse effect on our business, financial condition and results of operations, and you should carefully consider them. Accordingly, in evaluating our business, we encourage you to consider the following discussion of risk factors in its entirety, in addition to other information contained in this report as well as our other public filings with the Securities and Exchange Commission, or SEC.

Risks Related to Our Business and Industry

Our ability to generate revenues from our medicines is subject to attaining significant market acceptance among physicians, patients and healthcare payers.

Our current medicines, and other medicines or medicine candidates that we may develop or acquire, may not attain market acceptance among physicians, patients, healthcare payers or the medical community. We have a limited history of commercializing medicines and most of our medicines have not been on the market for an extensive period of time, which subjects us to numerous risks as we attempt to increase our market share. We believe that the degree of market acceptance and our ability to generate revenues from our medicines will depend on a number of factors, including:

- timing of market introduction of our medicines as well as competitive medicines;
- efficacy and safety of our medicines;
- continued projected growth of the markets in which our medicines compete;
- prevalence and severity of any side effects;

- if and when we are able to obtain regulatory approvals for additional indications for our medicines;
- acceptance by patients, primary care physicians and key specialists;
- availability of coverage and adequate reimbursement and pricing from government and other third-party payers;
- potential or perceived advantages or disadvantages of our medicines over alternative treatments, including cost of treatment and relative convenience and ease of administration;
- strength of sales, marketing and distribution support;
- the price of our medicines, both in absolute terms and relative to alternative treatments;
- impact of past and limitation of future medicine price increases;
- our ability to maintain a continuous supply of medicine for commercial sale;
- the effect of current and future healthcare laws;
- the performance of third-party distribution partners, over which we have limited control; and
- medicine labeling or medicine insert requirements of the U.S. Food and Drug Administration, or FDA, or other regulatory authorities.

With respect to RAVICTI, which is approved to treat a very limited patient population, our ability to grow sales will depend in large part on our ability to transition urea cycle disorder, or UCD, patients from BUPHENYL or generic equivalents, which are comparatively much less expensive, to RAVICTI and to encourage patients and physicians to continue RAVICTI therapy once initiated. With respect to PROCYSBI, which is also approved to treat a very limited patient population, our ability to grow sales will depend in large part on our ability to transition patients from the first-generation immediate-release cysteamine therapy to PROCYSBI, to identify additional patients with nephropathic cystinosis and to encourage patients and physicians to continue therapy once initiated. With respect to ACTIMMUNE, while it is the only FDA-approved treatment for chronic granulomatous disease, or CGD, and severe, malignant osteopetrosis, or SMO, they are very rare conditions and, as a result, our ability to grow ACTIMMUNE sales will depend on our ability to access a wider patient population and encourage patients and physicians to continue treatment once initiated. Unless QUINSAIR is approved for marketing in additional countries, our ability to drive growth of this medicine will largely depend on expanding its use in Canada. With respect to KRYSTEXXA, our ability to grow sales will be affected by the success of our sales, marketing and clinical strategies, which could expand the patient population and usage of KRYSTEXXA. This includes our marketing efforts in nephrology and our studies designed to improve the response rate to KRYSTEXXA and to evaluate the use of KRYSTEXXA in kidney transplant patients. With respect to each of BUPHENYL, RAYOS, PENNSAID 2% w/w, or PENNSAID 2%, DUEXIS and VIMOVO, their higher cost compared to the generic or branded forms of their active ingredients alone may limit adoption by physicians, patients and healthcare payers. With respect to DUEXIS and VIMOVO, studies indicate that physicians do not commonly co-prescribe gastrointestinal, or GI, protective agents to high-risk patients taking nonsteroidal anti-inflammatory drugs, or NSAIDs. We believe this is due in part to a lack of awareness among physicians prescribing NSAIDs regarding the risk of NSAID-induced upper GI ulcers, in addition to the inconvenience of prescribing two separate medications and patient compliance issues associated with multiple prescriptions. If physicians remain unaware of, or do not otherwise believe in, the benefits of combining GI protective agents with NSAIDs, our market opportunity for DUEXIS and VIMOVO will be limited. Some physicians may also be reluctant to prescribe DUEXIS or VIMOVO due to the inability to vary the dose of ibuprofen and naproxen, respectively, or if they believe treatment with NSAIDs or GI protective agents other than those contained in DUEXIS and VIMOVO, including those of its competitors, would be more effective for their patients. If our current medicines or any other medicine that we may seek approval for, or acquire, fail to attain market acceptance, we may not be able to generate significant revenue to achieve or sustain profitability, which would have a material adverse effect on our business, results of operations, financial condition and prospects (including, possibly, the value of our ordinary shares).

Our future prospects are highly dependent on our ability to successfully formulate and execute commercialization strategies for each of our medicines. Failure to do so would adversely impact our financial condition and prospects.

A substantial majority of our resources are focused on the commercialization of our current medicines. Our ability to generate significant medicine revenues and to achieve commercial success in the near-term will initially depend almost entirely on our ability to successfully commercialize these medicines in the United States.

With respect to our rare disease medicines, RAVICTI, PROCYSBI, ACTIMMUNE, BUPHENYL, QUINSAIR and KRYSTEXXA, our commercialization strategy includes efforts to increase awareness of the rare conditions that each medicine is designed to treat, enhancing efforts to identify target patients and in certain cases pursue opportunities for label expansion and more effective use through clinical trials. With respect to RAVICTI and PROCYSBI, our strategy includes accelerating the transition of patients from first-generation therapies, and increasing the diagnosis of the associated rare conditions through patient and physician outreach. Our strategy with respect to KRYSTEXXA includes supporting the three pillars of growth: existing rheumatology account growth, new rheumatology account growth and accelerating nephrology growth.

With respect to our primary care medicines, PENNSAID 2%, DUEXIS, and VIMOVO, our strategy has included entering into rebate agreements with pharmacy benefit managers, or PBMs, for certain of our primary care medicines where we believe the rebates and costs justify expanded formulary access for patients and ensuring patient access to these drugs when prescribed through our HorizonCares program. However, we cannot guarantee that we will be able to secure additional rebate agreements on commercially reasonable terms, that expected volume growth will sufficiently offset the rebates and fees paid to PBMs or that our existing agreements with PBMs will have the intended impact on formulary access. In addition, as the terms of our existing agreements with PBMs expire, we may not be able to renew the agreements on commercially favorable terms, or at all. For each of our primary care medicines, we expect that our commercial success will depend on our sales and marketing efforts in the United States, reimbursement decisions by commercial payers, the expense we incur through our patient access program for fully bought down contracts and the rebates we pay to PBMs, as well as the impact of numerous efforts at federal, state and local levels to further reduce reimbursement and net pricing of primary care medicines.

Our strategy for RAYOS in the United States is to focus on the rheumatology indications approved for RAYOS, including our collaboration with the Alliance for Lupus Research, or ALR, to study the effect of RAYOS on the fatigue experienced by systemic lupus erythematosus, or SLE, patients.

If any of our commercial strategies are unsuccessful or we fail to successfully modify our strategies over time due to changing market conditions, our ability to increase market share for our medicines, grow revenues and to achieve and sustain profitability will be harmed.

In order to increase adoption and sales of our medicines, we will need to continue developing our commercial organization as well as recruit and retain qualified sales representatives.

Part of our strategy is to continue to build a biopharma company to successfully execute the commercialization of our medicines in the U.S. market, and in selected markets outside the United States where we have commercial rights. We may not be able to successfully commercialize our medicines in the United States or in any other territories where we have commercial rights. In order to commercialize any approved medicines, we must continue to build our sales, marketing, distribution, managerial and other non-technical capabilities. As of December 31, 2018, we had approximately 420 sales representatives in the field, consisting of approximately 25 orphan disease sales representatives, 140 rheumatology sales specialists and 255 primary care sales representatives. We currently have limited resources compared to some of our competitors, and the continued development of our own commercial organization to market our medicines and any additional medicines we may acquire will be expensive and time-consuming. We also cannot be certain that we will be able to continue to successfully develop this capability.

As a result of the evolving role of various constituents in the prescription decision making process, we focus on hiring sales representatives for our primary care medicines and RAYOS with successful business to business experience. For example, we have faced challenges due to pharmacists increasingly switching a patient's intended prescription from DUEXIS and VIMOVO to a generic or over-the-counter brand of their active ingredients, despite such substitution being off-label in the case of DUEXIS and VIMOVO. We have faced similar challenges for BUPHENYL, RAYOS and PENNSAID 2% with respect to generic brands. While we believe the profile of our representatives is better suited for this evolving environment, we cannot be certain that our representatives will be able to successfully protect our market for BUPHENYL, RAYOS, PENNSAID 2%, DUEXIS and VIMOVO or that we will be able to continue attracting and retaining sales representatives with our desired profile and skills. We will also have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train and retain commercial personnel. To the extent we rely on additional third parties to commercialize any approved medicines, we may receive less revenue than if we commercialized these medicines ourselves. In addition, we may have little or no control over the sales efforts of any third parties involved in our commercialization efforts. In the event we are unable to successfully develop and maintain our own commercial organization or collaborate with a third-party sales and marketing organization, we may not be able to commercialize our medicines and medicine candidates and execute on our business plan.

If we are unable to effectively train and equip our sales force, our ability to successfully commercialize our medicines will be harmed.

As we continue to acquire additional medicines through acquisition transactions, the members of our sales force may have limited experience promoting certain of our medicines. To the extent we employ an acquired entity's original sales forces to promote acquired medicines, we may not be successful in continuing to retain these employees and we otherwise will have limited experience marketing these medicines under our commercial organization. As a result, we are required to expend significant time and resources to train our sales force to be credible and persuasive in convincing physicians to prescribe and pharmacists to dispense our medicines. In addition, we must train our sales force to ensure that a consistent and appropriate message about our medicines is being delivered to our potential customers. Our sales representatives may also experience challenges promoting multiple medicines when we call on physicians and their office staff. We have experienced, and may continue to experience, turnover of the sales representatives that we hired or will hire, requiring us to train new sales representatives. If we are unable to effectively train our sales force and equip them with effective materials, including medical and sales literature to help them inform and educate physicians about the benefits of our medicines and their proper administration and label indication, as well as our patient access programs, our efforts to successfully commercialize our medicines could be put in jeopardy, which could have a material adverse effect on our financial condition, share price and operations.

If we cannot successfully implement our patient access programs or increase formulary access and reimbursement for our medicines in the face of increasing pressure to reduce the price of medications, the adoption of our medicines by physicians, patients and payers may decline.

There continues to be immense pressure from healthcare payers, PBMs and others to use less expensive or generic medicines or over-the-counter brands instead of certain branded medicines. For example, some of the largest PBMs previously placed DUEXIS and VIMOVO on their formulary exclusion lists. Additional healthcare plans, including those that contract with these PBMs but use different formularies, may also choose to exclude our medicines from their formularies or restrict coverage to situations where a generic or over-the-counter medicine has been tried first. Many payers and PBMs also require patients to make co-payments for branded medicines, including many of our medicines, in order to incentivize the use of generic or other lower-priced alternatives instead. Legislation enacted in most states in the United States allows, or in some instances mandates, that a pharmacist dispenses an available generic equivalent when filling a prescription for a branded medicine, in the absence of specific instructions from the prescribing physician. Because our medicines (other than BUPHENYL) do not currently have FDA-approved generic equivalents in the United States, we do not believe our medicines should be subject to mandatory generic substitution laws. However, we understand that some pharmacies may attempt to obtain physician authorization to switch prescriptions for DUEXIS or VIMOVO to prescriptions for multiple generic medicines with similar active pharmaceutical ingredients, or APIs, to ensure payment for the medicine if the physician's prescription for the branded medicine is not immediately covered by the payer, despite such substitution being off-label in the case of DUEXIS and VIMOVO. If these limitations in coverage and other incentives result in patients refusing to fill prescriptions or being dissatisfied with the out-of-pocket costs of their medications, or if pharmacies otherwise seek and receive physician authorization to switch prescriptions, not only would we lose sales on prescriptions that are ultimately not filled, but physicians may be dissuaded from writing prescriptions for our medicines in the first place in order to avoid potential patient non-compliance or dissatisfaction over medication costs, or to avoid spending the time and effort of responding to pharmacy requests to switch prescriptions.

Part of our commercial strategy to increase adoption and access to our medicines in the face of these incentives to use generic alternatives is to offer physicians the opportunity to have patients fill prescriptions through independent pharmacies participating in our HorizonCares patient access program, including shipment of prescriptions to patients. We also have contracted with a third party prescription clearinghouse that offers physicians a single point of contact for processing prescriptions through these independent pharmacies, reducing physician administrative costs, increasing the fill rates for prescriptions and enabling physicians to monitor refill activity. Through HorizonCares, financial assistance may be available to reduce eligible patients' out-of-pocket costs for prescriptions filled. Because of this assistance, eligible patients' out-of-pocket cost for our medicines when dispensed through HorizonCares may be significantly lower than such costs when our medicines are dispensed outside of the HorizonCares program. However, to the extent physicians do not direct prescriptions currently filled through traditional pharmacies, including those associated with or controlled by PBMs, to pharmacies participating in our HorizonCares program, we may experience a significant decline in PENNSAID 2%, DUEXIS and VIMOVO prescriptions. Our ability to increase utilization of our patient access programs will depend on physician and patient awareness and comfort with the programs, and we have limited ability to influence whether physicians use our patient access programs to prescribe our medicines or whether patients will agree to receive our medicines through our HorizonCares program. In addition, the HorizonCares program is not available to federal health care program (such as Medicare and Medicaid) beneficiaries. We have also contracted with certain PBMs and other payers to secure formulary status and reimbursement for certain of our primary care medicines, which generally require us to pay administrative fees and rebates to the PBMs and other payers for qualifying prescriptions. While we have business relationships with two of the largest PBMs, Express Scripts, Inc., or Express Scripts, and CVS Caremark, that have resulted in DUEXIS and VIMOVO being removed from the Express Scripts and CVS Caremark exclusion lists starting in 2017, as well as a rebate agreement with another PBM, Prime Therapeutics LLC, and we believe these agreements will secure formulary status for certain of our medicines, we cannot guarantee that we will be able to agree to terms with other PBMs and other payers, or that such terms will be commercially reasonable to us. Despite our agreements with PBMs, the extent of formulary status and reimbursement will ultimately depend to a large extent upon individual healthcare plan formulary decisions. If healthcare plans that contract with PBMs with which we have agreements do not adopt formulary changes recommended by the PBMs with respect to our medicines, we may not realize the expected access and reimbursement benefits from these agreements. In addition, we generally pay higher rebates for prescriptions covered under plans that adopt a PBM-chosen formulary than for plans that adopt custom formularies. Consequently, the success of our PBM contracting strategy will depend not only on our ability to expand formulary adoption among healthcare plans, but also upon the relative mix of healthcare plans that have PBM-chosen formularies versus custom formularies. If we are unable to realize the expected benefits of our contractual arrangements with the PBMs we may continue to experience reductions in net sales from our primary care medicines and/or reductions in net pricing for our primary care medicines due to increasing patient assistance costs. If we are unable to increase adoption of HorizonCares for filling prescriptions of our medicines and to secure formulary status and reimbursement through arrangements with PBMs and other payers, particularly with healthcare plans that use custom formularies, our ability to achieve net sales growth for our primary care medicines would be impaired.

There has been negative publicity and inquiries from Congress and enforcement authorities regarding the use of specialty pharmacies and drug pricing. Our patient access programs are not involved in the prescribing of medicines and are solely to assist in ensuring that when a physician determines one of our medicines offers a potential clinical benefit to their patients and they prescribe one for an eligible patient, financial assistance may be available to reduce the patient's out-of-pocket costs. In addition, all pharmacies that fill prescriptions for our medicines are fully independent, including those that participate in HorizonCares. We do not own or possess any option to purchase an ownership stake in any pharmacy that distributes our medicines, and our relationship with each pharmacy is non-exclusive and arm's length. All of our sales are processed through pharmacies independent of us. Despite this, the negative publicity and interest from Congress and enforcement authorities regarding specialty pharmacies may result in physicians being less willing to participate in our patient access programs and thereby limit our ability to increase patient access and adoption of our medicines.

We may also encounter difficulty in forming and maintaining relationships with pharmacies that participate in our patient access programs. We currently depend on a limited number of pharmacies participating in HorizonCares to fulfill patient prescriptions under the HorizonCares program. If these HorizonCares participating pharmacies are unable to process and fulfill the volume of patient prescriptions directed to them under the HorizonCares program, our ability to maintain or increase prescriptions for our medicines will be impaired. The commercialization of our medicines and our operating results could be affected should any of the HorizonCares participating pharmacies choose not to continue participation in our HorizonCares program or by any adverse events at any of those HorizonCares participating pharmacies. For example, pharmacies that dispense our medicines could lose contracts that they currently maintain with managed care organizations, or MCOs, including PBMs. Pharmacies often enter into agreements with MCOs. They may be required to abide by certain terms and conditions to maintain access to MCO networks, including terms and conditions that could limit their ability to participate in patient access programs like ours. Failure to comply with the terms of their agreements with MCOs could result in a variety of penalties, including termination of their agreement, which could negatively impact the ability of those pharmacies to dispense our medicines and collect reimbursement from MCOs for such medicines.

The HorizonCares program may implicate certain federal and state laws related to, among other things, unlawful schemes to defraud, excessive fees for services, tortious interference with patient contracts and statutory or common law fraud. We have a comprehensive compliance program in place to address adherence with various laws and regulations relating to the selling, marketing and manufacturing of our medicines, as well as certain third-party relationships, including pharmacies. Specifically with respect to pharmacies, the compliance program utilizes a variety of methods and tools to monitor and audit pharmacies, including those that participate in the HorizonCares program, to confirm their activities, adjudication and practices are consistent with our compliance policies and guidance. Despite our compliance efforts, to the extent the HorizonCares program is found to be inconsistent with applicable laws or the pharmacies that participate in our patient access programs do not comply with applicable laws, we may be required to restructure or discontinue such programs, terminate our relationship with certain pharmacies, or be subject to other significant penalties. In November 2015, we received a subpoena from the U.S. Attorney's Office for the Southern District of New York requesting documents and information related to our patient access programs and other aspects of our marketing and commercialization activities. We are unable to predict how long this investigation will continue or its outcome, but we have incurred and anticipate that we may continue to incur significant costs in connection with the investigation, regardless of the outcome. We may also become subject to similar investigations by other governmental agencies or Congress. The investigation by the U.S. Attorney's Office and any additional investigations of our patient access programs and sales and marketing activities may result in damages, fines, penalties, exclusion, additional reporting requirements and/or oversight or other administrative sanctions against us.

If the cost of maintaining our patient access programs increases relative to our sales revenues, we could be forced to reduce the amount of patient financial assistance that we offer or otherwise scale back or eliminate such programs, which could in turn have a negative impact on physicians' willingness to prescribe and patients' willingness to fill prescriptions of our medicines. While we believe that our arrangements with PBMs will result in broader inclusion of certain of our primary care medicines on healthcare plan formularies, and therefore increase payer reimbursement and lower our cost of providing patient access programs, these arrangements generally require us to pay administrative and rebate payments to the PBMs and/or other payers and their effectiveness will ultimately depend to a large extent upon individual healthcare plan formulary decisions that are beyond the control of the PBMs. If our arrangements with PBMs and other payers do not result in increased prescriptions and reductions in our costs to provide our patient access programs that are sufficient to offset the administrative fees and rebate payments to the PBMs and/or other payers, our financial results may continue to be harmed.

If we are unable to successfully implement our commercial plans and facilitate adoption by patients and physicians of any approved medicines through our sales, marketing and commercialization efforts, then we will not be able to generate sustainable revenues from medicine sales which will have a material adverse effect on our business and prospects.

Coverage and reimbursement may not be available, or reimbursement may be available at only limited levels, for our medicines, which could make it difficult for us to sell our medicines profitably or to successfully execute planned medicine price increases.

Market acceptance and sales of our medicines will depend in large part on global coverage and reimbursement policies and may be affected by future healthcare reform measures, both in the United States and other key international markets. Successful commercialization of our medicines will depend in part on the availability of governmental and third-party payer reimbursement for the cost of our medicines. Government health administration authorities, private health insurers and other organizations generally provide reimbursement for healthcare. In particular, in the United States, private health insurers and other third-party payers often provide reimbursement for medicines and services based on the level at which the government (through the Medicare or Medicaid programs) provides reimbursement for such treatments. In the United States, the European Union, or EU, and other significant or potentially significant markets for our medicines and medicine candidates, government authorities and third-party payers are increasingly attempting to limit or regulate the price of medicines and services, particularly for new and innovative medicines and therapies, which has resulted in lower average selling prices. Further, the increased scrutiny of prescription drug pricing practices and emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the EU will put additional pressure on medicine pricing, reimbursement and usage, which may adversely affect our medicine sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical reimbursement policies and pricing in general. These pressures may create negative reactions to any medicine price increases, or limit the amount by which we may be able to increase our medicine prices, which may adversely affect our medicine sales and results of operations.

Patients are unlikely to use our medicines unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our medicines. Third-party payers may limit coverage to specific medicines on an approved list, also known as a formulary, which might not include all of the FDA-approved medicines for a particular indication. Moreover, a third-party payer's decision to provide coverage for a medicine does not imply that an adequate reimbursement rate will be approved. Additionally, one third-party payer's decision to cover a particular medicine does not ensure that other payers will also provide coverage for the medicine, or will provide coverage at an adequate reimbursement rate. Even though we have contracts with some PBMs in the United States, that does not guarantee that they will perform in accordance with the contracts, nor does that preclude them from taking adverse actions against us, which could materially adversely affect our operating results. In addition, the existence of such PBM contracts does not guarantee coverage by such PBM's contracted health plans or adequate reimbursement to their respective providers for our medicines. For example, two significant PBMs placed DUEXIS and VIMOVO on their exclusion lists beginning in 2015, which has resulted in a loss of coverage for patients whose healthcare plans have adopted these PBM lists. While DUEXIS and VIMOVO were removed from the Express Scripts and CVS Caremark exclusion lists starting in 2017, we cannot guarantee that Express Scripts or CVS Caremark will not later add these medicines back to their exclusion lists or that we will be able to otherwise expand formulary access for DUEXIS and VIMOVO under health plans that contract with Express Scripts and/or CVS Caremark. Additional healthcare plan formularies may also exclude our medicines from coverage due to the actions of certain PBMs, future price increases we may implement, our use of the HorizonCares program or any other co-pay programs, or other reasons. If our strategies to mitigate formulary exclusions are not effective, these events may reduce the likelihood that physicians prescribe our medicines and increase the likelihood that prescriptions for our medicines are not filled.

Outside of the United States, the success of our medicines and medicine candidates will depend largely on obtaining and maintaining government coverage, because in many countries patients are unlikely to use prescription drugs that are not covered by their government healthcare programs. We market RAVICTI, PROCYSBI, and QUINSAIR in Canada. Further, we cannot be certain that existing reimbursement in Canada will be maintained or that we will be able to secure reimbursement in additional countries. Negotiating coverage and reimbursement with governmental authorities can delay commercialization by twelve months or more. Coverage and reimbursement policies may adversely affect our ability to sell our medicines on a profitable basis. In many international markets, governments control the prices of prescription pharmaceuticals, including through the implementation of reference pricing, price cuts, rebates, revenue-related taxes and profit control, and we expect prices of prescription pharmaceuticals to decline over the life of the medicine or as volumes increase. As a result of these pricing practices, it may become difficult to achieve or sustain profitability or expected rates of growth in revenue or results of operations. Any shortfalls in revenue could adversely affect our business, financial condition and results of operations.

In light of such policies and the uncertainty surrounding proposed regulations and changes in the coverage and reimbursement policies of governments and third-party payers, we cannot be sure that coverage and reimbursement will be available for any of our medicines in any additional markets or for any other medicine candidates that we may develop. Also, we cannot be sure that reimbursement amounts will not reduce the demand for, or the price of, our medicines. If coverage and reimbursement are not available or are available only at limited levels, we may not be able to successfully commercialize our medicines.

We expect to experience pricing pressures in connection with the sale of our medicines due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative proposals relating to outcomes and quality. For example, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the ACA, increased the mandated Medicaid rebate from 15.1% to 23.1%, expanded the rebate to Medicaid managed care utilization and increased the types of entities eligible for the federal 340B drug discount program. As concerns continue to grow over the need for tighter oversight, there remains the possibility that the Health Resources and Services Administration or another agency under the U.S. Department of Health and Human Services, or HHS, will propose a similar regulation or that Congress will explore changes to the 340B program through legislation. For example, a bill was introduced in 2018 that would require hospitals to report their low-income utilization of the program. Further, the Centers for Medicare & Medicaid Services issued a final rule that would revise the Medicare hospital outpatient prospective payment system for calendar year 2019, including a new reimbursement methodology for drugs purchased under the 340B program for Medicare patients at the hospital setting and recently announced the same change for physician-based practices under 340B in 2019. Pursuant to the final rule, after January 1, 2019, manufacturers must calculate 340B program ceiling prices on a quarterly basis. Moreover, manufacturers could be subject to a $5,000 penalty for each instance where they knowingly and intentionally overcharge a covered entity under the 340B program. With respect to KRYSTEXXA, the "additional rebate" scheme of the 340B pricing rules, as applied to the historical pricing of KRYSTEXXA both before and after we acquired the medicine, have resulted in a 340B ceiling price of one penny. A material portion of KRYSEXXA prescriptions (approximately twenty to twenty-five percent) are written by healthcare

providers that are eligible for 340B drug pricing and therefore the reduction in 340B pricing to a penny has negatively impacted our net sales from KRYSTEXXA.

There may be additional pressure by payers, healthcare providers, state governments, federal regulators and Congress, to use generic drugs that contain the active ingredients found in our medicines or any other medicine candidates that we may develop or acquire. If we fail to successfully secure and maintain coverage and adequate reimbursement for our medicines or are significantly delayed in doing so, we will have difficulty achieving market acceptance of our medicines and expected revenue and profitability which would have a material adverse effect on our business, results of operations, financial condition and prospects.

We may also experience pressure from payers as well as state and federal government authorities concerning certain promotional approaches that we may implement such as our HorizonCares program or any other co-pay or free medicine programs whereby we assist qualified patients with certain out-of-pocket expenditures for our medicine. Certain state and federal enforcement authorities and members of Congress have initiated inquiries about co-pay assistance programs. Some state legislatures have been considering proposals that would restrict or ban co-pay coupons. For example, legislation was recently signed into law in California that would limit the use of co-pay coupons in cases where a lower cost generic drug is available and if individual ingredients in combination therapies are available over the counter at a lower cost. It is possible that similar legislation could be proposed and enacted in additional states. If we are unsuccessful with our HorizonCares program or any other co-pay initiatives or free medicine programs, or we alternatively are unable to secure expanded formulary access through additional arrangements with PBMs or other payers, we would be at a competitive disadvantage in terms of pricing versus preferred branded and generic competitors. We may also experience financial pressure in the future which would make it difficult to support investment levels in areas such as managed care contract rebates, HorizonCares and other access tools.

We are solely dependent on third parties to commercialize certain of our medicines outside the United States. Failure of these third parties or any other third parties to successfully commercialize our medicines and medicine candidates in the applicable jurisdictions could have an adverse effect on our business.

Innomar Strategies Inc., or Innomar, is our exclusive distributor for RAVICTI, PROCYSBI and QUINSAIR in Canada. We rely on Orphan Pacific, Inc., or Orphan Pacific, for commercialization of BUPHENYL in Japan for which we currently have rights. We have limited contractual rights to force these third parties to invest significantly in commercialization of these medicines in our markets. In the event that Innomar, Orphan Pacific or any other third party with any future commercialization rights to any of our medicines or medicine candidates fail to adequately commercialize those medicines or medicine candidates because they lack adequate financial or other resources, decide to focus on other initiatives or otherwise, our ability to successfully commercialize our medicines or medicine candidates in the applicable jurisdictions would be limited, which would adversely affect our business, financial condition, results of operations and prospects. In addition, our agreements with Innomar and Orphan Pacific, may be terminated by either party in the event of a bankruptcy of the other party or upon an uncured material breach by the other party. If these third parties terminated their agreements, we may not be able to secure an alternative distributor in the applicable territory on a timely basis or at all, in which case our ability to generate revenues from the sale of RAVICTI, PROCYSBI, BUPHENYL or QUINSAIR, outside the United States would be harmed.

Our medicines are subject to extensive regulation, and we may not obtain additional regulatory approvals for our medicines.

The clinical development, manufacturing, labeling, packaging, storage, recordkeeping, advertising, promotion, export, marketing and distribution and other possible activities relating to our medicines and our medicine candidates are, and will be, subject to extensive regulation by the FDA and other regulatory agencies. Failure to comply with FDA and other applicable regulatory requirements may, either before or after medicine approval, subject us to administrative or judicially imposed sanctions.

To market any drugs or biologics outside of the United States, we and current or future collaborators must comply with numerous and varying regulatory and compliance related requirements of other countries. Approval procedures vary among countries and can involve additional medicine testing and additional administrative review periods, including obtaining reimbursement and pricing approval in select markets. The time required to obtain approval in other countries might differ from that required to obtain FDA approval. The regulatory approval process in other countries may include all of the risks associated with FDA approval as well as additional, presently unanticipated, risks. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others.

Applications for regulatory approval, including a marketing authorization application, or MAA, for marketing new drugs in Europe, must be supported by extensive clinical and pre-clinical data, as well as extensive information regarding chemistry, manufacturing and controls, or CMC, to demonstrate the safety and effectiveness of the applicable medicine candidate. The number and types of pre-clinical studies and clinical trials that will be required for regulatory approval varies depending on the medicine candidate, the disease or the condition that the medicine candidate is designed to target and the regulations applicable to any particular medicine candidate. Despite the time and expense associated with pre-clinical and clinical studies, failure can occur at any stage, and we could encounter problems that cause us to repeat or perform additional pre-clinical studies, CMC studies or clinical trials. Regulatory authorities could delay, limit or deny approval of a medicine candidate for many reasons, including because they:

- may not deem a medicine candidate to be adequately safe and effective;
- may not find the data from pre-clinical studies, CMC studies and clinical trials to be sufficient to support a claim of safety and efficacy;
- may interpret data from pre-clinical studies, CMC studies and clinical trials significantly differently than we do;
- may not approve the manufacturing processes or facilities associated with our medicine candidates;
- may conclude that we have not sufficiently demonstrated long-term stability of the formulation for which we are seeking marketing approval;
- may change approval policies (including with respect to our medicine candidates' class of drugs) or adopt new regulations; or
- may not accept a submission due to, among other reasons, the content or formatting of the submission.

Even if we believe that data collected from our pre-clinical studies, CMC studies and clinical trials of our medicine candidates are promising and that our information and procedures regarding CMC are sufficient, our data may not be sufficient to support marketing approval by regulatory authorities, or regulatory interpretation of these data and procedures may be unfavorable. Even if approved, medicine candidates may not be approved for all indications requested and such approval may be subject to limitations on the indicated uses for which the medicine may be marketed, restricted distribution methods or other limitations. Our business and reputation may be harmed by any failure or significant delay in obtaining regulatory approval for the sale of any of our medicine candidates. We cannot predict when or whether regulatory approval will be obtained for any medicine candidate we develop.

We will evaluate all development opportunities, including all obligations to use commercial reasonable efforts to further develop QUINSAIR. However, we may determine not to pursue such further development.

The ultimate approval and commercial marketing of any of our medicines in additional indications or geographies is subject to substantial uncertainty. Failure to gain additional regulatory approvals would limit the potential revenues and value of our medicines and could cause our share price to decline.

We may be subject to penalties and litigation and large incremental expenses if we fail to comply with regulatory requirements or experience problems with our medicines.

Even after we achieve regulatory approvals, we are subject to ongoing obligations and continued regulatory review with respect to many operational aspects including our manufacturing processes, labeling, packaging, distribution, storage, adverse event monitoring and reporting, dispensation, advertising, promotion and recordkeeping. These requirements include submissions of safety and other post-marketing information and reports, ongoing maintenance of medicine registration and continued compliance with current good manufacturing practices, or cGMPs, good clinical practices, or GCPs, good pharmacovigilance practice, good distribution practices and good laboratory practices, or GLPs. If we, our medicines or medicine candidates, or the third-party manufacturing facilities for our medicines or medicine candidates fail to comply with applicable regulatory requirements, a regulatory agency may:

- impose injunctions or restrictions on the marketing, manufacturing or distribution of a medicine, suspend or withdraw medicine approvals, revoke necessary licenses or suspend medicine reimbursement;
- issue warning letters, show cause notices or untitled letters describing alleged violations, which may be publicly available;

- suspend any ongoing clinical trials or delay or prevent the initiation of clinical trials;
- delay or refuse to approve pending applications or supplements to approved applications we have filed;
- refuse to permit drugs or precursor or intermediary chemicals to be imported or exported to or from the United States;
- suspend or impose restrictions or additional requirements on operations, including costly new manufacturing quality or pharmacovigilance requirements;
- seize or detain medicines or require us to initiate a medicine recall; and/or
- commence criminal investigations and prosecutions.

Moreover, existing regulatory approvals and any future regulatory approvals that we obtain will be subject to limitations on the approved indicated uses and patient populations for which our medicines may be marketed, the conditions of approval, requirements for potentially costly, post-market testing and requirements for surveillance to monitor the safety and efficacy of the medicines. In the European Economic Area, or EEA, the advertising and promotion of pharmaceuticals is strictly regulated. The direct-to-consumer promotion of prescription pharmaceuticals is not permitted, and some countries in the EEA require the notification and/or prior authorization of promotional or advertising materials directed at healthcare professionals. The FDA, European Medicines Agency, or EMA, and other authorities in the EEA countries strictly regulate the promotional claims that may be made about prescription medicines, and our medicine labeling, advertising and promotion are subject to continuing regulatory review. Physicians nevertheless may prescribe our medicines to their patients in a manner that is inconsistent with the approved label or that is off-label. Positive clinical trial results in any of our medicine development programs increase the risk that approved pharmaceutical forms of the same APIs may be used off-label in those indications. If we are found to have improperly promoted off-label uses of approved medicines, we may be subject to significant sanctions, civil and criminal fines and injunctions prohibiting us from engaging in specified promotional conduct.

In addition, engaging in improper promotion of our medicines for off-label uses in the United States can subject us to false claims litigation under federal and state statutes. These false claims statutes in the United States include the federal False Claims Act, which allows any individual to bring a lawsuit against a pharmaceutical company on behalf of the federal government alleging submission of false or fraudulent claims or causing to present such false or fraudulent claims for payment by a federal program such as Medicare or Medicaid. Growth in false claims litigation has increased the risk that a pharmaceutical company will have to defend a false claim action, pay civil money penalties, settlement fines or restitution, agree to comply with burdensome reporting and compliance obligations and be excluded from Medicare, Medicaid and other federal and state healthcare programs.

The regulations, policies or guidance of regulatory agencies may change and new or additional statutes or government regulations may be enacted that could prevent or delay regulatory approval of our medicine candidates or further restrict or regulate post-approval activities. For example, in January 2014, the FDA released draft guidance on how drug companies can fulfill their regulatory requirements for post-marketing submission of interactive promotional media, and though the guidance provided insight into how the FDA views a company's responsibility for certain types of social media promotion, there remains a substantial amount of uncertainty regarding internet and social media promotion of regulated medical products. We cannot predict the likelihood, nature or extent of adverse government regulation that may arise from pending or future legislation or administrative action, either in the United States or abroad. If we are unable to achieve and maintain regulatory compliance, we will not be permitted to market our drugs, which would materially adversely affect our business, results of operations and financial condition.

Our limited history of commercial operations makes evaluating our business and future prospects difficult and may increase the risk of any investment in our ordinary shares.

We face considerable risks and difficulties as a company with limited commercial operating history, particularly as a global consolidated entity with operating subsidiaries that also have limited operating histories. If we do not successfully address these risks, our business, prospects, operating results and financial condition will be materially and adversely harmed. Our limited commercial operating history, including our limited history commercializing our current medicines, makes it particularly difficult for us to predict our future operating results and appropriately budget for our expenses. In the event that actual results differ from our estimates or we adjust our estimates in future periods, our operating results and financial position could be materially affected. For example, we may underestimate the resources we will require to successfully integrate recent or future medicine or company acquisitions, or to commercialize our medicines, or not realize the benefits we expect to derive from our recent or future acquisitions. In addition, we have a limited history implementing our commercialization strategy focused on patient access, and we cannot guarantee that we will be able to successfully implement this strategy or that it will represent a viable strategy over the long term.

We have rights to medicines in certain jurisdictions but have no control over third parties that have rights to commercialize those medicines in other jurisdictions, which could adversely affect our commercialization of these medicines.

Following our sale of the rights to RAVICTI and AMMONAPS (known as BUPHENYL in the United States) outside of North America and Japan to Medical Need Europe AB, part of the Immedica Group, or Immedica, in December 2018, Immedica has marketing and distribution rights to RAVICTI and AMMONAPS in those regions. Following our sale of the rights to interferon gamma 1b, known as IMUKIN, outside of the United States, Canada and Japan to Clinigen Group plc, or Clinigen, in July 2018, Clinigen has marketing and distribution rights to IMUKIN in those regions. Following our sale of the rights to PROCYSBI and QUINSAIR in the Europe, Middle East and Africa, or EMEA, regions to Chiesi Farmaceutici S.p.A, or Chiesi, in June 2017, or the Chiesi divestiture, Chiesi has marketing and distribution rights to PROCYSBI and QUINSAIR in the EMEA regions. Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.), or Nuvo, has retained its rights to PENNSAID 2% in territories outside of the United States. In March 2017, Nuvo announced that it had entered into an exclusive license agreement with Sayre Therapeutics PVT Ltd. to distribute, market and sell PENNSAID 2% in India, Sri Lanka, Bangladesh and Nepal, and in December 2017 Nuvo announced that it had entered into a license and distribution agreement with Gebro Pharma AG for the exclusive right to register, distribute, market and sell PENNSAID 2% in Switzerland and Liechtenstein. Grünenthal GmbH, or Grünenthal, acquired the rights to VIMOVO in territories outside of the United States, including the right to use the VIMOVO name and related trademark from AstraZeneca AB, or AstraZeneca, in October 2018. We have little or no control over Immedica's activities with respect to RAVICTI and AMMONAPS outside of North America and Japan, over Clinigen's activities with respect to IMUKIN outside the United States, Canada and Japan, over Chiesi's activities with respect to PROCYSBI and QUINSAIR in the EMEA, over Nuvo's or its existing and future commercial partners' activities with respect to PENNSAID 2% outside of the United States, or over Grünenthal's activities with respect to VIMOVO outside the United States even though those activities could impact our ability to successfully commercialize these medicines. For example, Immedica or its assignees, Clinigen or its assignees, Chiesi or its assignees, Nuvo or its assignees or Grünenthal or its assignees can make statements or use promotional materials with respect to RAVICTI and AMMONAPS, IMUKIN, PROCYSBI and QUINSAIR, PENNSAID 2% or VIMOVO, respectively, outside of the United States that are inconsistent with our positioning of the medicines in the United States, and could sell RAVICTI and AMMONAPS, IMUKIN, PROCYSBI and QUINSAIR, PENNSAID 2% or VIMOVO, respectively, in foreign countries at prices that are dramatically lower than the prices we charge in the United States. These activities and decisions, while occurring outside of the United States, could harm our commercialization strategy in the United States, in particular because Grünenthal is continuing to market VIMOVO outside the United States under the same VIMOVO brand name that we are using in the United States. In addition, medicine recalls or safety issues with these medicines outside the United States, even if not related to the commercial medicine we sell in the United States, could result in serious damage to the brand in the United States and impair our ability to successfully market them. We also rely on Immedica, Clinigen, Chiesi, Nuvo and Grünenthal or their assignees to provide us with timely and accurate safety information regarding the use of these medicines outside of the United States, as we have or will have limited access to this information ourselves.

We rely on third parties to manufacture commercial supplies of all of our medicines, and we currently intend to rely on third parties to manufacture commercial supplies of any other approved medicines. The commercialization of any of our medicines could be stopped, delayed or made less profitable if those third parties fail to provide us with sufficient quantities of medicine or fail to do so at acceptable quality levels or prices or fail to maintain or achieve satisfactory regulatory compliance.

The facilities used by our third-party manufacturers to manufacture our medicines and medicine candidates must be approved by the applicable regulatory authorities. We do not control the manufacturing processes of third-party manufacturers and are currently completely dependent on our third-party manufacturing partners. In addition, we are required to obtain Grünenthal's (formerly AstraZeneca) consent prior to engaging any third-party manufacturers for esomeprazole, one of the APIs in VIMOVO, other than the third-party manufacturer(s) used by Grünenthal or its affiliates or licensees. To the extent such manufacturers are unwilling or unable to manufacture esomeprazole for us on commercially acceptable terms, we cannot guarantee that Grünenthal would consent to our use of alternate sources of supply.

We rely on an exclusive supply agreement with Boehringer Ingelheim Biopharmaceuticals GmbH, or Boehringer Ingelheim Biopharmaceuticals, for manufacturing and supply of ACTIMMUNE. ACTIMMUNE is manufactured by starting with cells from working cell bank samples which are derived from a master cell bank. We and Boehringer Ingelheim Biopharmaceuticals separately store multiple vials of the master cell bank. In the event of catastrophic loss at our or Boehringer Ingelheim Biopharmaceuticals' storage facility, it is possible that we could lose multiple cell banks and have the manufacturing capacity of ACTIMMUNE severely impacted by the need to substitute or replace the cell banks. We rely on NOF Corporation, or NOF, as our exclusive supplier of the PEGylation agent that is a critical raw material in the manufacture of KRYSTEXXA. If NOF failed to supply such PEGylation agent, it may lead to KRYSTEXXA supply constraints. In addition, a key excipient used in PENNSAID 2% as a penetration enhancer is dimethyl sulfoxide, or DMSO. We and Nuvo, our exclusive supplier of PENNSAID 2%, rely on a sole proprietary form of DMSO for which we maintain a substantial safety stock. However, should this supply become inadequate, damaged, destroyed or unusable, we and Nuvo may not be able to qualify a second source.

If any of our third-party manufacturers cannot successfully manufacture material that conforms to our specifications and the applicable regulatory authorities' strict regulatory requirements, or pass regulatory inspection, they will not be able to secure or maintain regulatory approval for the manufacturing facilities. For example, BASF Corporation, or BASF, our manufacturer of one of the APIs in DUEXIS, ibuprofen in a direct compression blend called DC85, is not currently able to supply DC85 due to a technical issue at its manufacturing facility in Bishop, Texas. BASF is currently working to resolve the technical issue and recently notified us of its intention to resume supply of DC85. While we consider our DUEXIS inventory on hand to be sufficient to meet current and future commercial requirements during the resolution process, we cannot guarantee that BASF will ultimately be able to resolve the technical issue or that we will be able to enter into a new supply agreement with BASF for DC85. In addition, we have no control over the ability of third-party manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or any other applicable regulatory authorities do not approve these facilities for the manufacture of our medicines or if they withdraw any such approval in the future, or if our suppliers or third-party manufacturers decide they no longer want to supply our primary active ingredients or manufacture our medicines, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our medicines. To the extent any third-party manufacturers that we engage with respect to our medicines are different from those currently being used for commercial supply in the United States, the FDA will need to approve the facilities of those third-party manufacturers used in the manufacture of our medicines prior to our sale of any medicine using these facilities.

Although we have entered into supply agreements for the manufacture and packaging of our medicines, our manufacturers may not perform as agreed or may terminate their agreements with us. We currently rely on single source suppliers for certain of our medicines. If our manufacturers terminate their agreements with us, we may have to qualify new back-up manufacturers. We rely on safety stock to mitigate the risk of our current suppliers electing to cease producing bulk drug medicine or ceasing to do so at acceptable prices and quality. However, we can provide no assurance that such safety stocks would be sufficient to avoid supply shortfalls in the event we have to identify and qualify new contract manufacturers.

The manufacture of medicines requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of medicines often encounter difficulties in production, particularly in scaling up and validating initial production. These problems include difficulties with production costs and yields, quality control, including stability of the medicine, quality assurance testing, shortages of qualified personnel, as well as compliance with strictly enforced federal, state and foreign regulations. Furthermore, if microbial, viral or other contaminations are discovered in the medicines or in the manufacturing facilities in which our medicines are made, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the contamination. We cannot assure that issues relating to the manufacture of any of our medicines will not occur in the future. Additionally, our manufacturers may experience manufacturing difficulties due to resource constraints or as a result of labor disputes or unstable political environments. If our manufacturers were to encounter any of these difficulties, or otherwise fail to comply with their contractual obligations, our ability to commercialize our medicines or provide any medicine candidates to patients in clinical trials would be jeopardized.

Any delay or interruption in our ability to meet commercial demand for our medicines will result in the loss of potential revenues and could adversely affect our ability to gain market acceptance for these medicines. In addition, any delay or interruption in the supply of clinical trial supplies could delay the completion of clinical trials, increase the costs associated with maintaining clinical trial programs and, depending upon the period of delay, require us to commence new clinical trials at additional expense or terminate clinical trials completely.

Failures or difficulties faced at any level of our supply chain could materially adversely affect our business and delay or impede the development and commercialization of any of our medicines or medicine candidates and could have a material adverse effect on our business, results of operations, financial condition and prospects.

We have experienced growth and expanded the size of our organization substantially in connection with our acquisition transactions, and we may experience difficulties in managing this growth as well as potential additional growth in connection with future medicine, development program or company acquisitions.

As of December 31, 2013, we employed approximately 300 full-time employees as a consolidated entity. As of December 31, 2018, we employed approximately 1,000 full-time employees, including approximately 420 sales representatives, representing a substantial change to the size of our organization. We have also experienced, and may continue to experience, turnover of the sales representatives that we hired or will hire in connection with the commercialization of our medicines, requiring us to hire and train new sales representatives. Our management, personnel, systems and facilities currently in place may not be adequate to support anticipated growth, and we may not be able to retain or recruit qualified personnel in the future due to competition for personnel among pharmaceutical businesses.

As our commercialization plans and strategies continue to develop, we will need to continue to recruit and train sales and marketing personnel. Our ability to manage any future growth effectively may require us to, among other things:

- continue to manage and expand the sales and marketing efforts for our existing medicines;
- enhance our operational, financial and management controls, reporting systems and procedures;
- expand our international resources;
- successfully identify, recruit, hire, train, maintain, motivate and integrate additional employees;
- establish and increase our access to commercial supplies of our medicines and medicine candidates;
- expand our facilities and equipment; and
- manage our internal development efforts effectively while complying with our contractual obligations to licensors, licensees, contractors, collaborators, distributors and other third parties.

Our acquisitions have resulted in many changes, including significant changes in the corporate business and legal entity structure, the integration of other companies and their personnel with us, and changes in systems. We are currently undertaking numerous complex transition activities associated with our acquisitions, and we may encounter unexpected difficulties or incur unexpected costs, including:

- difficulties in achieving growth prospects from combining third-party businesses with our business;
- difficulties in the integration of operations and systems;
- difficulties in the assimilation of employees and corporate cultures;
- challenges in preparing financial statements and reporting timely results at both a statutory level for multiple entities and jurisdictions and at a consolidated level for public reporting;
- challenges in keeping existing physician prescribers and patients and increasing adoption of acquired medicines;
- difficulties in achieving anticipated cost savings, synergies, business opportunities and growth prospects from the combination;
- potential unknown liabilities, adverse consequences and unforeseen increased expenses associated with the transaction; and
- challenges in attracting and retaining key personnel.

If any of these factors impair our ability to continue to integrate our operations with those of any companies or businesses we acquire, we may not be able to realize the business opportunities, growth prospects and anticipated tax synergies from combining the businesses. In addition, we may be required to spend additional time or money on integration that otherwise would be spent on the development and expansion of our business.

We may not be successful in growing our commercial operations outside the United States, and could encounter other challenges in growing our commercial presence, including due to risks associated with political and economic instability, operating under different legal requirements and tax complexities. If we are unable to manage our commercial growth outside of the United States, our opportunities to expand sales in other countries will be limited or we may experience greater costs with respect to our ex-U.S. commercial operations.

We are also broadening our acquisition strategy to include development-stage assets or programs, which entails additional risk to us. For example, if we are unable to identify programs that ultimately result in approved medicines, we may spend material amounts of our capital and other resources evaluating, acquiring and developing medicines that ultimately do not provide a return on our investment. We have less experience evaluating development-stage assets and may be at a disadvantage compared to other entities pursuing similar opportunities. Regardless, development-stage programs generally have a high rate of failure and we cannot guarantee that any such programs will ultimately be successful. We will also need to enhance our clinical development and regulatory functions to properly evaluate and develop earlier-stage opportunities, which may include recruiting personnel that are knowledgeable in therapeutic areas we have not yet pursued. If we are unable to acquire promising development-stage assets or eventually obtain marketing approval for them, we may not be able to create a meaningful pipeline of new medicines and eventually realize a return on our investments.

Our management may also have to divert a disproportionate amount of its attention away from day-to-day activities and toward managing these growth and integration activities. Our future financial performance and our ability to execute on our business plan will depend, in part, on our ability to effectively manage any future growth and our failure to effectively manage growth could have a material adverse effect on our business, results of operations, financial condition and prospects.

We face significant competition from other biotechnology and pharmaceutical companies, including those marketing generic medicines and our operating results will suffer if we fail to compete effectively.

The biotechnology and pharmaceutical industries are intensely competitive. We have competitors both in the United States and international markets, including major multinational pharmaceutical companies, biotechnology companies and universities and other research institutions. Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff, experienced marketing and manufacturing organizations and well-established sales forces. Additional consolidations in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors and we will have to find new ways to compete and may have to potentially merge with or acquire other businesses to stay competitive. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or in-licensing on an exclusive basis, medicines that are more effective and/or less costly than our medicines.

RAVICTI and BUPHENYL face competition from generic NaPBA tablets and powder in treating UCD. Lucane Pharma, or Lucane, is seeking approval via an Abbreviated New Drug Application, or ANDA, in the United States for taste-masked NaPBA. If this ANDA is approved, this formulation may also compete with RAVICTI and BUPHENYL in treating UCD in the United States. PROCYSBI faces competition from Cystagon (immediate-release cysteamine bitartrate capsules) for the treatment of cystinosis and Cystaran (cysteamine ophthalmic solution) for treatment of corneal crystal accumulation in patients with cystinosis. While KRYSTEXXA faces limited direct competition, a number of competitors have drugs in Phase 1 or Phase 2 trials, including Selecta Biosciences Inc. who has presented clinical data from their Phase 2 study and has indicated that it plans to initiate a six-month head-to-head trial comparing their candidate to KRYSTEXXA in 2019. PENNSAID 2% faces competition from generic versions of diclofenac sodium topical solutions that are priced significantly less than the price we charge for PENNSAID 2%. The generic version of Voltaren Gel is the market leader in the topical NSAID category. Legislation enacted in most states in the United States allows, or in some instances mandates, that a pharmacist dispense an available generic equivalent when filling a prescription for a branded medicine, in the absence of specific instructions from the prescribing physician. DUEXIS and VIMOVO face competition from other NSAIDs, including Celebrex®, marketed by Pfizer Inc., and celecoxib, a generic form of the medicine marketed by other pharmaceutical companies. DUEXIS and VIMOVO also face significant competition from the separate use of NSAIDs for pain relief and GI protective medications to reduce the risk of NSAID-induced upper GI ulcers. Both NSAIDs and GI protective medications are available in generic form and may be less expensive to use separately than DUEXIS or VIMOVO, despite such substitution being off-label in the case of DUEXIS and VIMOVO. Because pharmacists often have economic and other incentives to prescribe lower-cost generics, if physicians prescribe PENNSAID 2%, DUEXIS, or VIMOVO, those prescriptions may not result in sales. If physicians do not complete prescriptions through our HorizonCares program or otherwise provide prescribing instructions prohibiting generic diclofenac sodium topical solutions as a substitute for PENNSAID 2%, the substitution of generic ibuprofen and famotidine separately as a substitution for DUEXIS or generic naproxen and branded Nexium® (esomeprazole) as a substitute for VIMOVO, sales of PENNSAID 2%, DUEXIS and VIMOVO may suffer despite any success we may have in promoting PENNSAID 2%, DUEXIS or VIMOVO to physicians. In addition, other medicine candidates that contain ibuprofen and famotidine in combination or naproxen and esomeprazole in combination, while not currently known or FDA approved, may be developed and compete with DUEXIS or VIMOVO, respectively, in the future.

We have also entered into settlement and license agreements that may allow certain of our competitors to sell generic versions of certain of our medicines in the United States, subject to the terms of such agreements. We granted (i) a non-exclusive license (that is only royalty-bearing in some circumstances) to manufacture and commercialize a generic version of DUEXIS in the United States after October 17, 2027, (ii) non-exclusive licenses to manufacture and commercialize generic versions of PENNSAID 2% in the United States after January 10, 2029, (iii) a non-exclusive license to manufacture and commercialize a generic version of RAYOS tablets in the United States after December 23, 2022, (iv) a non-exclusive license to manufacture and commercialize a generic version of VIMOVO in the United States after January 1, 2025, and (v) non-exclusive licenses to manufacture and commercialize generic versions of RAVICTI in the United States after July 1, 2025, or earlier under certain circumstances.

Patent litigation is currently pending in the United States District Court for the District of New Jersey against Actavis Laboratories UT, Inc., formerly known as Watson Laboratories, Inc., Actavis, Inc. and Actavis plc, or collectively Actavis, who intend to market a generic version of PENNSAID 2% prior to the expiration of certain of our patents listed in the FDA's Orange Book, or the Orange Book. These cases arise from Paragraph IV Patent Certification notice letters from Actavis advising it had filed an ANDA with the FDA seeking approval to market a generic version of PENNSAID 2% before the expiration of the patents-in-suit.

Patent litigation is currently pending in the United States District Court for the District of New Jersey and the Court of Appeals for the Federal Circuit against several companies intending to market a generic version of VIMOVO before the expiration of certain of our patents listed in the Orange Book. These cases are collectively known as the VIMOVO cases, and involve the following sets of defendants: (i) Dr. Reddy's Laboratories Inc. and Dr. Reddy's Laboratories Ltd., or collectively Dr. Reddy's; (ii) Lupin Limited and Lupin Pharmaceuticals, Inc., or collectively Lupin; and (iii) Mylan Pharmaceuticals Inc., Mylan Laboratories Limited, and Mylan Inc., or collectively Mylan. The cases arise from Paragraph IV Patent Certification notice letters from each of Dr. Reddy's, Lupin and Mylan advising each had filed an ANDA with the FDA seeking approval to market generic versions of VIMOVO before the expiration of the patents-in-suit.

Patent litigation is currently pending in the United States District Court for the District of Delaware against Alkem Laboratories, Inc., or Alkem, who intends to market a generic version of DUEXIS prior to the expiration of certain of our patents listed in the Orange Book. This case arises from Paragraph IV Patent Certification notice letters from Alkem advising it had filed an ANDA with the FDA seeking approval to market a generic version of DUEXIS before the expiration of the patents-in-suit.

If we are unsuccessful in any of the VIMOVO cases, PENNSAID 2% cases or DUEXIS case, we will likely face generic competition with respect to VIMOVO, PENNSAID 2% and/or DUEXIS and sales of VIMOVO, PENNSAID 2% and/or DUEXIS will be substantially harmed.

ACTIMMUNE is the only medicine currently approved by the FDA specifically for the treatment of CGD and SMO. While there are additional or alternative approaches used to treat patients with CGD and SMO, there are currently no medicines on the market that compete directly with ACTIMMUNE. A widely accepted protocol to treat CGD in the United States is the use of concomitant "triple prophylactic therapy" comprising ACTIMMUNE, an oral antibiotic agent and an oral antifungal agent. However, the FDA-approved labeling for ACTIMMUNE does not discuss this "triple prophylactic therapy," and physicians may choose to prescribe one or both of the other modalities in the absence of ACTIMMUNE. Because of the immediate and life-threatening nature of SMO, the preferred treatment option for SMO is often to have the patient undergo a bone marrow transplant which, if successful, will likely obviate the need for further use of ACTIMMUNE in that patient. Likewise, the use of bone marrow transplants in the treatment of patients with CGD is becoming more prevalent, which could have a material adverse effect on sales of ACTIMMUNE and its profitability. We are aware of a number of research programs investigating the potential of gene therapy as a possible cure for CGD. Additionally, other companies may be pursuing the development of medicines and treatments that target the same diseases and conditions which ACTIMMUNE is currently approved to treat. As a result, it is possible that our competitors may develop new medicines that manage CGD or SMO more effectively, cost less or possibly even cure CGD or SMO. In addition, U.S. healthcare legislation passed in March 2010 authorized the FDA to approve biological products, known as biosimilars, that are similar to or interchangeable with previously approved biological products, like ACTIMMUNE, based upon potentially abbreviated data packages. Biosimilars are likely to be sold at substantially lower prices than branded medicines because the biosimilar manufacturer would not have to recoup the research and development and marketing costs associated with the branded medicine. Though we are not currently aware of any biosimilar under development, the development and commercialization of any competing medicines or the discovery of any new alternative treatment for CGD or SMO could have a material adverse effect on sales of ACTIMMUNE and its profitability.

BUPHENYL's composition of matter patent protection and orphan drug exclusivity have expired. Because BUPHENYL has no regulatory exclusivity or listed patents, there is nothing to prevent a competitor from submitting an ANDA for a generic version of BUPHENYL and receiving FDA approval. Generic versions of BUPHENYL to date have been priced at a discount relative to BUPHENYL or RAVICTI, and physicians, patients, or payers may decide that this less expensive alternative is preferable to BUPHENYL and RAVICTI. If this occurs, sales of BUPHENYL and/or RAVICTI could be materially reduced, but we would nevertheless be required to make royalty payments to Bausch Health Companies Inc. (formerly Ucyclyd Pharma, Inc.), or Bausch, and another external party, at the same royalty rates. While Bausch and its affiliates are generally contractually prohibited from developing or commercializing new medicines, anywhere in the world, for the treatment of UCD or hepatic encephalopathy, or HE, which are chemically similar to RAVICTI, they may still develop and commercialize medicines that compete with RAVICTI. For example, medicines approved for indications other than UCD and HE may still compete with RAVICTI if physicians prescribe such medicines off-label for UCD or HE. We are also aware that Orphan Europe SARL, or Orphan Europe, is conducting a clinical trial of carglumic acid to assess the short-term (three-day) efficacy of hyperammonemia in some of the UCD enzyme deficiencies for which RAVICTI is approved for chronic treatment. Carglumic acid is approved for maintenance therapy for chronic hyperammonemia and to treat hyperammonenic crises in Nacetylglutamate synthase deficiency, a rare UCD subtype, and is sold under the name Carbaglu. If the results of this trial are successful and Orphan Europe is able to complete development and obtain approval of Carbaglu to treat additional UCD enzyme deficiencies, RAVICTI would face additional competition from this compound.

The availability and price of our competitors' medicines could limit the demand, and the price we are able to charge, for our medicines. We will not successfully execute on our business objectives if the market acceptance of our medicines is inhibited by price competition, if physicians are reluctant to switch from existing medicines to our medicines, or if physicians switch to other new medicines or choose to reserve our medicines for use in limited patient populations.

In addition, established pharmaceutical companies may invest heavily to accelerate discovery and development of novel compounds or to acquire novel compounds that could make our medicines obsolete. Our ability to compete successfully with these companies and other potential competitors will depend largely on our ability to leverage our experience in clinical, regulatory and commercial development to:

- develop and acquire medicines that are superior to other medicines in the market;
- attract qualified clinical, regulatory, and sales and marketing personnel;
- obtain patent and/or other proprietary protection for our medicines and technologies;
- obtain required regulatory approvals; and
- successfully collaborate with pharmaceutical companies in the discovery, development and commercialization of new medicine candidates.

If we are unable to maintain or realize the benefits of orphan drug exclusivity, we may face increased competition with respect to certain of our medicines.

Under the Orphan Drug Act of 1983, the FDA may designate a medicine as an orphan drug if it is a drug intended to treat a rare disease or condition affecting fewer than 200,000 people in the United States. A company that first obtains FDA approval for a designated orphan drug for the specified rare disease or condition receives orphan drug marketing exclusivity for that drug for a period of seven years from the date of its approval. RAVICTI and PROCYSBI have been granted orphan drug exclusivity by the FDA, which we expect will provide orphan drug marketing exclusivity in the United States until February 2020 and December 2020, respectively, with exclusivity for PROCYSBI extending to 2022 for patients ages one to six years. In addition, teprotumumab has been granted orphan drug designation for treatment of active (dynamic) phase Graves' orbitopathy and, if approved by the FDA for that indication, would be eligible for seven years of marketing exclusivity in the United States following such approval. However, despite orphan drug exclusivity, the FDA can still approve another drug containing the same active ingredient and used for the same orphan indication if it determines that a subsequent drug is safer, more effective or makes a major contribution to patient care, and orphan exclusivity can be lost if the orphan drug manufacturer is unable to ensure that a sufficient quantity of the orphan drug is available to meet the needs of patients with the rare disease or condition. Orphan drug exclusivity may also be lost if the FDA later determines that the initial request for designation was materially defective. In addition, orphan drug exclusivity does not prevent the FDA from approving competing drugs for the same or similar indication containing a different active ingredient. If orphan drug exclusivity is lost and we were unable to successfully enforce any remaining patents covering RAVICTI or PROCYSBI, we could be subject to generic competition and revenues from RAVICTI or PROCYSBI could decrease materially. In addition, if a subsequent drug is approved for marketing for the same or a similar indication as RAVICTI or PROCYSBI despite orphan drug exclusivity, we may face increased competition and lose market share with respect to these medicines.

Our business operations may subject us to numerous commercial disputes, claims and/or lawsuits and such litigation may be costly and time-consuming and could materially and adversely impact our financial position and results of operations.

Operating in the pharmaceutical industry, particularly the commercialization of medicines, involves numerous commercial relationships, complex contractual arrangements, uncertain intellectual property rights, potential product liability and other aspects that create heightened risks of disputes, claims and lawsuits. In particular, we may face claims related to the safety of our medicines, intellectual property matters, employment matters, tax matters, commercial disputes, competition, sales and marketing practices, environmental matters, personal injury, insurance coverage and acquisition or divestiture-related matters. Any commercial dispute, claim or lawsuit may divert management's attention away from our business, we may incur significant expenses in addressing or defending any commercial dispute, claim or lawsuit, and we may be required to pay damage awards or settlements or become subject to equitable remedies that could adversely affect our operations and financial results.

We are currently in litigation with multiple generic drug manufacturers regarding intellectual property infringement. For example, we are currently involved in Hatch Waxman litigation with generic drug manufacturers related to DUEXIS, PENNSAID 2% and VIMOVO.

Similarly, from time to time we are involved in disputes with distributors, PBMs and licensing partners regarding our rights and performance of obligations under contractual arrangements. For example, we were previously in litigation with Express Scripts related to alleged breach of contract claims.

Litigation related to these disputes may be costly and time-consuming and could materially and adversely impact our financial position and results of operations if resolved against us.

A variety of risks associated with operating our business and marketing our medicines internationally could adversely affect our business.

In addition to our U.S. operations, we have operations in Ireland, Bermuda, the Grand Duchy of Luxembourg, or Luxembourg, Switzerland, Germany, Canada and in Israel (through Andromeda Biotech Ltd). RAVICTI received marketing authorization from Health Canada, or HC, in March 2016 and we launched RAVICTI in Canada in November 2016. PROCYSBI received marketing authorization from HC in June 2017 and we launched PROCYSBI in Canada in October 2017. BUPHENYL is currently marketed in Japan by Orphan Pacific. QUINSAIR received marketing authorization from HC in June 2015 and we launched QUINSAIR in Canada in December 2016. We face risks associated with our international operations, including possible unfavorable regulatory, pricing and reimbursement, political, tax and labor conditions, which could harm our business. We are subject to numerous risks associated with international business activities, including:

- compliance with differing or unexpected regulatory requirements for our medicines;
- compliance with Irish laws and the maintenance of our Irish tax residency with respect to our overall corporate structure and administrative operations, including the need to generally hold meetings of our board of directors and make decisions in Ireland, which may make certain corporate actions more cumbersome, costly and time-consuming;
- difficulties in staffing and managing foreign operations;
- in certain circumstances, including with respect to the commercialization of DUEXIS in Mexico and Chile, increased dependence on the commercialization efforts and regulatory compliance of third-party distributors or strategic partners;
- foreign government taxes, regulations and permit requirements;
- U.S. and foreign government tariffs, trade restrictions, price and exchange controls and other regulatory requirements;
- anti-corruption laws, including the Foreign Corrupt Practices Act, or the FCPA;
- economic weakness, including inflation, natural disasters, war, events of terrorism or political instability in particular foreign countries;
- fluctuations in currency exchange rates, which could result in increased operating expenses and reduced revenues, and other obligations related to doing business in another country;
- compliance with tax, employment, immigration and labor laws, regulations and restrictions for employees living or traveling abroad;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad;
- changes in diplomatic and trade relationships; and
- challenges in enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States.

Our business activities outside of the United States are subject to the FCPA and similar anti-bribery or anti-corruption laws, regulations or rules of other countries in which we operate, including the United Kingdom's Bribery Act 2010, or the U.K. Bribery Act. The FCPA and similar anti-corruption laws generally prohibit offering, promising, giving, or authorizing others to give anything of value, either directly or indirectly, to non-U.S. government officials in order to improperly influence any act or decision, secure any other improper advantage, or obtain or retain business. The FCPA also requires public companies to make and keep books and records that accurately and fairly reflect the transactions of the company and to devise and maintain an adequate system of internal accounting controls. The U.K. Bribery Act prohibits giving, offering, or promising bribes to any person, including non-United Kingdom, or U.K., government officials and private persons, as well as requesting, agreeing to receive, or accepting bribes from any person. In addition, under the U.K. Bribery Act, companies which carry on a business or part of a business in the U.K. may be held liable for bribes given, offered or promised to any person, including non-U.K. government officials and private persons, by employees and persons associated with the company in order to obtain or retain business or a business advantage for the company. Liability is strict, with no element of a corrupt state of mind, but a defense of having in place adequate procedures designed to prevent bribery is available. Furthermore, under the U.K. Bribery Act there is no exception for facilitation payments. As described above, our business is heavily regulated and therefore involves significant interaction with public officials, including officials of non-U.S. governments. Additionally, in many other countries, the health care providers who prescribe pharmaceuticals are employed by their government, and the purchasers of pharmaceuticals are government entities; therefore, any dealings with these prescribers and purchasers may be subject to regulation under the FCPA. Recently the SEC and the U.S. Department of Justice have increased their FCPA enforcement activities with respect to pharmaceutical companies. In addition, under the Dodd–Frank Wall Street Reform and Consumer Protection Act, private individuals who report to the SEC original information that leads to successful enforcement actions may be eligible for a monetary award. We are engaged in ongoing efforts that are designed to ensure our compliance with these laws, including due diligence, training, policies, procedures and internal controls. However, there is no certainty that all employees and third-party business partners (including our distributors, wholesalers, agents, contractors, and other partners) will comply with anti-bribery laws. In particular, we do not control the actions of manufacturers and other third-party agents, although we may be liable for their actions. Violation of these laws may result in civil or criminal sanctions, which could include monetary fines, criminal penalties, and disgorgement of past profits, which could have a material adverse impact on our business and financial condition.

We are subject to tax audits around the world, and such jurisdictions may assess additional income tax against us. Although we believe our tax positions are reasonable, the final determination of tax audits could be materially different from our recorded income tax provisions and accruals. The ultimate results of an audit could have a material adverse effect on our operating results or cash flows in the period or periods for which that determination is made and could result in increases to our overall tax expense in subsequent periods.

These and other risks associated with our international operations may materially adversely affect our business, financial condition and results of operations.

If we fail to develop or acquire other medicine candidates or medicines, our business and prospects would be limited.

A key element of our strategy is to develop or acquire and commercialize a portfolio of other medicines or medicine candidates in addition to our current medicines, through business or medicine acquisitions. Because we do not engage in proprietary drug discovery, the success of this strategy depends in large part upon the combination of our regulatory, development and commercial capabilities and expertise and our ability to identify, select and acquire approved or clinically enabled medicine candidates for therapeutic indications that complement or augment our current medicines, or that otherwise fit into our development or strategic plans on terms that are acceptable to us. Identifying, selecting and acquiring promising medicines or medicine candidates requires substantial technical, financial and human resources expertise. Efforts to do so may not result in the actual acquisition or license of a particular medicine or medicine candidate, potentially resulting in a diversion of our management's time and the expenditure of our resources with no resulting benefit. If we are unable to identify, select and acquire suitable medicines or medicine candidates from third parties or acquire businesses at valuations and on other terms acceptable to us, or if we are unable to raise capital required to acquire businesses or new medicines, our business and prospects will be limited.

Moreover, any medicine candidate we acquire may require additional, time-consuming development or regulatory efforts prior to commercial sale or prior to expansion into other indications, including pre-clinical studies if applicable, and extensive clinical testing and approval by the FDA and applicable foreign regulatory authorities. All medicine candidates are prone to the risk of failure that is inherent in pharmaceutical medicine development, including the possibility that the medicine candidate will not be shown to be sufficiently safe and/or effective for approval by regulatory authorities. In addition, we cannot assure that any such medicines that are approved will be manufactured or produced economically, successfully commercialized or widely accepted in the marketplace or be more effective or desired than other commercially available alternatives.

In addition, if we fail to successfully commercialize and further develop our medicines, there is a greater likelihood that we will fail to successfully develop a pipeline of other medicine candidates to follow our existing medicines or be able to acquire other medicines to expand our existing portfolio, and our business and prospects would be harmed.

Our prior medicine and company acquisitions and any other strategic transactions that we may pursue in the future could have a variety of negative consequences, and we may not realize the benefits of such transactions or attempts to engage in such transactions.

We have completed multiple medicine and company acquisitions and our strategy is to engage in additional strategic transactions with third parties, such as acquisitions of companies or divisions of companies and asset purchases of medicines, medicine candidates or technologies that we believe will complement or augment our existing business. We may also consider a variety of other business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and other investments. Any such transaction may require us to incur non-recurring and other charges, increase our near and long-term expenditures, pose significant integration challenges, create additional tax, legal, accounting and operational complexities in our business, require additional expertise, result in dilution to our existing shareholders and disrupt our management and business, which could harm our operations and financial results. For example, we assumed responsibility for the patent infringement litigation with respect to RAVICTI upon the closing of our acquisition of Hyperion Therapeutics, Inc., or Hyperion, and we have assumed responsibility for completing post-marketing clinical trials of RAVICTI that are required by the FDA, one of which is ongoing.

In connection with our acquisition of Raptor Pharmaceutical Corp., or Raptor, we assumed contractual obligations under agreements with Tripex Pharmaceuticals, LLC, or Tripex, and PARI Pharma GmbH, or PARI, related to QUINSAIR. Under the agreement with Tripex, as amended, if we do not spend a specified amount on the development of QUINSAIR for non-cystic fibrosis, or CF, indications between January 1, 2018 and December 31, 2021 and if regulatory approval by the FDA for QUINSAIR for the CF indication is obtained prior to December 31, 2021, we may be obligated to pre-pay a milestone payment related to commercial sales of QUINSAIR for non-CF indications. This obligation is subject to certain exceptions due to, for example, manufacturing delays not under our control, or clinical trial suspension or delay ordered by the FDA. In October 2017, we triggered a milestone payment under this agreement and we paid Tripex $20.0 million in November 2017. Under the license agreement with PARI, we are required to comply with diligence milestones related to development and commercialization of QUINSAIR in the United States and to spend a specified minimum amount per year on development activities in the United States until submission of the new drug application, or NDA, for QUINSAIR in the United States. If we do not comply with these obligations, our licenses to certain intellectual property related to QUINSAIR may become non-exclusive in the United States or could be terminated. We are also subject to contractual obligations under an amended and restated license agreement with the Regents of the University of California, San Diego, or UCSD, as amended, with respect to PROCYSBI. To the extent that we fail to perform our obligations under the agreement, UCSD may, with respect to such indication, terminate the license or otherwise cause the license to become non-exclusive. If one or more of these licenses was terminated, we would have no further right to use or exploit the related intellectual property, which would limit our ability to develop PROCYSBI or QUINSAIR in other indications, and could impact our ability to continue commercializing PROCYSBI or QUINSAIR in their approved indications. In connection with our acquisition of the U.S. rights to VIMOVO, we assumed primary responsibility for the existing patent infringement litigation with respect to VIMOVO, and have also agreed to reimburse certain legal expenses of Nuvo (formerly Aralez Pharmaceuticals Inc.) with respect to its continued involvement in such litigation.

We face significant competition in seeking appropriate strategic transaction opportunities and the negotiation process for any strategic transaction can be time-consuming and complex. In addition, we may not be successful in our efforts to engage in certain strategic transactions because our financial resources may be insufficient and/or third parties may not view our commercial and development capabilities as being adequate. We may not be able to expand our business or realize our strategic goals if we do not have sufficient funding or cannot borrow or raise additional capital. There is no assurance that following any of our recent acquisition transactions or any other strategic transaction, we will achieve the anticipated revenues, net income or other benefits that we believe justify such transactions. In addition, any failures or delays in entering into strategic transactions anticipated by analysts or the investment community could seriously harm our consolidated business, financial condition, results of operations or cash flow.

We may not be able to successfully maintain our current advantageous tax status and resulting tax rates, which could adversely affect our business and financial condition, results of operations and growth prospects.

Our parent company is incorporated in Ireland and has subsidiaries maintained in multiple jurisdictions, including Ireland, the United States, Switzerland, Luxembourg, Germany, Canada and Bermuda. Prior to our merger transaction in September 2014 with Vidara Therapeutics International Public Limited Company, or Vidara, and such transaction, the Vidara Merger, Vidara was able to achieve a favorable tax rate through the performance of certain functions and ownership of certain assets in tax-efficient jurisdictions, including Ireland and Bermuda, together with intra-company service and transfer pricing agreements, each on an arm's length basis. We are continuing a substantially similar structure and arrangements. Nevertheless, our effective tax rate may be different than experienced in the past due to numerous factors, including passage of the Tax Act (as defined below), changes to the tax laws of jurisdictions that we operate in other than the United States, changes in the mix of our profitability from jurisdiction to jurisdiction, future changes to U.S. tax law (including for example, the enactment of new U.S. tax treaties or changes to existing tax treaties), the implementation of the EU Anti-Tax Avoidance Directive (see further discussion below), the implementation of the Bermuda Economic Substance Act of 2018 (effective after December 31, 2018) and our inability to secure or sustain acceptable agreements with tax authorities (if applicable). Any of these factors could cause us to experience an effective tax rate significantly different from previous periods or our current expectations. Taxing authorities, such as the U.S. Internal Revenue Service, or IRS, actively audit and otherwise challenge these types of arrangements, and have done so in the pharmaceutical industry. We expect that these challenges will continue as a result of the recent increase in scrutiny and political attention on corporate tax structures. The IRS and/or the Irish tax authorities may challenge our structure and transfer pricing arrangements through an audit or lawsuit. Responding to or defending such a challenge could be expensive and consume time and other resources, and divert management's time and focus from operating our business. We cannot predict whether taxing authorities will conduct an audit or file a lawsuit challenging this structure, the cost involved in responding to any such audit or lawsuit, or the outcome. If we are unsuccessful in defending such a challenge, we may be required to pay taxes for prior periods, interest, fines or penalties, and may be obligated to pay increased taxes in the future, any of which could require us to reduce our operating expenses, decrease efforts in support of our medicines or seek to raise additional funds, all of which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

The IRS may not agree with our conclusion that our parent company should be treated as a foreign corporation for U.S. federal income tax purposes following the combination of the businesses of Horizon Pharma, Inc., or HPI, and Vidara.

Although our parent company is incorporated in Ireland, the IRS may assert that it should be treated as a U.S. corporation (and, therefore, a U.S. tax resident) for U.S. federal income tax purposes pursuant to Section 7874 of the Internal Revenue Code of 1986, as amended, or the Code. A corporation is generally considered a tax resident in the jurisdiction of its organization or incorporation for U.S. federal income tax purposes. Because our parent company is an Irish incorporated entity, it would generally be classified as a foreign corporation (and, therefore, a non-U.S. tax resident) under these general rules. Section 7874 of the Code provides an exception pursuant to which a foreign incorporated entity may, in certain circumstances, be treated as a U.S. corporation for U.S. federal income tax purposes.

In July 2018, the IRS issued regulations under Section 7874 that finalized, with few changes, guidance that the IRS had previously issued in temporary form in 2016. We do not believe that our classification as a foreign corporation for U.S. federal income tax purposes is affected by Section 7874 or the regulations thereunder, though the IRS may disagree.

Recent and future changes to U.S. and non-U.S. tax laws could materially adversely affect our company.

Under current law, we expect our parent company to be treated as a foreign corporation for U.S. federal income tax purposes. However, changes to the rules in Section 7874 of the Code or regulations promulgated thereunder or other guidance issued by the U.S. Department of the Treasury, or the U.S. Treasury, or the IRS could adversely affect our parent company's status as a foreign corporation for U.S. federal income tax purposes or the taxation of transactions between members of our group, and any such changes could have prospective or retroactive application. If our parent company is treated as a domestic corporation, more of our income will be taxed by the United States which may substantially increase our effective tax rate.

In January 2017, the U.S. Treasury and the IRS issued final regulations that expand the scope of transactions subject to the rules designed to eliminate the U.S. tax benefits of so-called inversion transactions. Under the regulations, the former stockholders of U.S. corporations acquired by a foreign corporation within thirty-six months of the signing date of the last such acquisition are aggregated for the purpose of determining whether the foreign corporation will be treated as a domestic corporation for U.S. federal tax purposes because at least 80 percent of the stock of the foreign corporation is held by former stockholders of a U.S. corporation. The requirement to aggregate the stockholders in such acquisitions for the purpose of determining whether the 80 percent threshold is met may limit our ability to use our stock to acquire U.S. corporations or their assets in the future.

In addition, the Organization for Economic Co-operation and Development, or the OECD, released its Base Erosion and Profit Shifting project final report on October 5, 2015. This report provides the basis for international standards for corporate taxation that are designed to prevent, among other things, the artificial shifting of income to tax havens and low-tax jurisdictions, the erosion of the tax base through interest deductions on intra-company debt and the artificial avoidance of permanent establishments (i.e., tax nexus with a jurisdiction). Legislation to adopt these standards has been enacted or is currently under consideration in a number of jurisdictions. On June 7, 2017, several countries, including many countries that we operate and have subsidiaries in, participated in the signing ceremony adopting the OECD's Multilateral Convention to Implement Tax Treaty Related Measures to Prevent Base Erosion and Profit Shifting, commonly referred to as the MLI. The MLI came into effect on July 1, 2018. In January 2019, Ireland deposited the instrument of ratification of Ireland's MLI choices with the OECD. Ireland's MLI is expected to come into force on May 1, 2019. Depending on whether jurisdictions have ratified the MLI, the MLI could already, or may soon modify affected tax treaties making it more difficult for us to obtain advantageous tax-treaty benefits. The number of affected tax treaties could eventually be in the thousands. As a result, our income may be taxed in jurisdictions where it is not currently taxed and at higher rates of tax than it is currently taxed, which may substantially increase our effective tax rate.

On July 12, 2016, the Anti-Tax Avoidance Directive, or ATAD, was formally adopted by the Economic and Financial Affairs Council of the EU. The stated objective of the ATAD is to provide for the effective and swift coordinated implementation of anti-base erosion and profit shifting measures at EU level. Like all directives, the ATAD is binding as to the results it aims to achieve though EU Member States are free to choose the form and method of achieving those results. In addition, the ATAD contains a number of optional provisions that present an element of choice as to how it will be implemented into law. On December 25, 2018, the Finance Act 2018 was signed into Irish law, which introduced certain elements of the ATAD, such as the Controlled Foreign Company, or CFC, regime, into Irish law. The CFC regime became effective as of January 1, 2019. These legislative changes are not expected to have a material impact on our effective tax rate. The remaining provisions of the ATAD are expected to be incorporated into Irish law from 2020 onwards and, although it is difficult at this stage to determine with precision the impact that these remaining provisions will have, their implementation could materially increase our effective tax rate.

On December 22, 2017, U.S. federal income tax legislation was signed into law (H.R. 1, "An Act to provide for reconciliation pursuant to titles II and V of the concurrent resolution on the budget for fiscal year 2018", informally titled the Tax Cuts and Jobs Act, or the Tax Act) that significantly revises the Code in the United States. The Tax Act, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the tax deduction for interest expense to 30% of adjusted earnings (except for certain small businesses), implementation of a "base erosion anti-abuse tax" which requires U.S. corporations to make an alternative determination of taxable income without regard to tax deductions for certain payments to affiliates, taxation of certain non-U.S. corporations' earnings considered to be "global intangible low taxed income", or GILTI, repeal of the alternative minimum tax, or AMT, for corporations and changes to a taxpayer's ability to either utilize or refund the AMT credits previously generated, changes to the limitation on deductions for certain executive compensation particularly with respect to the removal of the previously allowed performance based compensation exception, changes in the attribution rules relating to shareholders of certain "controlled foreign corporations", limitation of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss carrybacks, one-time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing many business deductions and credits. For example, U.S. federal income tax law resulting in additional taxes owed by U.S. shareholders under the GILTI rules, together with Tax Act's change to the attribution rules related to "controlled foreign corporations" may discourage U.S. investors from owning or acquiring 10% or greater of our outstanding ordinary shares, which other shareholders may have viewed as beneficial or may otherwise negatively impact the trading price of our ordinary shares. We are unable to predict what federal tax law may be proposed or enacted in the future or what effect such changes would have on our business, but such changes, to the extent they are brought into tax legislation, regulations, policies or practices, could affect our effective tax rates in the future in countries where we have operations and have an adverse effect on our overall tax rate in the future, along with increasing the complexity, burden and cost of tax compliance. We urge our shareholders to consult with their legal and tax advisors with respect to this legislation and the potential tax consequences of investing in or holding our ordinary shares.

On December 20, 2018, the U.S. Treasury issued Proposed Regulations under Section 267A of the Code, or Section 267A Proposed Regulations, to clarify certain aspects of Section 267A (commonly referred to as the "Anti-Hybrid Rules"; rules enacted as part of the Tax Act). The 267A Proposed Regulations were the first administrative guidance on Section 267A and provided several rules which expanded the reach and scope of the Anti-Hybrid Rules particularly involving the payment of interest and royalties by certain branches, reverse hybrid entities, and other hybrid mismatch arrangements. While 267A as enacted under the Tax Act, does not appear to apply to the Company, the guidance and scope of the 267A Proposed Regulations with respect to Anti-Hybrid Rules may apply to the Company. We are currently in the process of assessing the provisions set forth in the 267A Proposed Regulations and their potential impact on the Company. To the extent that the Anti-Hybrid Rules are applicable to the Company, absent certain actions taken by the Company to restructure its intercompany financing arrangements, such application would have a material impact on our effective tax rate if and when the Section 267A Proposed Regulations become final as currently drafted.

If a United States person is treated as owning at least 10% of our ordinary shares, such holder may be subject to adverse U.S. federal income tax consequences.

If a United States person is treated as owning (directly, indirectly, or constructively) at least 10% of the value or voting power of our ordinary shares, such person may be treated as a "United States shareholder" with respect to each "controlled foreign corporation" in our group (if any). Because our group includes one or more U.S. subsidiaries, certain of our non-U.S. subsidiaries could be treated as controlled foreign corporations (regardless of whether or not we are treated as a controlled foreign corporation). A United States shareholder of a controlled foreign corporation may be required to report annually and include in its U.S. taxable income its pro rata share of "Subpart F income," "global intangible low-taxed income," and investments in U.S. property by controlled foreign corporations, regardless of whether we make any distributions. An individual that is a United States shareholder with respect to a controlled foreign corporation generally would not be allowed certain tax deductions or foreign tax credits that would be allowed to a United States shareholder that is a U.S. corporation. Failure to comply with these reporting and tax paying obligations may subject a United States shareholder to significant monetary penalties and may prevent the statute of limitations from starting with respect to such shareholder's U.S. federal income tax return for the year for which reporting was due. We cannot provide any assurances that we will assist investors in determining whether any of our non-U.S. subsidiaries is treated as a controlled foreign corporation or whether any investor is treated as a United States shareholder with respect to any such controlled foreign corporation or furnish to any United States shareholders information that may be necessary to comply with the aforementioned reporting and tax paying obligations. A United States investor should consult its advisors regarding the potential application of these rules to an investment in our ordinary shares.

If we are not successful in attracting and retaining highly qualified personnel, we may not be able to successfully implement our business strategy.

Our ability to compete in the highly competitive biotechnology and pharmaceuticals industries depends upon our ability to attract and retain highly qualified managerial, scientific and medical personnel. We are highly dependent on our management, sales and marketing and scientific and medical personnel, including our executive officers composed of our Chairman, President and Chief Executive Officer, Timothy P. Walbert; our Executive Vice President, Chief Business Officer, Robert F. Carey; our Executive Vice President, Chief Financial Officer, Paul W. Hoelscher; our Executive Vice President, Chief Administrative Officer, Barry J. Moze; our Executive Vice President, Head of Research and Development and Chief Scientific Officer, Shao-Lee Lin, M.D., Ph.D; our Executive Vice President, Chief Commercial Officer, Vikram Karnani; our Executive Vice President, Chief Human Resources Officer, Irina P. Konstantinovsky; our Executive Vice President, General Counsel, Brian K. Beeler; our Executive Vice President, Technical Operations, Michael A. DesJardin and our Executive Vice President, Corporate Affairs, Chief Communications Officer, Geoffrey M. Curtis and Senior Vice President, Head of Medical Affairs and Outcomes Research, Jeffrey Kent, M.D., FACP, FACG. In order to retain valuable employees at our company, in addition to salary and annual cash incentives, we provide a mix of performance stock units, or PSUs, that vest subject to attainment of specified corporate performance goals and continued services, stock options and restricted stock units, or RSUs, that vest over time subject to continued services. The value to employees of PSUs, stock options and RSUs will be significantly affected by movements in our share price that are beyond our control, and may at any time be insufficient to counteract more lucrative offers from other companies.

Despite our efforts to retain valuable employees, members of our management, sales and marketing, regulatory affairs, clinical development, medical affairs and development teams may terminate their employment with us on short notice. Although we have written employment arrangements with all of our employees, these employment arrangements generally provide for at-will employment, which means that our employees can leave our employment at any time, with or without notice. The loss of the services of any of our executive officers or other key employees and our inability to find suitable replacements could potentially harm our business, financial condition and prospects. We do not maintain "key man" insurance policies on the lives of these individuals or the lives of any of our other employees. Our success also depends on our ability to continue to attract, retain and motivate highly skilled junior, mid-level, and senior managers as well as junior, mid-level, and senior sales and marketing and scientific and medical personnel.

Many of the other biotechnology and pharmaceutical companies with whom we compete for qualified personnel have greater financial and other resources, different risk profiles and longer histories in the industry than we do. They also may provide more diverse opportunities and better chances for career advancement. Some of these characteristics may be more appealing to high quality candidates than that which we have to offer. If we are unable to continue to attract and retain high quality personnel, the rate and success at which we can develop and commercialize medicines and medicine candidates will be limited.

We are, with respect to our current medicines, and will be, with respect to any other medicine or medicine candidate for which we obtain FDA or EMA approval or which we acquire, subject to ongoing FDA or EMA obligations and continued regulatory review, which may result in significant additional expense. Additionally, any other medicine candidate, if approved by the FDA or the EMA, could be subject to labeling and other restrictions and market withdrawal, and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our medicines.

Any regulatory approvals that we obtain for our medicine candidates may also be subject to limitations on the approved indicated uses for which the medicine may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials and surveillance to monitor the safety and efficacy of the medicine candidate. In addition, with respect to our current FDA-approved medicines (and with respect to our medicine candidates, if approved), the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for the medicine are subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMPs, GCPs, International Council for Harmonisation, or ICH, guidelines and GLPs, which are regulations and guidelines enforced by the FDA for all of our medicines in clinical development, for any clinical trials that we conduct post-approval. With respect to RAVICTI, the FDA imposed several post-marketing requirements and a post-marketing commitment, which included obligations to conduct studies in UCD patients during the first two months of life, including a study of the pharmacokinetics in that age group and a randomized study to determine the safety and efficacy in UCD patients who are treatment naïve to phenylbutyrate treatment. In May 2017, the FDA approved our supplemental new drug application, or sNDA, for RAVICTI to expand the age range for chronic management of UCDs from two years of age and older to two months of age and older. In December 2018, we received FDA approval to expand the age range for the use of RAVICTI in the chronic management of UCDs in patients from birth to two months and as a result, we now have approval for patients of all ages. As part of these approvals to expand the age range for use of RAVICTI in the chronic management of UCDs in patients from birth, we have fulfilled, and subsequently received FDA confirmation of release from the requirement to conduct studies in UCD patients during the first two months of life. We are currently conducting a study to determine the effects of RAVICTI in patients with UCDs that are treatment naïve to phenylbutyrate.

In addition, the FDA closely regulates the marketing and promotion of drugs and biologics. The FDA does not regulate the behaviour of physicians in their choice of treatments. The FDA does, however, restrict manufacturers' promotional communications. A significant number of pharmaceutical companies have been the target of inquiries and investigations by various U.S. federal and state regulatory, investigative, prosecutorial and administrative entities in connection with the promotion of medicines for off-label uses and other sales practices. These investigations have alleged violations of various U.S. federal and state laws and regulations, including claims asserting antitrust violations, violations of the Food, Drug and Cosmetic Act, false claims laws, the Prescription Drug Marketing Act, anti-kickback laws, and other alleged violations in connection with the promotion of medicines for unapproved uses, pricing and Medicare and/or Medicaid reimbursement. While Congress has recently considered legislation that would modify or eliminate restrictions for off-label promotion, we do not have sufficient information to anticipate if the current regulatory environment will change.

Later discovery of previously unknown problems with a medicine, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on the marketing or manufacturing of the medicine, withdrawal of the medicine from the market, or voluntary or mandatory medicine recalls;
- refusal by the FDA to approve pending applications or supplements to approved applications filed by us or our strategic partners, or suspension or revocation of medicine license approvals;
- medicine seizure or detention, or refusal to permit the import or export of medicines; and
- injunctions, the imposition of civil or criminal penalties, or exclusion, debarment or suspension from government healthcare programs.

If we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would have a material adverse effect on our business, results of operations, financial condition and prospects.

We are subject to federal, state and foreign healthcare laws and regulations and implementation or changes to such healthcare laws and regulations could adversely affect our business and results of operations.

The United States and some foreign jurisdictions are considering or have enacted a number of legislative and regulatory proposals to regulate and to change the healthcare system in ways that could affect our ability to sell our medicines profitably. In the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs (including a number of proposals pertaining to prescription drugs, specifically), improving quality and/or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives.

If we are found to be in violation of any of these laws or any other federal or state regulations, we may be subject to civil and/or criminal penalties, damages, fines, exclusion, additional reporting requirements and/or oversight from federal health care programs and the restructuring of our operations. Any of these could have a material adverse effect on our business and financial results. Since many of these laws have not been fully interpreted by the courts, there is an increased risk that we may be found in violation of one or more of their provisions. Any action against us for violation of these laws, even if we ultimately are successful in our defense, will cause us to incur significant legal expenses and divert our management's attention away from the operation of our business.

In January 2017, the United States House of Representatives and Senate passed legislation, the concurrent budget resolution for fiscal year 2017, which initiates actions that would repeal certain aspects of the ACA. Further, on January 20, 2017, U.S. President Donald Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA, to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. In May 2017, following the passage of the budget resolution for fiscal year 2017, the U.S. House of Representatives passed legislation known as the American Health Care Act, which, if enacted, would have amended and repealed significant portions of the ACA. The U.S. Senate considered but did not adopt other legislation to amend and/or replace elements of the ACA and authority to act under the fiscal year 2017 budget resolution expired on September 30, 2017. However, on October 12, 2017, U.S. President Donald Trump signed another Executive Order directing certain federal agencies to propose regulations or guidelines to permit small businesses to form association health plans, expand the availability of short-term, limited duration insurance, and expand the use of health reimbursement arrangements, which may circumvent some of the requirements for health insurance mandated by the ACA. In addition, citing legal guidance from the U.S. Department of Justice and the HHS, the Trump administration has concluded that cost-sharing reduction, or CSR, payments to insurance companies required under the ACA have not received necessary appropriations from Congress and announced that it will discontinue these payments immediately until such appropriations are made. The loss of the CSR payments is expected to increase premiums on certain policies issued by qualified health plans under the ACA. Finally, while Congress has not passed comprehensive ACA repeal or replace legislation, the federal income tax legislation signed into law on December 22, 2017 includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate". We continue to evaluate the effect that the ACA, relevant legal challenges and additional actions by Congress to possibly repeal and replace it has on our business.

Likewise, in the countries in the EU, legislators, policymakers and healthcare insurance funds continue to propose and implement cost-containing measures to keep healthcare costs down, due in part to the attention being paid to healthcare cost containment in the EU. Certain of these changes could impose limitations on the prices we will be able to charge for our products and any approved product candidates or the amounts of reimbursement available for these products from governmental agencies or third party payers, may increase the tax obligations on pharmaceutical companies such as ours, or may facilitate the introduction of generic competition with respect to our products.

In addition, drug pricing by pharmaceutical companies has come under increased scrutiny. Specifically, there have been several recent state and U.S. Congressional inquiries, proposed federal and state legislation and state laws enacted designed to, among other things, bring more transparency to drug pricing by requiring drug companies to notify insurers and government regulators of price increases and provide an explanation of the reasons for the increase, reduce the out-of-pocket cost of prescription drugs, review the relationship between pricing and manufacturer patient programs, reduce the cost of drugs under Medicare, and reform government program reimbursement methodologies. For example, legislation was recently signed into law in California that requires drug manufactures to provide advance notice and explanation to state regulators, health plans and insurers and PBMs for price increases of more than 16% over two years. Moreover, in May 2018, the Trump administration released its "Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs", or Blueprint. The Blueprint contains several potential regulatory actions and legislative recommendations aimed at lowering prescription drug prices including measures to promote innovation and competition for biologics, changes to Medicare Part D to give plan sponsors more leverage when negotiating prices with manufacturers and updating the Medicare drug-pricing dashboard to make price increases and generic competition more transparent. In addition, HHS released a Request for Information, or RFI, soliciting public input on ways to lower drug pricing. Together, the recommendations in the Blueprint and RFI, if enacted by Congress and HHS, could lead to changes to Medicare Parts B and D. Further, the Bipartisan Budget Act of 2018, among other things, amends the ACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole". The majority of our medicines are purchased by private payers, and much of the focus of pending legislation is on government program reimbursement. However, we cannot know what form any such action may take, the likelihood it would be executed, enacted, effectuated or implemented or the market's perception of how such legislation would affect us. Any reduction in reimbursement from government programs may result in a similar reduction in payments from private payers. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our current medicines and/or those for which we may receive regulatory approval in the future.

We are subject, directly or indirectly, to federal and state healthcare fraud and abuse, transparency laws and false claims laws. Prosecutions under such laws have increased in recent years and we may become subject to such litigation. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

In the United States, we are subject directly, or indirectly or through our customers, to various state and federal fraud and abuse and transparency laws, including, without limitation, the federal Anti-Kickback Statute, the federal False Claims Act, civil monetary penalty statutes prohibiting beneficiary inducements, and similar state and local laws, federal and state privacy and security laws, sunshine laws, government price reporting laws, and other fraud laws. Some states, such as Massachusetts, make certain reported information public. In addition, there are state and local laws that require pharmaceutical representatives to be licensed and comply with codes of conduct, transparency reporting, and other obligations. Collectively, these laws may affect, among other things, our current and proposed sales, marketing and educational programs, as well as other possible relationships with customers, pharmacies, physicians, payers, and patients. We are subject to similar laws in the EU/EEA, including the EU General Data Protection Regulation (2016/679), or GDPR, under which fines of up to €20.0 million or up to 4% of the annual global turnover of the infringer, whichever is greater, could be imposed for significant non-compliance.

Compliance with these laws, including the development of a comprehensive compliance program, is difficult, costly and time consuming. Because of the breadth of these laws and the narrowness of available statutory and regulatory exemptions, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Moreover, state governmental agencies may propose or enact laws and regulations that extend or contradict federal requirements. These risks may be increased where there are evolving interpretations of applicable regulatory requirements, such as those applicable to manufacturer co-pay initiatives. Pharmaceutical manufacturer co-pay initiatives and free medicine programs are the subject of ongoing litigation (involving other manufacturers and to which we are not a party) and evolving interpretations of applicable regulatory requirements and certain state laws, and any change in the regulatory or enforcement environment regarding such programs could impact our ability to offer such programs. If we are unsuccessful with our HorizonCares programs, any other co-pay initiatives or free medicine programs, we would be at a competitive disadvantage in terms of pricing versus preferred branded and generic competitors, or be subject to significant penalties. We are engaged in various business arrangements with current and potential customers, and we can give no assurance that such arrangements would not be subject to scrutiny under such laws, despite our efforts to properly structure such arrangements. Even if we structure our programs with the intent of compliance with such laws, there can be no certainty that we would not need to defend our business activities against enforcement or litigation. Further, we cannot give any assurances that prior business activities or arrangements of other companies that we acquire will not be scrutinized or subject to enforcement or litigation.

There has also been a trend of increased federal and state regulation of payments made to physicians and other healthcare providers. The ACA, among other things, imposed reporting requirements on drug manufacturers for payments made by them to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit required information may result in significant civil monetary penalties.

We are unable to predict whether we could be subject to actions under any of these or other healthcare laws, or the impact of such actions. If we are found to be in violation of, or to encourage or assist the violation by third parties of any of the laws described above or other applicable state and federal fraud and abuse laws, we may be subject to penalties, including administrative, civil and criminal penalties, damages, fines, withdrawal of regulatory approval, imprisonment, exclusion from government healthcare reimbursement programs, contractual damages, reputational harm, diminished profits and future earnings, injunctions and other associated remedies, or private "qui tam" actions brought by individual whistleblowers in the name of the government, and the curtailment or restructuring of our operations, all of which could have a material adverse effect on our business and results of operations. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business.

Our medicines or any other medicine candidate that we develop may cause undesirable side effects or have other properties that could delay or prevent regulatory approval or commercialization, result in medicine re-labeling or withdrawal from the market or have a significant impact on customer demand.

Undesirable side effects caused by any medicine candidate that we develop could result in the denial of regulatory approval by the FDA or other regulatory authorities for any or all targeted indications, or cause us to evaluate the future of our development programs. With respect to RAVICTI, the most common side effects are diarrhea, nausea, decreased appetite, gas, vomiting, high blood levels of ammonia, headache, tiredness and dizziness. With respect to PROCYSBI, the most common side effects include vomiting, nausea, abdominal pain, breath odor, diarrhea, skin odor, fatigue, rash and headache. The most common side effects observed in pivotal trials for ACTIMMUNE were "flu-like" or constitutional symptoms such as fever, headache, chills, myalgia and fatigue. With respect to BUPHENYL, the most common side effects are change in the frequency of breathing, lack of or irregular menstruation, lower back, side, or stomach pain, mood or mental changes, muscle pain or twitching, nausea or vomiting, nervousness or restlessness, swelling of the feet or lower legs, unpleasant taste and unusual tiredness or weakness. With respect to QUINSAIR, the most common side effects include itching, wheezing, hives, rash, swelling, pale skin color, fast heartbeat and faintness. With respect to KRYSTEXXA, the most commonly reported serious adverse reactions in the pivotal trial were gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis, exacerbation of pre-existing congestive heart failure and vomiting. The most commonly reported treatment-emergent adverse events in the Phase 3 clinical trials with RAYOS included flare in rheumatoid arthritis related symptoms, abdominal pain, nasopharyngitis, headache, flushing, upper respiratory tract infection, back pain and weight gain. The most common adverse events reported in a Phase 2 clinical trial of PENNSAID 2% were application site reactions, such as dryness, exfoliation, erythema, pruritus, pain, induration, rash and scabbing. In our two Phase 3 clinical trials with DUEXIS, the most commonly reported treatment-emergent adverse events were nausea, dyspepsia, diarrhea, constipation and upper respiratory tract infection. In Phase 3 endoscopic registration clinical trials with VIMOVO, the most commonly reported treatment-emergent adverse events were erosive gastritis, dyspepsia, gastritis, diarrhea, gastric ulcer, upper abdominal pain, nausea and upper respiratory tract infection. With respect to MIGERGOT, the most commonly reported adverse reactions are ischemia, cyanosis, absence of pulse, cold extremities, gangrene, precordial distress and pain, electrocardiogram change, muscle pain, nausea and vomiting, rectal or anal ulcer, parathesias, numbness weakness, vertigo, localized edemas and itching.

The FDA or other regulatory authorities may also require, or we may undertake, additional clinical trials to support the safety profile of our medicines or medicine candidates.

In addition, if we or others identify undesirable side effects caused by our medicines or any other medicine candidate that we may develop that receives marketing approval, or if there is a perception that the medicine is associated with undesirable side effects:

- regulatory authorities may require the addition of labeling statements, such as a "black box" warning or a contraindication;
- regulatory authorities may withdraw their approval of the medicine or place restrictions on the way it is prescribed;
- we may be required to change the way the medicine is administered, conduct additional clinical trials or change the labeling of the medicine or implement a risk evaluation and mitigation strategy; and

- we may be subject to increased exposure to product liability and/or personal injury claims.

If any of these events occurred with respect to our medicines, our ability to generate significant revenues from the sale of these medicines would be significantly harmed.

We rely on third parties to conduct our pre-clinical and clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines or if they experience regulatory compliance issues, we may not be able to obtain regulatory approval for or commercialize our medicine candidates and our business could be substantially harmed.

We have agreements with third-party contract research organizations, or CROs, to conduct our clinical programs, including those required for post-marketing commitments, and we expect to continue to rely on CROs for the completion of on-going and planned clinical trials. We may also have the need to enter into other such agreements in the future if we were to develop other medicine candidates or conduct clinical trials in additional indications for our existing medicines. We have an agreement in place with Syneos Health, Inc. in connection with our Phase 3 confirmatory trial to evaluate teprotumumab for the treatment of thyroid eye disease. In connection with our ongoing study to evaluate RAYOS on the fatigue experienced by SLE patients, we are collaborating with the ALR. We also rely heavily on these parties for the execution of our clinical studies and control only certain aspects of their activities. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol. We, our CROs and our academic research organizations are required to comply with current GCP or ICH regulations. The FDA enforces these GCP or ICH regulations through periodic inspections of trial sponsors, principal investigators and trial sites. If we or our CROs or collaborators fail to comply with applicable GCP or ICH regulations, the data generated in our clinical trials may be deemed unreliable and our submission of marketing applications may be delayed or the FDA may require us to perform additional clinical trials before approving our marketing applications. We cannot assure that, upon inspection, the FDA will determine that any of our clinical trials comply or complied with GCP or ICH regulations. In addition, our clinical trials must be conducted with medicine produced under cGMP regulations, and may require a large number of test subjects. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. Moreover, our business may be implicated if any of our CROs or collaborators violates federal or state fraud and abuse or false claims laws and regulations or healthcare privacy and security laws. We must also obtain certain third-party institutional review board, or IRB, and ethics committee approvals in order to conduct our clinical trials. Delays by IRBs and ethics committees in providing such approvals may delay our clinical trials.

If any of our relationships with these third-party CROs or collaborators terminate, we may not be able to enter into similar arrangements on commercially reasonable terms, or at all. If CROs or collaborators do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our medicines and medicine candidates. As a result, our results of operations and the commercial prospects for our medicines and medicine candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed.

Switching or adding additional CROs or collaborators can involve substantial cost and require extensive management time and focus. In addition, there is a natural transition period when a new CRO or collaborator commences work. As a result, delays may occur, which can materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our CROs and collaborators, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition or prospects.

Clinical development of drugs and biologics involves a lengthy and expensive process with an uncertain outcome, and results of earlier studies and trials may not be predictive of future trial results.

Clinical testing is expensive and can take many years to complete, and its outcome is uncertain. Failure can occur at any time during the clinical trial process. The results of pre-clinical studies and early clinical trials of potential medicine candidates may not be predictive of the results of later-stage clinical trials. Medicine candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through pre-clinical studies and initial clinical testing. For example, in December 2016, we announced that the Phase 3 trial, Safety, Tolerability and Efficacy of ACTIMMUNE Dose Escalation in Friedreich's ataxia, evaluating ACTIMMUNE for the treatment of Friedreich's ataxia did not meet its primary endpoint. Additionally, we previously made a decision to discontinue our ACTIMMUNE investigator-initiated trials in oncology to focus on our strategic pipeline where we see more promise and long-term intellectual property.

With respect to investigator-initiated studies for several of our products, and with respect to the Phase 3 confirmatory clinical trial of teprotumumab in thyroid eye disease that we commenced in the fourth quarter of 2017, and to the extent that we are required to conduct additional clinical development of any of our existing or later acquired medicines or we conduct clinical development of earlier stage medicine candidates, we may experience delays in these clinical trials or investigator-initiated studies. We do not know whether any additional clinical trials will be initiated in the future, begin on time, need to be redesigned, enroll patients on time or be completed on schedule, if at all. Clinical trials can be delayed for a variety of reasons, including delays related to:

- obtaining regulatory approval to commence a trial;
- reaching agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- obtaining IRB or ethics committee approval at each site;
- recruiting suitable patients to participate in a trial;
- having patients complete a trial or return for post-treatment follow-up;
- clinical sites dropping out of a trial;
- adding new sites; or
- manufacturing sufficient quantities of medicine candidates for use in clinical trials.

Patient enrollment, a significant factor in the timing of clinical trials, is affected by many factors including the size and nature of the patient population, the proximity of patients to clinical sites, the eligibility criteria for the trial, the design of the clinical trial, competing clinical trials and clinicians' and patients' perceptions as to the potential advantages of the medicine candidate being studied in relation to other available therapies, including any new drugs or biologics that may be approved for the indications we are investigating. Furthermore, we rely and expect to rely on CROs and clinical trial sites to ensure the proper and timely conduct of our future clinical trials and while we have and intend to have agreements governing their committed activities, we will have limited influence over their actual performance.

We could encounter delays if prescribing physicians encounter unresolved ethical issues associated with enrolling patients in clinical trials of our medicine candidates in lieu of prescribing existing treatments that have established safety and efficacy profiles. Further, a clinical trial may be suspended or terminated by us, our collaborators, the FDA or other regulatory authorities due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a medicine candidate, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. If we experience delays in the completion of, or if we terminate, any clinical trial of our medicine candidates, the commercial prospects of our medicine candidates will be harmed, and our ability to generate medicine revenues from any of these medicine candidates will be delayed. In addition, any delays in completing our clinical trials will increase our costs, slow down our medicine development and approval process and jeopardize our ability to commence medicine sales and generate revenues.

Moreover, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and receive compensation in connection with such services. Under certain circumstances, we may be required to report some of these relationships to the FDA. The FDA may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected interpretation of the study. The FDA may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing applications by the FDA and may ultimately lead to the denial of marketing approval of one or more of our medicine candidates.

Any of these occurrences may harm our business, financial condition, results of operations and prospects significantly. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our medicine candidates.

Business interruptions could seriously harm our future revenue and financial condition and increase our costs and expenses.

Our operations could be subject to earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics and other natural or man-made disasters or business interruptions. While we carry insurance for certain of these events and have implemented disaster management plans and contingencies, the occurrence of any of these business interruptions could seriously harm our business and financial condition and increase our costs and expenses. We conduct significant management operations at both our global headquarters located in Dublin, Ireland and our U.S. office located in Lake Forest, Illinois. If our Dublin or Lake Forest offices were affected by a natural or man-made disaster or other business interruption, our ability to manage our domestic and foreign operations could be impaired, which could materially and adversely affect our results of operations and financial condition. We currently rely, and intend to rely in the future, on third-party manufacturers and suppliers to produce our medicines and third-party logistics partners to ship our medicines. Our ability to obtain commercial supplies of our medicines could be disrupted and our results of operations and financial condition could be materially and adversely affected if the operations of these third-party suppliers or logistics partners were affected by a man-made or natural disaster or other business interruption. The ultimate impact of such events on us, our significant suppliers and our general infrastructure is unknown.

We are dependent on information technology systems, infrastructure and data, which exposes us to data security risks.

We are dependent upon our own or third-party information technology systems, infrastructure and data, including mobile technologies, to operate our business. The multitude and complexity of our computer systems may make them vulnerable to service interruption or destruction, disruption of data integrity, malicious intrusion, or random attacks. Likewise, data privacy or security incidents or breaches by employees or others may pose a risk that sensitive data, including our intellectual property, trade secrets or personal information of our employees, patients, customers or other business partners may be exposed to unauthorized persons or to the public. Cyber-attacks are increasing in their frequency, sophistication and intensity. Cyber-attacks could include the deployment of harmful malware, denial-of-service, social engineering and other means to affect service reliability and threaten data confidentiality, integrity and availability. Our business partners face similar risks and any security breach of their systems could adversely affect our security posture. A security breach or privacy violation that leads to disclosure or modification of or prevents access to patient information, including personally identifiable information or protected health information, could harm our reputation, compel us to comply with federal and/or state breach notification laws and foreign law equivalents, subject us to mandatory corrective action, require us to verify the correctness of database contents and otherwise subject us to litigation or other liability under laws and regulations that protect personal data, any of which could disrupt our business and/or result in increased costs or loss of revenue. Moreover, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information, trade secrets or other intellectual property. While we have invested, and continue to invest, in the protection of our data and information technology infrastructure, there can be no assurance that our efforts will prevent service interruptions, or identify breaches in our systems, that could adversely affect our business and operations and/or result in the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm to us. In addition, our liability insurance may not be sufficient in type or amount to cover us against claims related to security breaches, cyber-attacks and other related breaches.

We are subject to extensive laws and regulations related to data privacy, and our failure to comply with these laws and regulations could harm our business.

We are subject to laws and regulations governing data privacy and the protection of personal information. These laws and regulations govern our processing of personal data, including the collection, access, use, analysis, modification, storage, transfer, security breach notification, destruction and disposal of personal data. There are foreign and state law versions of these laws and regulations to which we are currently and/or may in the future, be subject. For example, the collection and use of personal health data in the EU is governed by the GDPR. The GDPR, which is wide-ranging in scope, imposes several requirements relating to the consent of the individuals to whom the personal data relates, the information provided to the individuals, the security and confidentiality of the personal data, data breach notification and the use of third party processors in connection with the processing of personal data. The GDPR also imposes strict rules on the transfer of personal data out of the EU to the United States, provides an enforcement authority and imposes large monetary penalties for noncompliance. The GDPR requirements apply not only to third-party transactions, but also to transfers of information within our company, including employee information. The GDPR and similar data privacy laws of other jurisdictions place significant responsibilities on us and create potential liability in relation to personal data that we or our third party service providers process, including in clinical trials conducted in the United States and EU. In addition, we expect that there will continue to be new proposed laws, regulations and industry standards relating to privacy and data protection in the United States, the EU and other jurisdictions, and we cannot determine the impact such future laws, regulations and standards may have on our business.

Additionally, California recently enacted legislation that has been dubbed the first "GDPR-like" law in the United States. Known as the California Consumer Privacy Act, or CCPA, it creates new individual privacy rights for consumers (as that word is broadly defined in the law) and places increased privacy and security obligations on entities handling personal data of consumers or households. When it goes into effect on January 1, 2020, the CCPA will require covered companies to provide new disclosures to California consumers, provide such consumers new ways to opt-out of certain sales of personal information, and allow for a new cause of action for data breaches. Legislators have stated that amendments will be proposed to the CCPA before it goes into effect, but it remains unclear what, if any, modifications will be made to this legislation or how it will be interpreted. As currently written, the CCPA will likely impact our business activities and exemplifies the vulnerability of our business to not only cyber threats but also the evolving regulatory environment related to personal data and protected health information.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our medicines.

We face an inherent risk of product liability claims as a result of the commercial sales of our medicines and the clinical testing of our medicine candidates. For example, we may be sued if any of our medicines or medicine candidates allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the medicine, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our medicines and medicine candidates. Even a successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for our medicines or medicine candidates that we may develop;
- injury to our reputation;
- withdrawal of clinical trial participants;
- initiation of investigations by regulators;
- costs to defend the related litigation;
- a diversion of management's time and resources;
- substantial monetary awards to trial participants or patients;
- medicine recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- exhaustion of any available insurance and our capital resources; and

- the inability to commercialize our medicines or medicine candidates.

Our inability to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of medicines we develop. We currently carry product liability insurance covering our clinical studies and commercial medicine sales in the amount of $125.0 million in the aggregate. Although we maintain such insurance, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. If we determine that it is prudent to increase our product liability coverage due to the on-going commercialization of our current medicines in the United States, and/or the potential commercial launches of any of our medicines in additional markets or for additional indications, we may be unable to obtain such increased coverage on acceptable terms or at all. Our insurance policies also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We will have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts.

Our business involves the use of hazardous materials, and we and our third-party manufacturers must comply with environmental laws and regulations, which can be expensive and restrict how we do business.

Our third-party manufacturers' activities involve the controlled storage, use and disposal of hazardous materials owned by us, including the components of our medicine candidates and other hazardous compounds. We and our manufacturers are subject to federal, state and local as well as foreign laws and regulations governing the use, manufacture, storage, handling and disposal of these hazardous materials. Although we believe that the safety procedures utilized by our third-party manufacturers for handling and disposing of these materials comply with the standards prescribed by these laws and regulations, we cannot eliminate the risk of accidental contamination or injury from these materials. In the event of an accident, state, federal or foreign authorities may curtail the use of these materials and interrupt our business operations. We do not currently maintain hazardous materials insurance coverage. If we are subject to any liability as a result of our third-party manufacturers' activities involving hazardous materials, our business and financial condition may be adversely affected. In the future we may seek to establish longer-term third-party manufacturing arrangements, pursuant to which we would seek to obtain contractual indemnification protection from such third-party manufacturers potentially limiting this liability exposure.

Our employees, independent contractors, principal investigators, consultants, vendors, distributors and CROs may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk that our employees, independent contractors, principal investigators, consultants, vendors, distributors and CROs may engage in fraudulent or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct or unauthorized activities that violate FDA regulations, including those laws that require the reporting of true, complete and accurate information to the FDA, manufacturing standards, federal and state healthcare fraud and abuse laws and regulations, and laws that require the true, complete and accurate reporting of financial information or data. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Misconduct by our employees and other third parties may also include the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. We have adopted a Code of Business Conduct and Ethics, but it is not always possible to identify and deter misconduct by our employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs and imprisonment.

Risks Related to our Financial Position and Capital Requirements

In the past we have incurred significant operating losses.

We have a limited operating history and even less history operating as a combined organization following the acquisitions of Vidara, Hyperion, Crealta Holdings LLC, or Crealta, Raptor and River Vision Development Corp., or River Vision. We have financed our operations primarily through equity and debt financings and have incurred significant operating losses in the past. We recorded operating income of $2.4 million for the year ended December 31, 2018, an operating loss of $383.4 million for the year ended December 31, 2017 and an operating loss of $145.9 million for the year ended December 31, 2016. We recorded net losses of $74.2 million, $401.6 million and $165.6 million for the years ended December 31, 2018, 2017 and 2016, respectively. As of December 31, 2018, we had an accumulated deficit of $1,314.7 million. Our prior losses have resulted principally from costs incurred in our development activities for our medicines and medicine candidates, commercialization activities related to our medicines, costs associated with our acquisition transactions and costs associated with derivative liability accounting. Our prior losses, combined with possible future losses, have had and will continue to have an adverse effect on our shareholders' equity and working capital. While we anticipate that we will generate operating profits in the future, whether we can sustain this will depend on the revenues we generate from the sale of our medicines being sufficient to cover our operating expenses.

We have limited sources of revenues and significant expenses. We cannot be certain that we will achieve or sustain profitability, which would depress the market price of our ordinary shares and could cause our investors to lose all or a part of their investment.

Our ability to achieve and sustain profitability depends upon our ability to generate sales of our medicines. We have a limited history of commercializing our medicines as a company, and commercialization has been primarily in the United States. We may never be able to successfully commercialize our medicines or develop or commercialize other medicines in the United States, which we believe represents our most significant commercial opportunity. Our ability to generate future revenues depends heavily on our success in:

- continued commercialization of our existing medicines and any other medicine candidates for which we obtain approval;
- obtaining FDA approvals for teprotumumab;
- securing additional foreign regulatory approvals for our medicines in territories where we have commercial rights; and
- developing, acquiring and commercializing a portfolio of other medicines or medicine candidates in addition to our current medicines.

Even if we do generate additional medicine sales, we may not be able to achieve or sustain profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the market price of our ordinary shares and could impair our ability to raise capital, expand our business, diversify our medicine offerings or continue our operations.

We may need to obtain additional financing to fund additional acquisitions.

Our operations have consumed substantial amounts of cash since inception. We expect to continue to spend substantial amounts to:

- commercialize our existing medicines in the United States, including the substantial expansion of our sales force in recent years;
- complete the regulatory approval process, and any future required clinical development related thereto, for our medicines and medicine candidates;
- potentially acquire other businesses or additional complementary medicines or medicines that augment our current medicine portfolio, including costs associated with refinancing debt of acquired companies; and
- conduct clinical trials with respect to potential additional indications, as well as conduct post-marketing requirements and commitments, with respect to our medicines and medicines we acquire.

While we believe that our existing cash and cash equivalents will be sufficient to fund our operations based on our current expectations of continued revenue growth, we may need to raise additional funds if we choose to expand our commercialization or development efforts more rapidly than presently anticipated, if we develop or acquire additional medicines or acquire companies, or if our revenue does not meet expectations.

We cannot be certain that additional funding will be available on acceptable terms, or at all. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of one or more of our medicines or medicine candidates or one or more of our other research and development initiatives, or delay, cut back or abandon our plans to grow the business through acquisitions. We also could be required to:

- seek collaborators for one or more of our current or future medicine candidates at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available; or
- relinquish or license on unfavorable terms our rights to technologies or medicine candidates that we would otherwise seek to develop or commercialize ourselves.

In addition, if we are unable to secure financing to support future acquisitions, our ability to execute on a key aspect of our overall growth strategy would be impaired.

Any of the above events could significantly harm our business, financial condition and prospects.

We have incurred a substantial amount of debt, which could adversely affect our business, including by restricting our ability to engage in additional transactions or incur additional indebtedness, and prevent us from meeting our debt obligations.

As of December 31, 2018, we had $1,896.7 million book value, or $1,993.0 million aggregate principal amount, of indebtedness, including $818.0 million in secured indebtedness. In October 2018, we borrowed approximately $818.0 million aggregate principal amount of loans pursuant to an amendment to our credit agreement to refinance the then outstanding senior secured term loans incurred in October 2017 under our credit agreement. In connection with the acquisition of Hyperion, we issued $475.0 million aggregate principal amount of 6.625% Senior Notes due 2023, or the 2023 Senior Notes, in April 2015. In connection with the acquisition of Raptor, we issued $300.0 million aggregate principal amount of 8.750% Senior Notes due 2024, or the 2024 Senior Notes, in October 2016. In March 2015, we issued $400.0 million aggregate principal amount of 2.50% Exchangeable Senior Notes due 2022, or the Exchangeable Senior Notes. Accordingly, we have a significant amount of debt outstanding on a consolidated basis.

This substantial level of debt could have important consequences to our business, including, but not limited to:

- reducing the benefits we expect to receive from our prior and any future acquisition transactions;
- making it more difficult for us to satisfy our obligations;
- requiring a substantial portion of our cash flows from operations to be dedicated to the payment of principal and interest on our indebtedness, therefore reducing our ability to use our cash flows to fund acquisitions, capital expenditures, and future business opportunities;
- exposing us to the risk of increased interest rates to the extent of any future borrowings, including borrowings under our credit agreement, at variable rates of interest;
- making it more difficult for us to satisfy our obligations with respect to our indebtedness, including our outstanding notes, our credit agreement, and any failure to comply with the obligations of any of our debt instruments, including restrictive covenants and borrowing conditions, could result in an event of default under the agreements governing such indebtedness;
- increasing our vulnerability to, and reducing our flexibility to respond to, changes in our business or general adverse economic and industry conditions;
- limiting our ability to obtain additional financing for working capital, capital expenditures, debt service requirements, acquisitions, and general corporate or other purposes and increasing the cost of any such financing;

- limiting our flexibility in planning for, or reacting to, changes in our business and the industry in which we operate; and placing us at a competitive disadvantage as compared to our competitors, to the extent they are not as highly leveraged and who, therefore, may be able to take advantage of opportunities that our leverage may prevent us from exploiting; and
- restricting us from pursuing certain business opportunities.

The credit agreement and the indentures governing the 2024 Senior Notes and the 2023 Senior Notes impose, and the terms of any future indebtedness may impose, various covenants that limit our ability and/or the ability of our restricted subsidiaries' (as designated under such agreements) to, among other things, pay dividends or distributions, repurchase equity, prepay junior debt and make certain investments, incur additional debt and issue certain preferred stock, incur liens on assets, engage in certain asset sales, consolidate with or merge or sell all or substantially all of our assets, enter into transactions with affiliates, designate subsidiaries as unrestricted subsidiaries, and allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to us.

Our ability to obtain future financing and engage in other transactions may be restricted by these covenants. In addition, any credit ratings will impact the cost and availability of future borrowings and our cost of capital. Our ratings at any time will reflect each rating organization's then opinion of our financial strength, operating performance and ability to meet our debt obligations. There can be no assurance that we will achieve a particular rating or maintain a particular rating in the future. A reduction in our credit ratings may limit our ability to borrow at acceptable interest rates. If our credit ratings were downgraded or put on watch for a potential downgrade, we may not be able to sell additional debt securities or borrow money in the amounts, at the times or interest rates or upon the more favorable terms and conditions that might otherwise be available. Any impairment of our ability to obtain future financing on favorable terms could have an adverse effect on our ability to refinance any of our then-existing debt and may severely restrict our ability to execute on our business strategy, which includes the continued acquisition of additional medicines or businesses.

We may not be able to generate sufficient cash to service all of our indebtedness and may be forced to take other actions to satisfy our obligations under our indebtedness, which may not be successful.

Our ability to make scheduled payments under or to refinance our debt obligations depends on our financial condition and operating performance, which is subject to prevailing economic, industry and competitive conditions and to certain financial, business and other factors beyond our control. Our ability to generate cash flow to meet our payment obligations under our debt may also depend on the successful implementation of our operating and growth strategies. Any refinancing of our debt could be at higher interest rates and may require us to comply with more onerous covenants, which could further restrict our business operations. We cannot assure that we will maintain a level of cash flows from operating activities sufficient to pay the principal, premium, if any, and interest on our indebtedness.

If our cash flows and capital resources are insufficient to fund our debt service obligations, we may be forced to reduce or delay capital expenditures, sell assets or business operations, seek additional capital or restructure or refinance our indebtedness. We cannot ensure that we would be able to take any of these actions, that these actions would be successful and permit us to meet our scheduled debt service obligations or that these actions would be permitted under the terms of existing or future debt agreements, including the indentures that govern the 2024 Senior Notes and the 2023 Senior Notes and the credit agreement. In addition, any failure to make payments of interest and principal on our outstanding indebtedness on a timely basis would likely result in a reduction of our credit rating, which could harm our ability to incur additional indebtedness.

If we cannot make scheduled payments on our debt, we will be in default and, as a result:

- our debt holders could declare all outstanding principal and interest to be due and payable;
- the administrative agent and/or the lenders under the credit agreement could foreclose against the assets securing the borrowings then outstanding; and
- we could be forced into bankruptcy or liquidation, which could result in you losing your investment.

We generally have broad discretion in the use of our cash and may not use it effectively.

Our management has broad discretion in the application of our cash, and investors will be relying on the judgment of our management regarding the use of our cash. Our management may not apply our cash in ways that ultimately increase the value of any investment in our securities. We expect to use our existing cash to fund commercialization activities for our medicines, to potentially fund additional medicine, medicine candidate or business acquisitions, to potentially fund additional regulatory approvals of certain of our medicines, to potentially fund development, life cycle management or manufacturing activities of our medicines and medicine candidates, to potentially fund share repurchases, and for working capital, milestone payments, capital expenditures and general corporate purposes. We may also invest our cash in short-term, investment-grade, interest-bearing securities. These investments may not yield a favorable return to our shareholders. If we do not invest or apply our cash in ways that enhance shareholder value, we may fail to achieve expected financial results, which could cause the price of our ordinary shares to decline.

Our ability to use net operating loss carryforwards and certain other tax attributes to offset U.S. income taxes may be limited.

Under Sections 382 and 383 of the Code, if a corporation undergoes an "ownership change" (generally defined as a greater than 50 percent change (by value) in its equity ownership over a three-year period), the corporation's ability to use pre-change net operating loss carryforwards and other pre-change tax attributes to offset post-change income may be limited. We continue to carry forward our annual limitation resulting from an ownership change date of August 2, 2012. The limitation on pre-change net operating losses incurred prior to the August 2, 2012 change date is approximately $7.7 million for 2019 through 2028. We continue to carry forward the annual limitation related to Hyperion of $50.0 million resulting from the last ownership change date in 2014 and the annual limitation related to Raptor of $0.2 million resulting from the last ownership change date in 2009. In addition, we recognized $32.2 million of federal net operating losses, $2.2 million of state net operating losses and $9.5 million of federal tax credits following our acquisition of River Vision. These acquired federal net operating losses and tax credits are subject to an annual limitation of $2.6 million. The net operating loss carryforward and tax credit carryforward limitations are cumulative such that any use of the carryforwards below the limitations in one year will result in a corresponding increase in the limitations for the subsequent tax year. Under the Tax Act, U.S. federal net operating losses incurred in 2018 and in future years may be carried forward indefinitely, but the deductibility of such federal net operating losses is limited to 80 percent of the current year's taxable income. It is uncertain if and to what extent various U.S. states will conform to the Tax Act.

Following certain acquisitions of a U.S. corporation by a foreign corporation, Section 7874 of the Code limits the ability of the acquired U.S. corporation and its U.S. affiliates to utilize U.S. tax attributes such as net operating losses to offset U.S. taxable income resulting from certain transactions. Based on the limited guidance available, we expect this limitation is applicable for approximately ten years following the Vidara Merger with respect to certain intra-company transactions. As a result, we or our other U.S. affiliates may not be able to utilize their U.S. tax attributes to offset their U.S. taxable income or U.S. tax liability respectively, if any, resulting from certain intra-company taxable transactions during such period. Notwithstanding this limitation, we expect that we will be able to fully use our U.S. net operating losses and tax credits prior to their expiration. As a result of this limitation, however, it may take Horizon Pharma USA, Inc. (as the successor to HPI) longer to use its net operating losses and tax credits. Moreover, contrary to these expectations, it is possible that the limitation under Section 7874 of the Code on the utilization of U.S. tax attributes could prevent us from fully utilizing our U.S. tax attributes prior to their expiration if we do not generate sufficient taxable income or tax obligations.

Any limitation on our ability to use our net operating loss and tax credit carryforwards, including the carryforwards of companies that we acquire, will likely increase the taxes we would otherwise pay in future years if we were not subject to such limitations.

Unstable market and economic conditions may have serious adverse consequences on our business, financial condition and share price.

From time to time, global credit and financial markets have experienced extreme disruptions, including severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates, and uncertainty about economic stability. Our general business strategy may be adversely affected by any such economic downturn, volatile business environment and continued unpredictable and unstable market conditions. If the equity and credit markets deteriorate, it may make any necessary debt or equity financing more difficult to complete, more costly, and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and share price and could require us to delay or abandon commercialization or development plans. There is a risk that one or more of our current service providers, manufacturers and other partners may not survive an economic down-turn, which could directly affect our ability to attain our operating goals on schedule and on budget.

The United Kingdom's referendum to leave the EU, or "Brexit," has caused and may continue to cause disruptions to capital and currency markets worldwide. The full impact of the Brexit decision, however, remains uncertain. A process of negotiation will determine the future terms of the United Kingdom's relationship with the EU and there is the potential that the United Kingdom and the EU may not agree to a withdrawal arrangement before the date the United Kingdom leaves the EU. During this period of negotiation and afterwards, our results of operations and access to capital may be negatively affected by interest rate, exchange rate and other market and economic volatility, as well as political uncertainty. In the short and medium term, there is a risk of disrupted import and export processes due to a lack of administrative processing capacity by the respective United Kingdom and EU customs agencies that may delay time-sensitive shipments and may negatively impact our product supply chain. Brexit may also have a detrimental effect on our customers, distributors and suppliers, which would, in turn, adversely affect our revenues and financial condition.

At December 31, 2018, we had $958.7 million of cash and cash equivalents consisting of cash and money market funds. While we are not aware of any downgrades, material losses, or other significant deterioration in the fair value of our cash equivalents since December 31, 2018, no assurance can be given that deterioration in conditions of the global credit and financial markets would not negatively impact our current portfolio of cash equivalents or our ability to meet our financing objectives. Dislocations in the credit market may adversely impact the value and/or liquidity of marketable securities owned by us.

If the London Inter-Bank Offered Rate, or LIBOR, is discontinued, interest payments under our credit agreement may be calculated using another reference rate.

In July 2017, the Chief Executive of the United Kingdom Financial Conduct Authority, or FCA, which regulates LIBOR, announced that the FCA intends to phase out the use of LIBOR by the end of 2021. In addition, the U.S. Federal Reserve, in conjunction with the Alternative Reference Rates Committee, a steering committee comprised of large U.S. financial institutions, is considering replacing U.S. dollar LIBOR with the Secured Overnight Financing Rate, or SOFR, a new index calculated by short-term repurchase agreements, backed by Treasury securities. Although there have been certain issuances utilizing SOFR, it is unknown whether this or any other alternative reference rate will attain market acceptance as a replacement for LIBOR. LIBOR is used as a benchmark rate throughout our credit agreement, and our credit agreement does not provide fallback language for all circumstances in which LIBOR ceases to be published. There remains uncertainty regarding the future utilization of LIBOR and the nature of any replacement rate, and any potential effects of the transition away from LIBOR on us are not known. The transition process may involve, among other things, increased volatility and illiquidity in markets for instruments that currently rely on LIBOR and may result in increased borrowing costs, the effectiveness of related transactions such as hedges, uncertainty under applicable documentation, including the credit agreement, or difficult and costly processes to amend such documentation. As a result, our ability to refinance our credit agreement or other indebtedness or to hedge our exposure to floating rate instruments may be impaired, which would adversely affect the operations of our business.

Changes in accounting rules or policies may affect our financial position and results of operations.

Accounting principles generally accepted in the United States, or GAAP, and related implementation guidelines and interpretations can be highly complex and involve subjective judgments. Changes in these rules or their interpretation, the adoption of new guidance or the application of existing guidance to changes in our business could significantly affect our financial position and results of operations. In addition, our operation as an Irish company with multiple subsidiaries in different jurisdictions adds additional complexity to the application of GAAP and this complexity will be exacerbated further if we complete additional strategic transactions. Changes in the application of existing rules or guidance applicable to us or our wholly owned subsidiaries could significantly affect our consolidated financial position and results of operations.

Covenants under the indentures governing our 2024 Senior Notes and 2023 Senior Notes and our credit agreement may restrict our business and operations in many ways, and if we do not effectively manage our covenants, our financial conditions and results of operations could be adversely affected.

The indentures governing the 2024 Senior Notes and the 2023 Senior Notes and the credit agreement impose various covenants that limit our ability and/or our restricted subsidiaries' ability to, among other things:

- pay dividends or distributions, repurchase equity, prepay, redeem or repurchase certain debt and make certain investments;
- incur additional debt and issue certain preferred stock;
- provide guarantees in respect of obligations of other persons;
- incur liens on assets;
- engage in certain asset sales;
- merge, consolidate with or sell all or substantially all of our assets to another person;
- enter into transactions with affiliates;
- sell assets and capital stock of our subsidiaries;
- enter into agreements that restrict distributions from our subsidiaries;
- designate subsidiaries as unrestricted subsidiaries; and
- allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to us.

These covenants may:

- limit our ability to borrow additional funds for working capital, capital expenditures, acquisitions or other general business purposes;
- limit our ability to use our cash flow or obtain additional financing for future working capital, capital expenditures, acquisitions or other general business purposes;
- require us to use a substantial portion of our cash flow from operations to make debt service payments;
- limit our flexibility to plan for, or react to, changes in our business and industry;
- place us at a competitive disadvantage compared to less leveraged competitors; and
- increase our vulnerability to the impact of adverse economic and industry conditions.

If we are unable to successfully manage the limitations and decreased flexibility on our business due to our significant debt obligations, we may not be able to capitalize on strategic opportunities or grow our business to the extent we would be able to without these limitations.

Our failure to comply with any of the covenants could result in a default under the credit agreement or the indentures governing the 2024 Senior Notes or the 2023 Senior Notes, which could permit the administrative agent or the trustee, as applicable, or permit the lenders or the holders of the 2024 Senior Notes or the 2023 Senior Notes to cause the administrative agent or the trustee, as applicable, to declare all or part of any outstanding senior secured term loans, the 2023 Senior Notes or the 2024 Senior Notes to be immediately due and payable or to exercise any remedies provided to the administrative agent or the trustee, including, in the case of the credit agreement proceeding against the collateral granted to secure our obligations under the credit agreement. An event of default under the credit agreement or the indentures governing the 2024 Senior Notes or the 2023 Senior Notes could also lead to an event of default under the terms of the other agreements and the indenture governing our Exchangeable Senior Notes. Any such event of default or any exercise of rights and remedies by our creditors could seriously harm our business.

If intangible assets that we have recorded in connection with our acquisition transactions become impaired, we could have to take significant charges against earnings.

In connection with the accounting for our various acquisition transactions, we have recorded significant amounts of intangible assets. Under GAAP, we must assess, at least annually and potentially more frequently, whether the value of goodwill and other indefinite-lived intangible assets has been impaired. Amortizing intangible assets will be assessed for impairment in the event of an impairment indicator. For example, during the year ended December 31, 2018, we recorded an impairment of $37.9 million to fully write off the book value of developed technology related to PROCYSBI in Canada and Latin America. Such impairment and any reduction or other impairment of the value of goodwill or other intangible assets will result in a charge against earnings, which could materially adversely affect our results of operations and shareholders' equity in future periods.

Risks Related to Our Intellectual Property

If we are unable to obtain or protect intellectual property rights related to our medicines and medicine candidates, we may not be able to compete effectively in our markets.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our medicines and medicine candidates. The strength of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions and can be uncertain. The patent applications that we own may fail to result in issued patents with claims that cover our medicines in the United States or in other foreign countries. If this were to occur, early generic competition could be expected against our current medicines and other medicine candidates in development. There is no assurance that all potentially relevant prior art relating to our patents and patent applications has been found, which prior art can invalidate a patent or prevent a patent from issuing based on a pending patent application. In particular, because the APIs in RAYOS, DUEXIS and VIMOVO have been on the market as separate medicines for many years, it is possible that these medicines have previously been used off-label in such a manner that such prior usage would affect the validity of our patents or our ability to obtain patents based on our patent applications. In addition, claims directed to dosing and dose adjustment may be substantially less likely to issue in light of the Supreme Court decision in Mayo Collaborative Services v. Prometheus Laboratories, Inc., where the court held that claims directed to methods of determining whether to adjust drug dosing levels based on drug metabolite levels in the red blood cells were not patent eligible because they were directed to a law of nature. This decision may have wide-ranging implications on the validity and scope of pharmaceutical method claims.

Even if patents do successfully issue, third parties may challenge their validity, enforceability or scope, which may result in such patents being narrowed or invalidated.

Patent litigation is currently pending in the United States District Court for the District of New Jersey against Actavis, who intend to market a generic version of PENNSAID 2% prior to the expiration of certain of our patents listed in the Orange Book. These cases arise from Paragraph IV Patent Certification notice letters from Actavis advising they had filed an ANDA with the FDA seeking approval to market a generic version of PENNSAID 2% before the expiration of the patents-in-suit. For a more detailed description of the PENNSAID 2% litigation, see Note 18, *Legal Proceedings*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K.

Patent litigation is currently pending in the United States District Court for the District of New Jersey and the Court of Appeals for the Federal Circuit against several companies intending to market a generic version of VIMOVO before the expiration of certain of our patents listed in the Orange Book. These cases are collectively known as the VIMOVO cases, and involve the following sets of defendants: (i) Dr. Reddy's; (ii) Lupin; and (iii) Mylan. The cases arise from Paragraph IV Patent Certification notice letters from each of Dr. Reddy's, Lupin and Mylan, advising each had filed an ANDA with the FDA seeking approval to market generic versions of VIMOVO before the expiration of the patents-in-suit. For a more detailed description of the VIMOVO litigation, see Note 18, *Legal Proceedings*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K.

Patent litigation is currently pending in the United States District Court for the District of Delaware against Alkem, who intends to market a generic version of DUEXIS prior to the expiration of certain of our patents listed in the Orange Book. This case arises from Paragraph IV Patent Certification notice letters from Alkem advising it had filed an ANDA with the FDA seeking approval to market a generic version of DUEXIS before the expiration of the patents-in-suit. For a more detailed description of the DUEXIS litigation, see Note 18, *Legal Proceedings*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K.

We intend to vigorously defend our intellectual property rights relating to our medicines, but we cannot predict the outcome of the DUEXIS case, the PENNSAID 2% cases and the VIMOVO cases. Any adverse outcome in these matters or any new generic challenges that may arise could result in one or more generic versions of our medicines being launched before the expiration of the listed patents, which could adversely affect our ability to successfully execute our business strategy to increase sales of our medicines, and would negatively impact our financial condition and results of operations, including causing a significant decrease in our revenues and cash flows.

Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property or prevent others from designing around our claims. If the patent applications we hold with respect to our medicines fail to issue or if their breadth or strength of protection is threatened, it could dissuade companies from collaborating with us to develop them and threaten our ability to commercialize our medicines. We cannot offer any assurances about which, if any, patents will issue or whether any issued patents will be found not invalid and not unenforceable or will go unthreatened by third parties. Since patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we were the first to file any patent application related to our medicines or any other medicine candidates. Furthermore, if third parties have filed such patent applications, an interference proceeding in the United States can be provoked by a third-party or instituted by us to determine which party was the first to invent any of the subject matter covered by the patent claims of our applications.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable, processes for which patents are difficult to enforce and any other elements of our drug discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. Although we expect all of our employees to assign their inventions to us, and all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques.

Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. For example, if the issuance, in a given country, of a patent to us, covering an invention, is not followed by the issuance, in other countries, of patents covering the same invention, or if any judicial interpretation of the validity, enforceability, or scope of the claims in, or the written description or enablement in, a patent issued in one country is not similar to the interpretation given to the corresponding patent issued in another country, our ability to protect our intellectual property in those countries may be limited. Changes in either patent laws or in interpretations of patent laws in the United States and other countries may materially diminish the value of our intellectual property or narrow the scope of our patent protection. If we are unable to prevent material disclosure of the non-patented intellectual property related to our technologies to third parties, and there is no guarantee that we will have any such enforceable trade secret protection, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, results of operations and financial condition.

Third-party claims of intellectual property infringement may prevent or delay our development and commercialization efforts.

Our commercial success depends in part on us avoiding infringement of the patents and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions and inter party reexamination proceedings before the United States Patent and Trademark Office, or the U.S. PTO. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which our collaborators are developing medicine candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our medicine candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our medicines and/or any other medicine candidates. Because patent applications can take many years to issue, there may be currently pending patent applications, which may later result in issued patents that our medicine candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our medicine candidates, any molecules formed during the manufacturing process or any final medicine itself, the holders of any such patents may be able to block our ability to commercialize such medicine candidate unless we obtained a license under the applicable patents, or until such patents expire. Similarly, if any third-party patent were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or methods of use, including combination therapy, the holders of any such patent may be able to block our ability to develop and commercialize the applicable medicine candidate unless we obtained a license or until such patent expires. In either case, such a license may not be available on commercially reasonable terms or at all.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our medicine candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties or redesign our infringing medicines, which may be impossible or require substantial time and monetary expenditure. We cannot predict whether any such license would be available at all or whether it would be available on commercially reasonable terms. Furthermore, even in the absence of litigation, we may need to obtain licenses from third parties to advance our research or allow commercialization of our medicine candidates, and we have done so from time to time. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. In that event, we would be unable to further develop and commercialize one or more of our medicine candidates, which could harm our business significantly. We cannot provide any assurances that third-party patents do not exist which might be enforced against our medicines, resulting in either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties.

If we fail to comply with our obligations in the agreements under which we license rights to technology from third parties, we could lose license rights that are important to our business.

We are party to a number of technology licenses that are important to our business and expect to enter into additional licenses in the future. For example, we rely on a license from Bausch with respect to technology developed by Bausch in connection with the manufacturing of RAVICTI. The purchase agreement under which Hyperion purchased the rights to RAVICTI contains obligations to pay Bausch regulatory and sales milestone payments relating to RAVICTI, as well as royalties on the net sales of RAVICTI. On May 31, 2013, when Hyperion acquired BUPHENYL under a restated collaboration agreement with Bausch, Hyperion received a license to use some of the manufacturing technology developed by Bausch in connection with the manufacturing of BUPHENYL. The restated collaboration agreement also contains obligations to pay Bausch regulatory and sales milestone payments, as well as royalties on net sales of BUPHENYL. If we fail to make a required payment to Bausch and do not cure the failure within the required time period, Bausch may be able to terminate the license to use its manufacturing technology for RAVICTI and BUPHENYL. If we lose access to the Bausch manufacturing technology, we cannot guarantee that an acceptable alternative method of manufacture could be developed or acquired. Even if alternative technology could be developed or acquired, the loss of the Bausch technology could still result in substantial costs and potential periods where we would not be able to market and sell RAVICTI and/or BUPHENYL. We also license intellectual property necessary for commercialization of RAVICTI from an external party. This party may be entitled to terminate the license if we breach the agreement, including failure to pay required royalties on net sales of RAVICTI, or we do not meet specified diligence obligations in our development and commercialization of RAVICTI, and we do not cure the failure within the required time period. If the license is terminated, it may be difficult or impossible for us to continue to commercialize RAVICTI, which would have a material adverse effect on our business, financial condition and results of operations.

We also license rights to patents, know-how and trademarks for ACTIMMUNE from Genentech Inc., or Genentech. Genentech may terminate the agreement upon our material default, if not cured within a specified period of time. Genentech may also terminate the agreement in the event of our bankruptcy or insolvency. Upon such a termination of the agreement, all intellectual property rights conveyed to us under the agreement, including the rights to the ACTIMMUNE trademark, revert to Genentech. If we fail to comply with our obligations under this agreement, we could lose the ability to market and distribute ACTIMMUNE, which would have a material adverse effect on our business, financial condition and results of operations.

In addition, we are subject to contractual obligations under our agreements with Tripex and PARI related to QUINSAIR. Under the agreement with Tripex, as amended, if we do not spend a specified amount on the development of QUINSAIR for non-CF indications between January 1, 2018 and December 31, 2021 and regulatory approval by the FDA for QUINSAIR for the CF indication is obtained prior to December 31, 2021, we may be obligated to pre-pay a milestone payment related to commercial sales of QUINSAIR for non-CF indications. This obligation is subject to certain exceptions due to, for example, manufacturing delays not under our control, or clinical trial suspension or delay ordered by the FDA. In October 2017, we triggered a milestone payment under this agreement and we paid Tripex $20.0 million in November 2017. Under the license agreement with PARI, we are required to comply with diligence milestones related to development and commercialization of QUINSAIR in the United States and to spend a specified minimum amount per year on development activities in the United States until submission of the NDA for QUINSAIR in the United States. If we do not comply with these obligations, our licenses to certain intellectual property related to QUINSAIR may become non-exclusive in the United States or could be terminated. We are also subject to contractual obligations under our amended and restated license agreement with UCSD, as amended, with respect to PROCYSBI. If one or more of these licenses was terminated, we would have no further right to use or exploit the related intellectual property, which would limit our ability to develop PROCYSBI or QUINSAIR in other indications, and could impact our ability to continue commercializing PROCYSBI or QUINSAIR in their approved indications.

We also hold an exclusive license to patents and technology from Duke University, or Duke, and Mountain View Pharmaceuticals, Inc., or MVP, covering KRYSTEXXA. Duke and MVP may terminate the license if we commit fraud or for our willful misconduct or illegal conduct. Duke and MVP may also terminate the license upon our material breach of the agreement, if not cured within a specified period of time, or upon written notice if we have committed two or more material breaches under the agreement. Duke and MVP may also terminate the license in the event of our bankruptcy or insolvency. If the license is terminated, it may be impossible for us to continue to commercialize KRYSTEXXA, which would have a material adverse effect on our business, financial condition and results of operations.

We hold an exclusive license to Vectura Group plc's, or Vectura, proprietary technology and know-how covering the delayed-release of corticosteroids relating to RAYOS. If we fail to comply with our obligations under our agreement with Vectura or our other license agreements, or if we are subject to a bankruptcy, the licensor may have the right to terminate the license, in which event we would not be able to market medicines covered by the license, including RAYOS.

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our patents or the patents of our licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that one of our patents, or a patent of one of our licensors, is not valid or is unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing.

There are numerous post grant review proceedings available at the U.S. PTO (including inter partes review, post-grant review and ex-parte reexamination) and similar proceedings in other countries of the world that could be initiated by a third-party that could potentially negatively impact our issued patents.

Interference proceedings provoked by third parties or brought by us may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our collaborators or licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our ordinary shares.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees on any issued patent are due to be paid to the U.S. PTO and foreign patent agencies in several stages over the lifetime of the patent. The U.S. PTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we or licensors that control the prosecution and maintenance of our licensed patents fail to maintain the patents and patent applications covering our medicine candidates, our competitors might be able to enter the market, which would have a material adverse effect on our business.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties.

We employ individuals who were previously employed at other biotechnology or pharmaceutical companies. We may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed confidential information of our employees' former employers or other third parties. We may also be subject to claims that former employers or other third parties have an ownership interest in our patents. Litigation may be necessary to defend against these claims. There is no guarantee of success in defending these claims, and even if we are successful, litigation could result in substantial cost and be a distraction to our management and other employees.

Risks Related to Ownership of Our Ordinary Shares

The market price of our ordinary shares historically has been volatile and is likely to continue to be volatile, and you could lose all or part of any investment in our ordinary shares.

The trading price of our ordinary shares has been volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. In addition to the factors discussed in this "Risk Factors" section and elsewhere in this report, these factors include:

- our failure to successfully execute our commercialization strategy with respect to our approved medicines, particularly our commercialization of our medicines in the United States;
- actions or announcements by third-party or government payers with respect to coverage and reimbursement of our medicines;
- disputes or other developments relating to intellectual property and other proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our medicines and medicine candidates;
- unanticipated serious safety concerns related to the use of our medicines;
- adverse regulatory decisions;

- changes in laws or regulations applicable to our business, medicines or medicine candidates, including but not limited to clinical trial requirements for approvals or tax laws;
- inability to comply with our debt covenants and to make payments as they become due;
- inability to obtain adequate commercial supply for any approved medicine or inability to do so at acceptable prices;
- developments concerning our commercial partners, including but not limited to those with our sources of manufacturing supply;
- our decision to initiate a clinical trial, not to initiate a clinical trial or to terminate an existing clinical trial;
- adverse results or delays in clinical trials;
- our failure to successfully develop and/or acquire additional medicine candidates or obtain approvals for additional indications for our existing medicine candidates;
- introduction of new medicines or services offered by us or our competitors;
- overall performance of the equity markets, including the pharmaceutical sector, and general political and economic conditions;
- failure to meet or exceed revenue and financial projections that we may provide to the public;
- actual or anticipated variations in quarterly operating results;
- failure to meet or exceed the estimates and projections of the investment community;
- inaccurate or significant adverse media coverage;
- publication of research reports about us or our industry or positive or negative recommendations or withdrawal of research coverage by securities analysts;
- our inability to successfully enter new markets;
- the termination of a collaboration or the inability to establish additional collaborations;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us or our competitors;
- our inability to maintain an adequate rate of growth;
- ineffectiveness of our internal controls or our inability to otherwise comply with financial reporting requirements;
- adverse U.S. and foreign tax exposure;
- additions or departures of key management, commercial or regulatory personnel;
- issuances of debt or equity securities;
- significant lawsuits, including patent or shareholder litigation;
- changes in the market valuations of similar companies to us;
- sales of our ordinary shares by us or our shareholders in the future;
- trading volume of our ordinary shares;
- effects of natural or man-made catastrophic events or other business interruptions; and
- other events or factors, many of which are beyond our control.

In addition, the stock market in general, and The Nasdaq Global Select Market and the stock of biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may adversely affect the market price of our ordinary shares, regardless of our actual operating performance.

We have never declared or paid dividends on our share capital and we do not anticipate paying dividends in the foreseeable future.

We have never declared or paid any cash dividends on our ordinary shares. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future, including due to limitations that are currently imposed by our credit agreement and the indentures governing the 2024 Senior Notes and the 2023 Senior Notes. Any return to shareholders will therefore be limited to the increase, if any, of our ordinary share price.

We have incurred and will continue to incur significant increased costs as a result of operating as a public company and our management will be required to devote substantial time to compliance initiatives.

As a public company, we have incurred and will continue to incur significant legal, accounting and other expenses that we did not incur as a private company. In particular, the Sarbanes-Oxley Act of 2000, or the Sarbanes-Oxley Act, as well as rules subsequently implemented by the SEC and the Nasdaq Stock Market, Inc., or Nasdaq, impose significant requirements on public companies, including requiring establishment and maintenance of effective disclosure and financial controls and changes in corporate governance practices. These rules and regulations have substantially increased our legal and financial compliance costs and have made some activities more time-consuming and costly. These effects are exacerbated by our transition to an Irish company and the integration of numerous acquired businesses and operations into our historical business and operating structure. If these requirements divert the attention of our management and personnel from other business concerns, they could have a material adverse effect on our business, financial condition and results of operations. The increased costs will continue to decrease our net income or increase our net loss, and may require us to reduce costs in other areas of our business or increase the prices of our medicines or services. For example, these rules and regulations make it more difficult and more expensive for us to obtain and maintain director and officer liability insurance. We cannot predict or estimate the amount or timing of additional costs that we may incur to respond to these requirements. The impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers. If we fail to comply with the continued listing requirements of Nasdaq, our ordinary shares could be delisted from The Nasdaq Global Select Market, which would adversely affect the liquidity of our ordinary shares and our ability to obtain future financing.

The Sarbanes-Oxley Act requires, among other things, that we maintain effective internal controls for financial reporting and disclosure controls and procedures. In particular, we are required to perform annual system and process evaluation and testing of our internal controls over financial reporting to allow management to report on the effectiveness of our internal controls over financial reporting, as required by Section 404 of the Sarbanes-Oxley Act, or Section 404. Our independent registered public accounting firm is also required to deliver a report on the effectiveness of our internal control over financial reporting. Our testing, or the testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses. Our compliance with Section 404 requires that we incur substantial expense and expend significant management efforts, particularly because of our Irish parent company structure and international operations. If we are not able to comply with the requirements of Section 404 or if we or our independent registered public accounting firm identify deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses, the market price of our ordinary shares could decline and we could be subject to sanctions or investigations by Nasdaq, the SEC or other regulatory authorities, which would require additional financial and management resources.

New laws and regulations as well as changes to existing laws and regulations affecting public companies, including the provisions of the Sarbanes-Oxley Act and rules adopted by the SEC and by Nasdaq, would likely result in increased costs as we respond to their requirements.

Sales of a substantial number of our ordinary shares in the public market could cause our share price to decline.

If our existing shareholders sell, or indicate an intention to sell, substantial amounts of our ordinary shares in the public market, the trading price of such ordinary shares could decline. In addition, our ordinary shares that are either subject to outstanding options or reserved for future issuance under our employee benefit plans are or may become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules and Rule 144 under the Securities Act of 1933, as amended, or the Securities Act. If these additional ordinary shares are sold, or if it is perceived that they will be sold, in the public market, the trading price of our ordinary shares could decline.

In addition, any conversion or exchange of our Exchangeable Senior Notes, whether pursuant to their terms or pursuant to privately negotiated transactions between the issuer and/or us and a holder of such securities, could depress the market price for our ordinary shares.

Future sales and issuances of our ordinary shares, securities convertible into our ordinary shares or rights to purchase ordinary shares or convertible securities could result in additional dilution of the percentage ownership of our shareholders and could cause our share price to decline.

Additional capital may be needed in the future to continue our planned operations. To the extent we raise additional capital by issuing equity securities or securities convertible into or exchangeable for ordinary shares, our shareholders may experience substantial dilution. We may sell ordinary shares, and we may sell convertible or exchangeable securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell such ordinary shares, convertible or exchangeable securities or other equity securities in subsequent transactions, existing shareholders may be materially diluted. New investors in such subsequent transactions could gain rights, preferences and privileges senior to those of holders of ordinary shares. We also maintain equity incentive plans, including our Amended and Restated 2014 Equity Incentive Plan, 2014 Non-Employee Equity Plan and 2014 Employee Stock Purchase Plan, and intend to grant additional ordinary share awards under these and future plans, which will result in additional dilution to our existing shareholders.

Irish law differs from the laws in effect in the United States and may afford less protection to holders of our securities.

It may not be possible to enforce court judgments obtained in the United States against us in Ireland based on the civil liability provisions of the U.S. federal or state securities laws. In addition, there is some uncertainty as to whether the courts of Ireland would recognize or enforce judgments of U.S. courts obtained against us or our directors or officers based on the civil liabilities provisions of the U.S. federal or state securities laws or hear actions against us or those persons based on those laws. We have been advised that the United States currently does not have a treaty with Ireland providing for the reciprocal recognition and enforcement of judgments in civil and commercial matters. Therefore, a final judgment for the payment of money rendered by any U.S. federal or state court based on civil liability, whether or not based solely on U.S. federal or state securities laws, would not automatically or necessarily be enforceable in Ireland.

As an Irish company, we are governed by the Irish Companies Act 2014 (as amended), which differs in some material respects from laws generally applicable to U.S. corporations and shareholders, including, among others, differences relating to interested director and officer transactions and shareholder lawsuits. Likewise, the duties of directors and officers of an Irish company generally are owed to the company only. Shareholders of Irish companies generally do not have a personal right of action against directors or officers of the company and may exercise such rights of action on behalf of the company only in limited circumstances. Accordingly, holders of our securities may have more difficulty protecting their interests than would holders of securities of a corporation incorporated in a jurisdiction of the United States.

Provisions of our articles of association could delay or prevent a takeover of us by a third-party.

Our articles of association could delay, defer or prevent a third-party from acquiring us, despite the possible benefit to our shareholders, or otherwise adversely affect the price of our ordinary shares. For example, our articles of association:

- impose advance notice requirements for shareholder proposals and nominations of directors to be considered at shareholder meetings;
- stagger the terms of our board of directors into three classes; and
- require the approval of a supermajority of the voting power of the shares of our share capital entitled to vote generally at a meeting of shareholders to amend or repeal our articles of association.

In addition, several mandatory provisions of Irish law could prevent or delay an acquisition of us. For example, Irish law does not permit shareholders of an Irish public limited company to take action by written consent with less than unanimous consent. We are also subject to various provisions of Irish law relating to mandatory bids, voluntary bids, requirements to make a cash offer and minimum price requirements, as well as substantial acquisition rules and rules requiring the disclosure of interests in our ordinary shares in certain circumstances.

These provisions may discourage potential takeover attempts, discourage bids for our ordinary shares at a premium over the market price or adversely affect the market price of, and the voting and other rights of the holders of, our ordinary shares. These provisions could also discourage proxy contests and make it more difficult for you and our other shareholders to elect directors other than the candidates nominated by our board of directors, and could depress the market price of our ordinary shares.

Any attempts to take us over will be subject to Irish Takeover Rules and subject to review by the Irish Takeover Panel.

We are subject to the Irish Takeover Rules, under which our board of directors will not be permitted to take any action which might frustrate an offer for our ordinary shares once it has received an approach which may lead to an offer or has reason to believe an offer is imminent.

A transfer of our ordinary shares may be subject to Irish stamp duty.

In certain circumstances, the transfer of shares in an Irish incorporated company will be subject to Irish stamp duty, which is a legal obligation of the buyer. This duty is currently charged at the rate of 1.0 percent of the price paid or the market value of the shares acquired, if higher. Because our ordinary shares are traded on a recognized stock exchange in the United States, an exemption from this stamp duty is available to transfers by shareholders who hold ordinary shares beneficially through brokers, which in turn hold those shares through the Depositary Trust Company, or DTC, to holders who also hold through DTC. However, a transfer by or to a record holder who holds ordinary shares directly in his, her or its own name could be subject to this stamp duty. We, in our absolute discretion and insofar as the Irish Companies Act 2014 (as amended) or any other applicable law permit, may, or may provide that one of our subsidiaries will pay Irish stamp duty arising on a transfer of our ordinary shares on behalf of the transferee of such ordinary shares. If stamp duty resulting from the transfer of ordinary shares which would otherwise be payable by the transferee is paid by us or any of our subsidiaries on behalf of the transferee, then in those circumstances, we will, on our behalf or on behalf of such subsidiary (as the case may be), be entitled to (i) seek reimbursement of the stamp duty from the transferee, (ii) set-off the stamp duty against any dividends payable to the transferee of those ordinary shares and (iii) claim a first and permanent lien on the ordinary shares on which stamp duty has been paid by us or such subsidiary for the amount of stamp duty paid. Our lien shall extend to all dividends paid on those ordinary shares.

Dividends paid by us may be subject to Irish dividend withholding tax.

In certain circumstances, as an Irish tax resident company, we will be required to deduct Irish dividend withholding tax (currently at the rate of 20%) from dividends paid to our shareholders. Shareholders that are resident in the United States, EU countries (other than Ireland) or other countries with which Ireland has signed a tax treaty (whether the treaty has been ratified or not) generally should not be subject to Irish withholding tax so long as the shareholder has provided its broker, for onward transmission to our qualifying intermediary or other designated agent (in the case of shares held beneficially), or our or its transfer agent (in the case of shares held directly), with all the necessary documentation by the appropriate due date prior to payment of the dividend. However, some shareholders may be subject to withholding tax, which could adversely affect the price of our ordinary shares.

If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, our share price and trading volume could decline.

The trading market for our ordinary shares will depend in part on the research and reports that securities or industry analysts publish about us or our business. If one or more of the analysts who cover us downgrade our rating or publish inaccurate or unfavorable research about our business, our share price could decline. If one or more of these analysts cease coverage of our company or fail to publish reports on our company regularly, demand for our ordinary shares could decrease, which might cause our share price and trading volume to decline.

Securities class action litigation could divert our management's attention and harm our business and could subject us to significant liabilities.

The stock markets have from time to time experienced significant price and volume fluctuations that have affected the market prices for the equity securities of pharmaceutical companies. These broad market fluctuations may cause the market price of our ordinary shares to decline. In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology and biopharma companies have experienced significant stock price volatility in recent years. For example, following declines in our stock price, two federal securities class action lawsuits were filed in March 2016 against us and certain of our current and former officers alleging violations of the Securities Exchange Act of 1934, as amended, which lawsuits were dismissed by the plaintiffs in June 2018. Even if we are successful in defending any similar claims that may be brought in the future, such litigation could result in substantial costs and may be a distraction to our management, and may lead to an unfavorable outcome that could adversely impact our financial condition and prospects.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Location	Approximate Square Footage	Lease Expiry Date
Dublin, Ireland	18,900	November 4, 2029
Lake Forest, Illinois (1)	160,000	March 31, 2031
Novato, California (2)	61,000	August 31, 2021
Brisbane, California	20,100	November 19, 2019
Chicago, Illinois	9,200	December 31, 2028
Mannheim, Germany	4,800	December 31, 2020
Other	12,400	May 31, 2020 to September 15, 2022

(1) In connection with the Lake Forest lease, we have provided a $2.0 million letter of credit to the landlord, through a commercial bank.

(2) In March 2017, we vacated an area of the office space in Novato, California and in March and April 2017, we entered into sublease arrangements for this space with third parties.

Item 3. Legal Proceedings

For a description of our legal proceedings, see Note 18 of the Notes to consolidated financial statements, included in Item 15 of this Annual Report on Form 10-K.

Item 4. Mine Safety Disclosures

None.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Information

Our ordinary shares trade on The Nasdaq Global Select Market under the trading symbol "HZNP".

Holders of Record

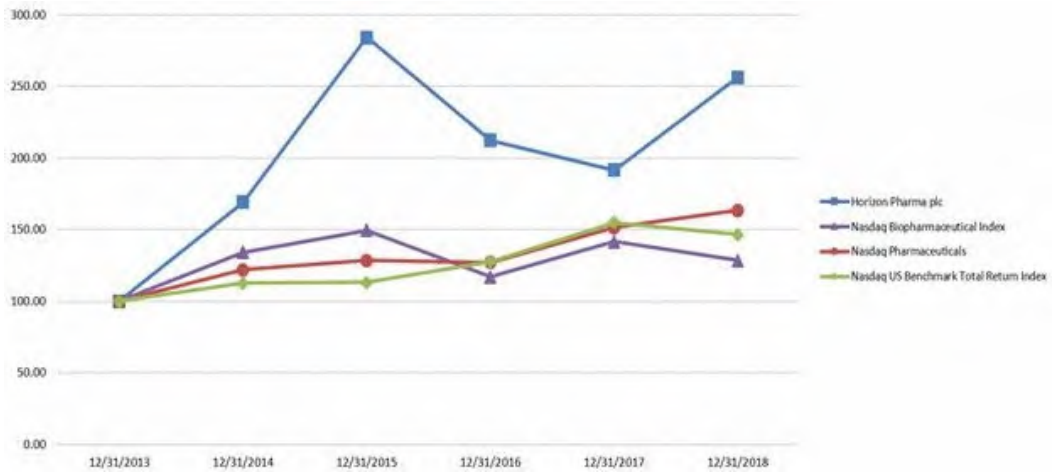
The closing price of our ordinary shares on February 20, 2019 was $21.54. As of February 20, 2019, there were approximately thirteen holders of record of our ordinary shares. Because almost all of our ordinary shares are held by brokers, nominees and other institutions on behalf of shareholders, we are unable to estimate the total number of shareholders represented by these record holders.

Performance Graph

The following graph shows a comparison from December 31, 2013, through December 31, 2018, of the cumulative total return for (i) our ordinary shares, (ii) the Nasdaq Biopharmaceutical Index, (iii) Nasdaq Pharmaceuticals and (iv) the Nasdaq U.S. Benchmark Total Return Index.

Going forward, our performance graphs will no longer include the Nasdaq Pharmaceuticals Index as we believe the Nasdaq Biopharmaceutical Index is more closely aligned with our peer group.

Information set forth in the graph below represents the performance of the Horizon Pharma, Inc. common stock from December 31, 2013, until September 18, 2014, the day before the consummation of the Vidara Merger, and the performance of our ordinary shares from September 19, 2014, through December 31, 2018. Our ordinary shares trade on the same exchange, the Nasdaq Global Select Market, and under the same trading symbol, "HZNP", as the Horizon Pharma, Inc. common stock prior to the Vidara Merger. The graph assumes an initial investment of $100 on December 31, 2013. The comparisons in the graph are required by the Securities and Exchange Commission and are not intended to forecast or be indicative of possible future performance of our ordinary shares.



	12/31/2013	12/31/2014	12/31/2015	12/31/2016	12/31/2017	12/31/2018
Cumulative Returns						
Horizon Pharma plc	$ 100.00	$ 169.16	$ 284.38	$ 212.34	$ 191.60	$ 256.43
Nasdaq Biopharmaceuticals Index	100.00	134.10	149.42	117.02	141.66	128.45
Nasdaq Pharmaceuticals	100.00	121.82	128.44	127.04	151.33	163.37
Nasdaq U.S. Benchmark Total Return Index	100.00	112.46	113.00	127.70	155.01	146.57

The foregoing graph and table are furnished solely with this report, and are not filed with this report, and shall not be deemed incorporated by reference into any other filing under the Securities Act of 1933, as amended, or the Securities Act, or the Securities Exchange Act of 1934, as amended, whether made by us before or after the date hereof, regardless of any general incorporation language in any such filing, except to the extent we specifically incorporate this material by reference into any such filing.

Dividend Policy

We have never declared or paid cash dividends on our common equity. We currently intend to retain all available funds and any future earnings to support operations and finance the growth and development of our business and do not intend to pay cash dividends on our ordinary shares for the foreseeable future. Under Irish law, dividends may only be paid, and share repurchases and redemptions must generally be funded only out of, "distributable reserves". In addition, our ability to pay cash dividends is currently prohibited by the terms of our credit agreement with Citibank, N.A., as administrative and collateral agent, $475.0 million aggregate principal amount of 6.625% Senior Notes due 2023 and the $300.0 million aggregate principal amount of 8.75% Senior Notes due 2024, subject to customary exceptions. Any future determination as to the payment of dividends will, subject to Irish legal requirements, be at the sole discretion of our board of directors and will depend on our financial condition, results of operations, capital requirements and other factors our board of directors deems relevant.

Securities Authorized for Issuance under Equity Compensation Plans

See Item 12 of Part III of this Annual Report on Form 10-K regarding information about securities authorized for issuance under our equity compensation plans.

Recent Sales of Unregistered Securities

There were no unregistered sales of equity securities by us during the year ended December 31, 2018.

Issuer Repurchases of Equity Securities

None.

Irish Law Matters

See *Irish Law Matters* included in Item 1 of Part I of this Annual Report on Form 10-K.

Item 6. Selected Financial Data

The selected statement of comprehensive loss data and selected statement of cash flows data for the years ended December 31, 2018, 2017 and 2016, and the balance sheet data as of December 31, 2018 and 2017 have been derived from our audited financial statements included elsewhere in this Annual Report on Form 10-K. The selected statements of comprehensive loss data and selected statement of cash flows data for the years ended December 31, 2015 and 2014, and the balance sheet data as of December 31, 2016, 2015 and 2014 have been derived from audited financial statements which are not included in this Annual Report on Form 10-K.

Our historical results are not necessarily indicative of future results. The selected financial data should be read in conjunction with "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our financial statements and related notes included elsewhere in this Annual Report on Form 10-K.

On September 19, 2014, the businesses of Horizon Pharma, Inc., our predecessor, and Vidara Therapeutics International Public Limited Company were combined in a merger transaction, on May 7, 2015, we completed our acquisition of Hyperion Therapeutics, Inc., on January 13, 2016, we completed our acquisition of Crealta Holdings LLC and on October 25, 2016, we completed our acquisition of Raptor Pharmaceutical Corp. The financial data presented below include the results of operations of the merged or acquired Vidara, Hyperion, Crealta and Raptor businesses from the applicable dates of merger or acquisition.

	As of December 31,				
	2018	2017	2016	2015	2014
	(in thousands)				
Selected Balance Sheet Data					
Cash and cash equivalents	$ 958,712	$ 751,368	$ 509,055	$ 859,616	$ 218,807
Working capital	786,522	473,199	440,430	748,595	106,024
Total assets (1)(4)(7)	4,146,371	4,202,298	4,305,477	3,073,060	1,126,302
Total debt, net (1)	1,896,684	1,901,655	1,807,493	1,136,756	334,012
Accumulated deficit (2)(3)(4)(7)	(1,314,718)	(1,242,117)	(846,750)	(681,187)	(720,719)
Total shareholders' equity (2)(3)(4)(7)	1,054,157	1,001,310	1,265,050	1,313,145	540,204

	For the Years Ended December 31,				
	2018	2017	2016	2015	2014
	(in thousands, except per share data)				
Selected Statement of Comprehensive Loss Data					
Net sales	$ 1,207,570	$ 1,056,231	$ 981,120	$ 757,044	$ 296,955
Cost of goods sold (7)	422,317	537,334	392,001	219,502	78,753
Gross profit (7)	785,253	518,897	589,119	537,542	218,202
Loss before benefit for income taxes (7)	(119,146)	(504,334)	(226,814)	(132,712)	(269,687)
Net (loss) income (7)	(74,187)	(401,585)	(165,563)	39,532	(263,603)
Net (loss) income per ordinary share – basic (7)	(0.45)	(2.46)	(1.03)	0.27	(3.15)
Net (loss) income per ordinary share – diluted (7)	(0.45)	(2.46)	(1.03)	0.25	(3.15)
Selected Statement of Cash Flows Data					
Net cash provided by operating activities (6)	$ 194,543	$ 284,340	$ 369,456	$ 249,536	$ 44,239
Net cash provided by (used in) investing activities (5)	27,653	(102,185)	(1,370,646)	(1,049,299)	(244,410)
Net cash (used in) provided by financing activities (6)	(16,596)	54,276	657,074	1,442,481	338,285

(1) On January 1, 2016, we retrospectively adopted Accounting Standards Update, or ASU, No. 2015-03, *Interest-Imputation of Interest (Subtopic 835-30): Simplifying the Presentation of Debt Issuance Costs*, simplifying the presentation of debt issuance costs. As a result, deferred financing costs of $11.5 million that were classified within "total assets" at December 31, 2014, were reclassified to "total debt, net" in the above table to conform prior-period classifications as a result of the new guidance.

(2) On January 1, 2017, we adopted ASU No. 2016-09, *Improvements to Employee Share-Based Payment Accounting*, on a modified retrospective basis and recorded a decrease of $7.2 million in net deferred tax liabilities and a corresponding decrease in accumulated deficit during the year ended December 31, 2017.

(3) On January 1, 2018, we adopted ASU No. 2016-16, *Income Taxes,* on a modified retrospective basis through a cumulative-effect adjustment to retained earnings and we reclassified $9.3 million of unrecognized deferred charges directly to retained earnings.

(4) On January 1, 2018, we adopted ASU No. 2014-09, *Revenue from Contracts with Customers,* on a modified retrospective basis and we reclassified $11.3 million of deferred revenue directly to retained earnings. In addition, as a result of the adoption of ASU No. 2014-09, we now present all allowances for medicine returns in accrued expenses on the consolidated balance sheets. This resulted in a reclassification of $37.9 million, $15.2 million and $14.5 million, and $3.2 million, respectively, of allowances for medicine returns from "accounts receivable, net" to "accrued expenses" in the consolidated balance sheets at December 31, 2017, 2016, 2015 and 2014.

(5) On January 1, 2018, we adopted ASU No. 2016-18, Statement of Cash Flows (Topic 230): Restricted Cash. This resulted in movements in restricted cash of $0.6 million, $5.2 million and $1.1 million in the consolidated statement of cash flows for the years ended December 31, 2017, 2016 and 2015, respectively, no longer being included in "net cash provided by (used in) investing activities".

(6) On January 1, 2018, we adopted ASU No. 2016-15, Statement of Cash Flows (Topic 230): Classification of Certain Cash Receipts and Cash Payments. This resulted in a reclassification of $4.1 million, $55.4 million and $16.7 million in the consolidated statement of cash flows for the years ended December 31, 2017, 2015 and 2014, respectively, from "net cash provided by operating activities" to "net cash (used in) provided by financing activities".

(7) During the course of preparing the consolidated financial statements for the year ended December 31, 2018, we identified an error in the measurement of the contingent royalty liability calculation pertaining to the royalty end date for one of our medicines. The revision resulted in certain adjustments to the consolidated financial statements as of and for the years ended December 31, 2017 and December 31, 2016, and the revised amounts are presented above. See Note 1 of the Notes to consolidated financial statements, included in Item 15 of this Annual Report on Form 10-K, for further details of this error and the related revisions.

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and the related notes appearing at the end of this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. You should read the "Risk Factors" section of this Annual Report on Form 10-K for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

The discussion below contains "forward-looking statements," as defined in Section 21E of the Securities Exchange Act of 1934, as amended, that reflect our current expectations regarding our future growth, results of operations, business strategy and plans, financial condition, cash flows, performance, business prospects and opportunities, as well as assumptions made by, and information currently available to, our management. We have tried to identify forward-looking statements by using words such as "anticipate," "believe," "plan," "expect," "intend," "will," and similar expressions, but these words are not the exclusive means of identifying forward-looking statements. These statements are based on information currently available to us and are subject to various risks, uncertainties, and other factors, including, but not limited to, those matters discussed in Item 1A. "Risk Factors" in Part I of this Annual Report on Form 10-K, that could cause our actual growth, results of operations, business strategy and plans, financial condition, cash flows, performance, business prospects and opportunities to differ materially from those expressed in, or implied by, these statements. Except as expressly required by the federal securities laws, we undertake no obligation to update such factors or to publicly announce the results of any of the forward-looking statements contained herein to reflect future events, developments, or changed circumstances, or for any other reason.

Unless otherwise indicated or the context otherwise requires, references to "we", "us" and "our" refer to Horizon Pharma plc and its consolidated subsidiaries.

During the course of preparing the consolidated financial statements for the year ended December 31, 2018, we identified an error in the measurement of the contingent royalty liability calculation pertaining to the royalty end date for one of our medicines. The revision resulted in certain adjustments to the consolidated financial statements as of and for the years ended December 31, 2017 and December 31, 2016, and the revised amounts are presented below. See Note 1 of the Notes to consolidated financial statements, included in Item 15 of this Annual Report on Form 10-K, for further details of this error and the related revisions. These revisions had no impact on adjusted EBITDA, non-GAAP net income or non-GAAP earnings per share that are presented in our Non-GAAP Financial Measures.

OUR BUSINESS

Horizon Pharma plc is focused on researching, developing and commercializing innovative medicines that address unmet treatment needs for rare and rheumatic diseases. By expanding our growing pipeline of medicines in development and exploring all potential uses for currently marketed medicines, we strive to make a powerful difference for patients, their caregivers and physicians.

Effective as of the second quarter of 2018, we realigned our reportable segments to reflect changes in the manner in which our chief operating decision maker assesses financial information for decision-making purposes. All prior year amounts have been reclassified to conform to our current reporting structure.

We have two reportable segments, (i) the orphan and rheumatology segment, our strategic growth business, and (ii) the primary care segment, and we report net sales and segment operating income for each segment.

Our marketed medicines are:

Orphan and Rheumatology
KRYSTEXXA® (pegloticase injection), for intravenous infusion
RAVICTI® (glycerol phenylbutyrate) oral liquid
PROCYSBI® (cysteamine bitartrate) delayed-release capsules, for oral use
ACTIMMUNE® (interferon gamma-1b) injection, for subcutaneous use
RAYOS® (prednisone) delayed-release tablets
BUPHENYL® (sodium phenylbutyrate) Tablets and Powder
QUINSAIR™ (levofloxacin) solution for inhalation
Primary Care
PENNSAID® (diclofenac sodium topical solution) 2% w/w, or PENNSAID 2%, for topical use
DUEXIS® (ibuprofen/famotidine) tablets, for oral use
VIMOVO® (naproxen/esomeprazole magnesium) delayed-release tablets, for oral use
MIGERGOT® (ergotamine tartrate & caffeine suppositories), for rectal use

Since January 1, 2016, we completed the following acquisitions and divestitures:

- Effective January 1, 2019, we amended our license and supply agreements with Jagotec AG and Skyepharma AG, which are affiliates of Vectura Group plc, or Vectura. Under these amendments, we agreed to transfer all economic benefits of LODOTRA® in Europe to Vectura during an initial transition period, with full rights transferring to Vectura when certain transfer activities have been completed. We will no longer record LODOTRA revenue from January 1, 2019. See the "Manufacturing, Commercial, Supply and License Agreements" section, included in Item 1 of this Annual Report on Form 10-K, for further details of the amendments.
- On December 28, 2018, we sold our rights to RAVICTI and AMMONAPS (known as BUPHENYL in the United States) outside of North America and Japan to Medical Need Europe AB, part of the Immedica Group, or Immedica. We previously distributed RAVICTI and AMMONAPS through a commercial partner in Europe and other non-U.S. markets. We have retained the rights to RAVICTI and BUPHENYL in North America and Japan.
- On June 30, 2017, we completed our acquisition of certain rights to interferon gamma-1b from Boehringer Ingelheim International GmbH, or Boehringer Ingelheim International, in all territories outside of the United States, Canada and Japan. Interferon gamma-1b is known as IMUKIN outside of the United States, Canada and Japan. On July 24, 2018, we sold the rights to IMUKIN in all territories outside of the United States, Canada and Japan to Clinigen Group plc, or Clinigen, for an upfront payment and a potential additional contingent consideration payment, or the IMUKIN sale.
- On June 23, 2017, we sold our European subsidiary that owned the marketing rights to PROCYSBI (cysteamine bitartrate) delayed-release capsules and QUINSAIR (levofloxacin inhalation solution) in Europe, the Middle East and Africa, or EMEA, regions, or the Chiesi divestiture, to Chiesi Farmaceutici S.p.A., or Chiesi.
- On May 8, 2017, we completed our acquisition of River Vision Development Corp., or River Vision, which added the late development-stage rare disease biologic medicine candidate teprotumumab to our research and development pipeline.
- On October 25, 2016, we completed our acquisition of Raptor Pharmaceutical Corp., or Raptor, which added the rare disease medicines PROCYSBI and QUINSAIR to our medicine portfolio.
- On January 13, 2016, we completed our acquisition of Crealta Holdings LLC, or Crealta, which added the rare disease medicine KRYSTEXXA and the primary care medicine MIGERGOT to our medicine portfolio.

The consolidated financial statements presented herein include the results of operations of the acquired businesses from the applicable dates of acquisition. See Note 4 of the Notes to consolidated financial statements, included in Item 15 of this Annual Report on Form 10-K, for further details of our acquisitions and divestitures.

Teprotumumab, our fully human monoclonal antibody IGF-IR inhibitor, is currently in Phase 3 development for thyroid eye disease and we expect topline results from the Phase 3 trial in the first quarter of 2019. We are currently

investing in the teprotumumab clinical program as well as initiatives to prepare for its potential U.S. commercial launch. Should our Phase 3 trial be successful, we anticipate incurring significant additional costs related to the launch of the medicine. However, if our Phase 3 trial is unsuccessful, we expect to incur additional expense, including the write-off of our inventory on hand at December 31, 2018, of $2.6 million, the write-off of other non-current assets at December 31, 2018 of $4.3 million, payments related to future purchase commitments of approximately $7.3 million and costs we could incur to wind down the clinical program.

Strategy

We aspire to be a leading rare disease biopharma company that delivers innovative therapies to patients and generates high returns for our shareholders. Our strategy is to build a robust and differentiated pipeline and to maximize the growth of our marketed rare disease medicines, in particular, KRYSTEXXA, our medicine for uncontrolled gout. We are executing on our strategy by accelerating the growth of our rare disease medicine portfolio through differentiated commercial strategies, business development efforts, and the expansion of our pipeline with post-marketing and development-stage programs. We are strongly committed to helping ensure patients have access to medicines and support services and to investing in the further development of medicines for patients with rare or underserved diseases.

Orphan and Rheumatology

RAVICTI, PROCYSBI, ACTIMMUNE, BUPHENYL and QUINSAIR, are our marketed orphan medicines – all for rare diseases. Our strategy for RAVICTI is to drive growth through increased awareness and diagnosis of urea cycle disorders; to drive conversion to RAVICTI from older-generation nitrogen scavengers, such as generic forms of sodium phenylbutyrate based on the medicine's differentiated benefits; and to increase awareness of label expansion to position RAVICTI as first line of therapy. With respect to PROCYSBI, our strategy is to drive conversion of patients to PROCYSBI from older-generation immediate-release capsules of cysteamine bitartrate; increase the uptake of diagnosed but untreated patients; identify previously undiagnosed patients who are suitable for treatment; and increase awareness of the expanded label to position PROCYSBI as a first line of therapy. Our strategy with respect to ACTIMMUNE includes driving growth by increasing awareness and diagnosis of chronic granulomatous disease and increasing the persistence of and adherence to treatment.

With our May 2017 acquisition of River Vision, we added the late-stage rare disease biologic medicine candidate teprotumumab to our pipeline. Teprotumumab, which successfully completed a Phase 2 clinical trial, targets the treatment of thyroid eye disease, a debilitating autoimmune condition for which there is no approved treatment. Our strategy for teprotumumab is to support its continued clinical development and pursue regulatory approval. The River Vision acquisition further demonstrates our commitment to rare disease medicines and expands and diversifies our rare disease medicine pipeline to support sustainable longer-term growth. We initiated the Phase 3 confirmatory clinical trial evaluating teprotumumab for the treatment of moderate-to-severe active thyroid eye disease during the fourth quarter of 2017 and enrollment was completed in September 2018, well ahead of schedule. We anticipate that data from the trial will be available during the first quarter of 2019.

The rare disease medicine KRYSTEXXA is our primary marketed rheumatology medicine, indicated for the treatment of uncontrolled gout, or gout that is refractory (unresponsive) to conventional therapies. We are focused on optimizing and maximizing the peak sales potential of KRYSTEXXA by expanding our commercialization efforts as well as investing in education, patient and physician outreach, and investigation programs that demonstrate KRYSTEXXA as an effective treatment of uncontrolled gout. We believe that KRYSTEXXA represents a significant opportunity and potential growth driver within our orphan and rheumatology segment. We also market the rheumatology medicine RAYOS.

Primary Care

Our strategy with respect to our primary care medicines, which include PENNSAID 2%, DUEXIS, VIMOVO and MIGERGOT, is to educate physicians about these clinically differentiated medicines and the benefits they offer. Patients are able to fill prescriptions for these medicines through pharmacies participating in our HorizonCares patient access program, as well as other pharmacies. In addition, we have entered into business arrangements with pharmacy benefit managers, or PBMs, and other payers to secure formulary status and reimbursement of our primary care medicines. The business arrangements with the PBMs generally require us to pay administrative fees and rebates to the PBMs and other payers for qualifying prescriptions.

We market all of our medicines in the United States through our field sales force, which numbered approximately 420 representatives as of December 31, 2018.

RESULTS OF OPERATIONS

Year Ended December 31, 2018 Compared to Year Ended December 31, 2017

Consolidated Results

	For the Years Ended December 31,		
	2018	2017	Change
	(in thousands)		
Net sales	$ 1,207,570	$ 1,056,231	$ 151,339
Cost of goods sold	422,317	537,334	(115,017)
Gross profit	**785,253**	**518,897**	**266,356**
Operating expenses:			
Research and development	82,762	224,962	(142,200)
Selling, general and administrative	692,485	655,093	37,392
Impairment of long-lived assets	50,302	22,270	28,032
Gain on sale of assets	(42,688)	—	(42,688)
Total operating expenses	**782,861**	**902,325**	**(119,464)**
Operating income (loss)	**2,392**	**(383,428)**	**385,820**
Other expense, net:			
Interest expense, net	(121,692)	(126,523)	4,831
Foreign exchange loss	(192)	(260)	68
Gain on divestiture	—	6,267	(6,267)
Loss on debt extinguishment	—	(978)	978
Other income, net	346	588	(242)
Total other expense, net	**(121,538)**	**(120,906)**	**(632)**
Loss before benefit for income taxes	**(119,146)**	**(504,334)**	**385,188**
Benefit for income taxes	(44,959)	(102,749)	57,790
Net loss	**$ (74,187)**	**$ (401,585)**	**$ 327,398**

Net sales. Net sales increased $151.3 million, or 14.3%, to $1,207.6 million during the year ended December 31, 2018, from $1,056.2 million during the year ended December 31, 2017. The increase in net sales during the year ended December 31, 2018, was primarily due to higher net sales in our orphan and rheumatology segment.

The following table presents a summary of total net sales attributed to geographic sources for the years ended December 31, 2018 and 2017 (in thousands, except percentages):

	Year Ended December 31, 2018		Year Ended December 31, 2017	
	Amount	% of Total Net Sales	Amount	% of Total Net Sales
United States	$ 1,186,519	98%	$ 1,026,527	97%
Rest of world	21,051	2%	29,704	3%
Total net sales	**$ 1,207,570**		**$ 1,056,231**	

The following table reflects the components of net sales for the years ended December 31, 2018 and 2017 (in thousands, except percentages):

	Year Ended December 31,		Change	Change
	2018	2017	$	%
KRYSTEXXA	$ 258,920	$ 156,483	$ 102,437	65%
RAVICTI	226,650	193,918	32,732	17%
PROCYSBI	154,895	137,740	17,155	12%
ACTIMMUNE	105,563	110,993	(5,430)	(5)%
RAYOS	61,067	52,125	8,942	17%
BUPHENYL	21,810	20,792	1,018	5%
LODOTRA	2,067	5,393	(3,326)	(62)%
QUINSAIR	504	3,442	(2,938)	(85)%
Orphan and Rheumatology net sales	**$ 831,476**	**$ 680,886**	**$ 150,590**	**22%**
PENNSAID 2%	190,206	191,050	(844)	(0)%
DUEXIS	114,672	121,161	(6,489)	(5)%
VIMOVO	67,646	57,666	9,980	17%
MIGERGOT	3,570	5,468	(1,898)	(35)%
Primary care net sales	**$ 376,094**	**$ 375,345**	**$ 749**	**0%**
Total net sales	**$ 1,207,570**	**$ 1,056,231**	**$ 151,339**	**14%**

Orphan and Rheumatology

KRYSTEXXA. Net sales increased $102.4 million, or 65%, to $258.9 million during the year ended December 31, 2018, from $156.5 million during the year ended December 31, 2017. Net sales increased by approximately $108.5 million resulting from volume growth, partially offset by a decrease of approximately $6.1 million due to lower net pricing.

RAVICTI. Net sales increased $32.7 million, or 17%, to $226.6 million during the year ended December 31, 2018, from $193.9 million during the year ended December 31, 2017. Net sales in the United States increased by approximately $30.8 million, which was composed of an increase of $24.4 million due to higher net pricing and $6.4 million due to volume growth. Net sales outside the United States increased by approximately $1.9 million primarily due to higher sales volume. On December 28, 2018, we sold our rights to RAVICTI outside of North America and Japan to Immedica.

PROCYSBI. Net sales increased $17.2 million, or 12%, to $154.9 million during the year ended December 31, 2018, from $137.7 million during the year ended December 31, 2017. Net sales in the United States increased by approximately $22.7 million, which was composed of $15.6 million due to higher net pricing and $7.1 million resulting from volume growth. Net sales outside the United States decreased by approximately $5.5 million primarily as a result of the Chiesi divestiture in June 2017.

ACTIMMUNE. Net sales decreased $5.4 million, or 5%, to $105.6 million during the year ended December 31, 2018, from $111.0 million during the year ended December 31, 2017. Net sales decreased by approximately $11.2 million resulting from lower volume, partially offset by an increase of approximately $5.8 million due to higher net pricing.

RAYOS. Net sales increased $8.9 million, or 17%, to $61.0 million during the year ended December 31, 2018, from $52.1 million during the year ended December 31, 2017. Net sales increased by approximately $5.0 million resulting from volume growth and approximately $3.9 million due to higher net pricing.

BUPHENYL. Net sales increased $1.0 million, or 5%, to $21.8 million during the year ended December 31, 2018, from $20.8 million during the year ended December 31, 2017. Net sales increased by approximately $2.0 million due to volume growth, partially offset by a decrease of approximately $1.0 million resulting from lower net pricing. On December 28, 2018, we sold our rights to AMMONAPS outside of North America and Japan to Immedica.

LODOTRA. Net sales decreased $3.3 million, or 62%, to $2.1 million during the year ended December 31, 2018, from $5.4 million during the year ended December 31, 2017. The decrease was due to decreased shipments to our European distribution partner, Mundipharma International Corporation Limited, or Mundipharma. LODOTRA sales to Mundipharma occurred at the time we shipped, based on Mundipharma's estimated requirements. Accordingly, LODOTRA sales were not linear or directly tied to Mundipharma's in-market sales and could therefore fluctuate significantly from period to period. Effective January 1, 2019, we amended our license and supply agreements with Jagotec AG and Skyepharma AG, which are affiliates of Vectura. Under these amendments, we agreed to transfer all economic benefits of LODOTRA in Europe to Vectura during an initial transition period, with full rights transferring to Vectura when certain transfer activities have been completed. We will no longer record LODOTRA revenue from January 1, 2019. See the "Manufacturing, Commercial, Supply and License Agreements" section, included in Item 1 of this Annual Report on Form 10-K, for further details of the amendments.

QUINSAIR. Net sales decreased $2.9 million, or 85%, to $0.5 million during the year ended December 31, 2018, from $3.4 million during the year ended December 31, 2017, primarily due to lower volume following the Chiesi divestiture.

Primary Care

PENNSAID 2%. Net sales decreased $0.8 million to $190.2 million during the year ended December 31, 2018, from $191.0 million during the year ended December 31, 2017. Net sales decreased by approximately $12.1 million due to lower volume, partially offset by an increase of approximately $11.3 million due to higher net pricing.

DUEXIS. Net sales decreased $6.5 million, or 5%, to $114.7 million during the year ended December 31, 2018, from $121.2 million during the year ended December 31, 2017. Net sales decreased by approximately $6.4 million due to lower volume and approximately $0.1 million due to lower net pricing.

VIMOVO. Net sales increased $10.0 million, or 17%, to $67.6 million during the year ended December 31, 2018, from $57.6 million during the year ended December 31, 2017. Net sales increased by approximately $23.2 million due to higher net pricing, partially offset by a decrease of approximately $13.2 million resulting from lower volume.

MIGERGOT. Net sales decreased $1.9 million, or 35%, to $3.6 million during the year ended December 31, 2018, from $5.5 million during the year ended December 31, 2017. Net sales decreased by approximately $1.6 million due to lower volume and approximately $0.3 million due to lower net pricing.

The table below reconciles our gross to net sales for the years ended December 31, 2018 and 2017 (in millions, except percentages):

	Year Ended December 31, 2018		Year Ended December 31, 2017	
	Amount	% of Gross Sales	Amount	% of Gross Sales
Gross sales	$ 4,264.5	100.0%	$ 4,057.8	100.0%
Adjustments to gross sales:				
Prompt pay discounts	(75.1)	(1.8)%	(80.2)	(2.0)%
Medicine returns	(25.1)	(0.6)%	(45.6)	(1.1)%
Co-pay and other patient assistance	(1,970.4)	(46.2)%	(1,907.6)	(47.0)%
Commercial rebates and wholesaler fees	(589.6)	(13.8)%	(641.5)	(15.8)%
Government rebates and chargebacks	(396.7)	(9.3)%	(326.7)	(8.1)%
Total adjustments	**(3,056.9)**	**(71.7)%**	**(3,001.6)**	**(74.0)%**
Net sales	**$ 1,207.6**	**28.3%**	**$ 1,056.2**	**26.0%**

During the year ended December 31, 2018, commercial rebates and wholesaler fees, as a percentage of gross sales, decreased to 13.8% from 15.8% during the year ended December 31, 2017, primarily as a result of a change in the mix of medicines sold and lower rates paid to distributors during 2018 compared to 2017.

During the year ended December 31, 2018, government rebates and chargebacks, as a percentage of gross sales, increased to 9.3% from 8.1% during the year ended December 31, 2017, primarily as a result of a change in the mix of medicines sold.

On a quarter-to-quarter basis, our net sales have traditionally been lower in first half of the year, particularly in the first quarter, with the second half of the year representing a greater share of overall net sales each year. This is due to annual managed care plan changes and the re-setting of patients' medical insurance deductibles at the beginning of each year, resulting in higher co-pay and other patient assistance costs as patients meet their annual medical insurance deductibles during the first and second quarters, and higher net sales in the second half of the year after patients meet their deductibles and healthcare plans reimburse a greater portion of the total cost of our medicines.

Additionally, on January 1, 2019, the 340B ceiling price rule became effective. With respect to KRYSTEXXA, the "additional rebate" scheme of the 340B pricing program, as applied to the historical pricing of KRYSTEXXA both before and after we acquired the medicine, have resulted in a 340B ceiling price of one penny. A material portion of KRYSTEXXA prescriptions (approximately twenty to twenty-five percent) are written by healthcare providers that are eligible for 340B drug pricing and therefore the reduction in 340B pricing to a penny has negatively impacted our net sales from KRYSTEXXA.

Cost of Goods Sold. Cost of goods sold decreased $115.0 million to $422.3 million during the year ended December 31, 2018, from $537.3 million during the year ended December 31, 2017. As a percentage of net sales, cost of goods sold was 35.0% during the year ended December 31, 2018, compared to 50.9% during the year ended December 31, 2017. The decrease in cost of goods sold was primarily attributable to a $101.8 million decrease in inventory step-up expense.

Because inventory step-up expense is acquisition-related, will not continue indefinitely and has a significant effect on our gross profit, gross margin percentage and net income (loss) for all affected periods, we disclose balance sheet and income statement amounts related to inventory step-up within the notes to the consolidated financial statements. The decrease in inventory step-up expense of $101.8 million recorded to cost of goods sold during the year ended December 31, 2018 compared to the prior year was primarily related to KRYSTEXXA, PROCYSBI and QUINSAIR inventory step-up expense. KRYSTEXXA inventory step-up expense recorded during the year ended December 31, 2018 was $17.0 million compared to $78.3 million recorded during the year ended December 31, 2017. PROCYSBI and QUINSAIR inventory step-up expense recorded during the year ended December 31, 2018 was $0.3 million compared to $40.8 million recorded during the year ended December 31, 2017.

Research and Development Expenses. Research and development expenses decreased $142.2 million to $82.8 million during the year ended December 31, 2018, from $225.0 million during the year ended December 31, 2017. The decrease was primarily attributable to $150.3 million related to the acquisition of River Vision during the year ended December 31, 2017. Pursuant to Accounting Standards Codification Topic 805, Business Combinations, or ASC 805, as amended by ASU No. 2017-01, we accounted for the River Vision acquisition as the purchase of an in-process research and development, or IPR&D, asset and, pursuant to ASC 730, Research and Development, or ASC 730, recorded the purchase as a research and development expense during the year ended December 31, 2017. Additionally, during the year ended December 31, 2017, we entered into an agreement to license HZN-003, a rheumatology pipeline program with the objective of enhancing our leadership position in the uncontrolled gout market, from MedImmune LLC, or MedImmune, and we paid MedImmune an upfront cash payment of $12.0 million which we recorded as a "research and development" expense in the consolidated statement of comprehensive loss during the year ended December 31, 2017 and included in "accrued expenses" as of December 31, 2017. The upfront payment was subsequently paid in January 2018. Excluding the costs attributable to the acquisition of River Vision and HZN-003, research and development expenses increased by $20.1 million during the year ended December 31, 2018, compared to the year ended December 31, 2017, primarily due to the costs associated with the development of teprotumumab.

Selling, General and Administrative Expenses. Selling, general and administrative expenses increased $37.4 million to $692.5 million during the year ended December 31, 2018, from $655.1 million during the year ended December 31, 2017. The increase was primarily attributable to the expansion of our KRYSTEXXA sales force that was initiated during the second half of 2017 and other activities to support the growth in sales of the medicine, and pre-launch costs for teprotumumab.

Impairment of Long-Lived Assets. During the year ended December 31, 2018, we recorded an impairment of $37.9 million to fully write off the book value of developed technology related to PROCYSBI in Canada and Latin America due primarily to lower anticipated future net sales based on a Patented Medicine Prices Review Board, or PMPRB, review. We also recorded an impairment of $10.6 million during the year ended December 31, 2018, to fully write off the book value of developed technology related to LODOTRA as result of amendments to our license and supply agreements with Jagotec AG and Skyepharma AG, which are affiliates of Vectura. Under these amendments, effective January 1, 2019, we agreed to transfer all economic benefits of LODOTRA in Europe to Vectura during an initial transition period, with full rights transferring to Vectura when certain transfer activities have been completed. We will no longer record LODOTRA revenue from January 1, 2019. Impairment of long-lived assets of $22.3 million during the year ended December 31, 2017, represents the impairment of a non-current asset recorded following payment to Boehringer Ingelheim International for the acquisition of certain rights to interferon gamma-1b. This was previously included within "selling, general and administrative" expenses. On July 24, 2018, we completed the IMUKIN sale as further described in the next paragraph.

Gain on sale of assets. During the year ended December 31, 2018, we completed the sale of rights to RAVICTI and AMMONAPS outside of North America and Japan for cash proceeds of $35.0 million, and we recorded a gain of $30.4 million on the sale. Additionally, we completed the IMUKIN sale for cash proceeds of $9.5 million, with a potential additional contingent consideration payment and we recorded a gain of $12.3 million on the sale.

Interest Expense, Net. Interest expense, net, decreased $4.8 million to $121.7 million during the year ended December 31, 2018, from $126.5 million during the year ended December 31, 2017. The decrease in net interest expense was primarily due to an increase in interest income of $8.5 million primarily due to higher cash balances, partially offset by an increase of $3.7 million in interest expense.

Gain on divestiture. During the year ended December 31, 2017, we completed the Chiesi divestiture for an upfront payment of $72.5 million, which reflects $3.1 million of cash divested, with additional potential milestone payments based on sales thresholds, and we recorded a gain of $6.3 million on the divestiture.

Benefit for Income Taxes. During the year ended December 31, 2018, we recorded a benefit for income taxes of $45.0 million compared to $102.7 million during the year ended December 31, 2017. The reduction in benefit for income taxes of $57.7 million during the year ended December 31, 2018, compared to year ended December 31, 2017, was primarily due to a decrease in pre-tax losses and the tax rate at which some of these reduced losses were tax effected resulting in a tax provision of $61.1 million and income tax expense of $45.8 million generated on an intra-company transfer of assets other than inventory during the year ended December 31, 2018.

Additionally, during the year ended December 31, 2017, we recorded a provisional estimate of $74.9 million net benefit following the enactment in the United States of H.R. 1, "An Act to provide for reconciliation pursuant to titles II and V of the concurrent resolution on the budget for fiscal year 2018", informally titled the Tax Cuts and Jobs Act, or the Tax Act, in December 2017, which net benefit included a $134.2 million tax benefit from the revaluation of our U.S. net deferred tax liability based on the revised U.S. federal tax rate of 21 percent, partially offset by the write-off of the $59.2 million deferred tax asset related to our U.S. interest expense carryforwards under Section 163(j) of the Internal Revenue Code of 1986, as amended, or the Code. On December 22, 2017, the SEC staff issued Staff Accounting Bulletin No. 118, or SAB 118, which provides guidance on accounting for the tax effects of the Tax Act. SAB 118 provided a measurement period that should not extend beyond one year from the date of enactment for companies to complete the accounting under ASC 740, Income Taxes. In accordance with SAB 118, we reflected the income tax effects of those aspects of the Tax Act for which the accounting under ASC 740 was complete. To the extent that our accounting for certain income tax effects of the Tax Act was incomplete but it was possible to determine a reasonable estimate, we recorded a provisional estimate in the consolidated financial statements as of December 31, 2017.

On April 2, 2018, the U.S. Treasury Department and the U.S. Internal Revenue Service issued Notice 2018-28, or the Notice, which provided guidance for computing the business interest expense limitation under the Tax Act and clarified the treatment of interest disallowed and carried forward under Section 163(j) of the Code prior to enactment of the Tax Act. In accordance with the measurement period provisions under SAB 118 and the guidance in the Notice we reinstated the deferred tax asset related to our U.S. interest expense carryforwards under Section 163(j) based on the revised U.S. federal tax rate of 21 percent. The impact of the deferred tax asset reinstatement in accordance with SAB 118 during the year ended December 31, 2018 was a $37.4 million increase to our benefit for income taxes and a corresponding decrease to the U.S. group net deferred tax liability position. We had no other material measurement period adjustments under SAB 118.

The remainder of the decrease in benefit for income taxes during the year ended December 31, 2018, compared to year ended December 31, 2017 resulted from a tax provision of $8.1 million attributable to the remeasurement of net U.S. deferred tax liabilities for the year ended December 31, 2018 due to an increase in U.S. state effective tax rates attributable to the enactment of certain U.S. state legislation during the year ended December 31, 2018. These decreases to the benefit for income taxes during the year ended December 31, 2018 were partially offset by an income tax expense of $51.1 million on non-deductible research and development costs which occurred during the year ended December 31, 2017 and did not re-occur for the year ended December 31, 2018, a tax benefit of $42.7 million U.S. federal tax and $7.9 million U.S. state tax benefit on the liquidation of a foreign partnership owned by us during the year ended December 31, 2018 and decreases to our current state income tax expense of $6.8 million resulting from current year pre-tax losses incurred in the U.S. group.

During the year ended December 31, 2017, the first of three tranches of our outstanding performance stock unit awards, or PSUs, issued in 2015 expired without payout as the minimum total compounded annual shareholder rate of return was not achieved. As a result, we wrote off to income tax expense $16.4 million of deferred tax assets related to previously recognized share-based compensation.

In relation to our outstanding PSUs at December 31, 2017, as our share price was lower than $32.70 for the twenty trading days ended March 22, 2018, and lower than $33.86 for the twenty trading days ended June 22, 2018, the second two tranches of PSU awards granted in 2015 expired without payment as the minimum total compounded annual shareholder rate of return was not achieved, and approximately $10.7 million and $12.6 million, respectively, of deferred tax assets at December 31, 2017, related to previously recognized share-based compensation expense was charged to income tax expense during the year ended December 31, 2018.

Information by Segment

See Note 13, *Segment and Other Information,* of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K for a reconciliation of our segment operating income to our total loss before benefit for income taxes for the years ended December 31, 2018 and 2017.

Orphan and Rheumatology

The following table reflects our orphan and rheumatology net sales and segment operating income for the years ended December 31, 2018 and 2017 (in thousands, except percentages).

	For the Year Ended December 31,			
	2018	2017	Change	% Change
Net sales	$ 831,476	$ 680,886	$ 150,590	22%
Segment operating income	290,014	241,135	48,879	20%

The increase in orphan and rheumatology net sales during the year ended December 31, 2018 is described in the *Consolidated Results* section above.

Segment operating income. Orphan and rheumatology segment operating income increased $48.9 million to $290.0 million during the year ended December 31, 2018, from $241.1 million during the year ended December 31, 2017. The increase was primarily attributable to an increase in net sales of $150.6 million as described above, partially offset by an increase in selling, general and administrative expenses of $68.2 million and an increase in research and development expenses of $17.6 million. The increase in selling, general and administrative expenses was mainly due to the expansion of our KRYSTEXXA sales force that was initiated during the second half of 2017 and other activities to support the growth in sales of the medicine, and pre-launch costs for teprotumumab. The increase in research and development expenses was primarily due to costs associated with the development of teprotumumab.

Primary Care

The following table reflects our primary care net sales and segment operating income for the years ended December 31, 2018 and 2017 (in thousands, except percentages).

	For the Year Ended December 31,			
	2018	2017	Change	% Change
Net sales	$ 376,094	$ 375,345	$ 749	0%
Segment operating income	160,447	149,133	11,314	8%

The increase in primary care net sales during the year ended December 31, 2018, is described in the *Consolidated Results* section above.

Segment operating income. Primary care segment operating income increased $11.3 million to $160.4 million during the year ended December 31, 2018, from $149.1 million during the year ended December 31, 2017. The increase was primarily attributable to stability in net sales and a decrease in selling, general and administrative expenses of $10.7 million.

Year Ended December 31, 2017 Compared to Year Ended December 31, 2016

Consolidated Results

	For the Years Ended December 31,		
	2017	2016	Change
	(in thousands)		
Net sales	$ 1,056,231	$ 981,120	$ 75,111
Cost of goods sold	537,334	392,001	145,333
Gross profit	**518,897**	**589,119**	**(70,222)**
Operating expenses			
Research and development	224,962	60,707	164,255
Selling, general and administrative	655,093	603,048	52,045
Impairment of long-lived assets	22,270	71,260	(48,990)
Total operating expenses	**902,325**	**735,015**	**167,310**
Operating loss	**(383,428)**	**(145,896)**	**(237,532)**
Other expense, net:			
Interest expense, net	(126,523)	(86,610)	(39,913)
Foreign exchange loss	(260)	(1,005)	745
Gain on divestiture	6,267	—	6,267
Loss on debt extinguishment	(978)	—	(978)
Other income, net:	588	6,697	(6,109)
Total other expense, net	**(120,906)**	**(80,918)**	**(39,988)**
Loss before benefit for income taxes	**(504,334)**	**(226,814)**	**(277,520)**
Benefit for income taxes	(102,749)	(61,251)	(41,498)
Net loss	**$ (401,585)**	**$ (165,563)**	**$ (236,022)**

Net sales. Net sales increased $75.1 million, or 8%, to $1,056.2 million during the year ended December 31, 2017, from $981.1 million during the year ended December 31, 2016, primarily due to lower net sales during the year ended December 31, 2016, as a result of the $65.0 million litigation settlement with Express Scripts, Inc., or Express Scripts.

The following table presents a summary of total net sales attributed to geographic sources for the years ended December 31, 2017 and 2016 (in thousands, except percentages):

	Year Ended December 31, 2017		Year Ended December 31, 2016	
	Amount	% of Total Net Sales	Amount	% of Total Net Sales
United States	$ 1,026,527	97%	$ 964,041	98%
Rest of world	29,704	3%	17,079	2%
Total net sales	**$ 1,056,231**		**$ 981,120**	

The following table reflects the components of net sales for the years ended December 31, 2017 and 2016 (in thousands, except percentages):

	Year Ended December 31,		Change	Change
	2017	2016	$	%
RAVICTI	$ 193,918	$ 151,532	$ 42,386	28%
KRYSTEXXA	156,483	91,102	65,381	72%
PROCYSBI	137,740	25,268	112,472	445%
ACTIMMUNE	110,993	104,624	6,369	6%
RAYOS	52,125	47,356	4,769	10%
BUPHENYL	20,792	16,879	3,913	23%
LODOTRA	5,393	4,193	1,200	29%
QUINSAIR	3,442	1,039	2,403	231%
Orphan and Rheumatology segment net sales	**$ 680,886**	**$ 441,993**	**$ 238,893**	**54%**
PENNSAID 2%	$ 191,050	$ 304,433	$ (113,383)	(37)%
DUEXIS	121,161	173,728	(52,567)	(30)%
VIMOVO	57,666	121,315	(63,649)	(52)%
MIGERGOT	5,468	4,651	817	18%
Primary care segment net sales	**$ 375,345**	**$ 604,127**	**$ (228,782)**	**(38)%**
Litigation settlement	—	(65,000)	65,000	(100)%
Total net sales	**$ 1,056,231**	**$ 981,120**	**$ 75,111**	**8%**

Orphan and Rheumatology

RAVICTI. Net sales increased $42.4 million, or 28%, to $193.9 million during the year ended December 31, 2017, from $151.5 million during the year ended December 31, 2016. Net sales in the United States increased by approximately $39.4 million, which was composed of $31.5 million resulting from prescription volume growth and $7.9 million due to higher net pricing. Net sales outside the United States increased by approximately $3.0 million primarily due to higher sales volume.

KRYSTEXXA. Net sales increased $65.4 million, or 72%, to $156.5 million during the year ended December 31, 2017, from $91.1 million during the year ended December 31, 2016. Net sales increased by approximately $40.1 million resulting from prescription volume growth and approximately $25.3 million due to higher net pricing.

PROCYSBI. Net sales increased $112.5 million, or 445%, to $137.7 million during the year ended December 31, 2017, from $25.2 million during the year ended December 31, 2016. Net sales increased by approximately $101.8 million resulting from prescription volume growth and approximately $10.7 million due to higher net pricing. We began recognizing PROCYSBI sales following our acquisition of Raptor in October 2016.

ACTIMMUNE. Net sales increased $6.4 million, or 6%, to $111.0 million during the year ended December 31, 2017, from $104.6 million during the year ended December 31, 2016. Net sales increased by approximately $12.9 million due to higher net pricing, partially offset by a decrease of approximately $6.5 million resulting from lower prescription volume.

RAYOS. Net sales increased $4.8 million, or 10%, to $52.1 million during the year ended December 31, 2017, from $47.3 million during the year ended December 31, 2016. Net sales increased by approximately $17.2 million resulting from prescription volume growth, partially offset by a decrease of approximately $12.4 million due to lower net pricing.

BUPHENYL. Net sales increased $3.9 million, or 23%, to $20.8 million during the year ended December 31, 2017, from $16.9 million during the year ended December 31, 2016. Net sales increased by approximately $7.3 million due to higher net pricing, partially offset by a decrease of approximately $3.4 million resulting from lower prescription volume.

LODOTRA. Net sales increased $1.2 million, or 29%, to $5.4 million during the year ended December 31, 2017, from $4.2 million during the year ended December 31, 2016. The increase was due to increased shipments to our European

distribution partner, Mundipharma. LODOTRA sales to Mundipharma occurred at the time we shipped, based on Mundipharma's estimated requirements. Accordingly, LODOTRA sales were not linear or directly tied to Mundipharma's in-market sales and could therefore fluctuate significantly from period to period.

QUINSAIR. Net sales increased $2.4 million, or 231%, to $3.4 million during the year ended December 31, 2017, from $1.0 million during the year ended December 31, 2016. Net sales increased by approximately $2.7 million resulting from prescription volume growth, partially offset by a decrease of approximately $0.3 million due to lower net pricing. We began recognizing QUINSAIR sales following our acquisition of Raptor in October 2016. In June 2017, following the Chiesi divestiture, our QUINSAIR sales in EMEA ceased, and post-June 2017 sales were in Canada and Latin America.

Primary Care

PENNSAID 2%. Net sales decreased $113.4 million, or 37%, to $191.1 million during the year ended December 31, 2017, from $304.5 million during the year ended December 31, 2016. Net sales decreased by approximately $90.2 million due to lower net pricing, as further described after the next table, and approximately $23.2 million resulting from lower prescription volume.

DUEXIS. Net sales decreased $52.6 million, or 30%, to $121.2 million during the year ended December 31, 2017, from $173.8 million during the year ended December 31, 2016. Net sales decreased by approximately $59.4 million due to lower net pricing, as further described after the next table, partially offset by an increase of $6.8 million resulting from prescription volume growth.

VIMOVO. Net sales decreased $63.6 million, or 52%, to $57.7 million during the year ended December 31, 2017, from $121.3 million during the year ended December 31, 2016. Net sales decreased by approximately $47.1 million due to lower net pricing, as further described after the next table, and approximately $16.5 million resulting from lower prescription volume.

MIGERGOT. Net sales increased $0.8 million, or 18%, to $5.5 million during the year ended December 31, 2017, from $4.7 million during the year ended December 31, 2016. Net sales increased by approximately $1.1 million due to higher net pricing, partially offset by a decrease of approximately $0.3 million resulting from lower prescription volume.

Litigation Settlement

In September 2016, we entered into a settlement agreement and mutual release with Express Scripts pursuant to which we and Express Scripts were released from any and all claims relating to our then ongoing litigation without admitting any fault or wrongdoing and we agreed to pay Express Scripts $65.0 million. This settlement has been accounted for as a reduction of "net sales" in the consolidated statement of comprehensive loss for the year ended December 31, 2016.

The table below reconciles our gross to net sales for the years ended December 31, 2017 and 2016 (in millions):

	Year Ended December 31, 2017		Year Ended December 31, 2016	
	Amount	% of Gross Sales	Amount	% of Gross Sales
Gross sales	$ 4,057.8	100.0%	$ 3,234.2	100.0%
Adjustments to gross sales:				
Prompt pay discounts	(80.2)	(2.0)%	(64.0)	(2.0)%
Medicine returns	(45.6)	(1.1)%	(17.1)	(0.5)%
Co-pay and other patient assistance	(1,907.6)	(47.0)%	(1,701.3)	(52.6)%
Wholesaler fees and commercial rebates	(641.5)	(15.8)%	(133.7)	(4.2)%
Government rebates and chargebacks	(326.7)	(8.1)%	(272.0)	(8.4)%
Litigation settlement	—	—	(65.0)	(2.0)%
Total adjustments	**(3,001.6)**	**(74.0)%**	**(2,253.1)**	**(69.7)%**
Net sales	**$ 1,056.2**	**26.0%**	**$ 981.1**	**30.3%**

During the year ended December 31, 2017, wholesaler fees and commercial rebates, as a percentage of gross sales, increased to 15.8% from 4.2% during the year ended December 31, 2016, and co-pay and other patient assistance, as a percentage of gross sales, decreased to 47.0% from 52.6% during the year ended December 31, 2016. During the second half

of 2016, we entered into business arrangements with PBMs and other payers in an effort to secure formulary status and reimbursement of our medicines, such as our arrangements with Express Scripts, CVS Caremark and Prime Therapeutics LLC, which resulted in lower co-pay and other patient assistance costs as a percentage of gross sales during the year ended December 31, 2017. The mix of PBM healthcare plans that adopted our primary care medicines onto their formulary during 2017 was more heavily weighted towards those plans for which we pay a higher commercial rebate. In addition, we also experienced a higher rate of managed care control in our non-contracted business, which resulted in significantly lower net pricing during the year ended December 31, 2017, when compared to the year ended December 31, 2016.

Cost of Goods Sold. Cost of goods sold increased $145.3 million to $537.3 million during the year ended December 31, 2017, from $392.0 million during the year ended December 31, 2016. As a percentage of net sales, cost of goods sold was 50.9% during the year ended December 31, 2017, compared to 40.0% during the year ended December 31, 2016. Costs of goods sold as a percentage of net sales was higher during the year ended December 31, 2016 due to the one-time reduction in net sales in the year ended December 31, 2016 as a result of the litigation settlement with Express Scripts. Additionally, we recorded an increase in cost of goods sold in the year ended December 31, 2017. The increase in cost of goods sold was primarily attributable to a $59.9 million increase in intangible amortization expense, a $48.0 million increase in inventory step-up expense, a $12.2 million increase in royalty remeasurement expense, a $10.7 million increase in drug substance harmonization costs, a $10.5 million increase in royalty accretion expense and a $9.6 million increase in employee costs, which reflects the increase in manufacturing activities resulting from the growth of our medicine portfolio. During the year ended December 31, 2016 we recorded a loss of $14.3 million in relation to purchase commitments with Boehringer Ingelheim, which related to additional units of ACTIMMUNE following the cancellation of the Phase 3 trial, Safety, Tolerability and Efficacy of ACTIMMUNE Dose Escalation in Friedreich's Ataxia study, or the FA program. During the year ended December 31, 2017, we updated our forecast for future demand and renegotiated our purchase commitments with Boehringer Ingelheim and recorded additional net expense of $1.7 million to cost of goods sold.

The increase in intangible amortization of $59.9 million during the year ended December 31, 2017 compared to the prior year was primarily due to an increase of $59.1 million in amortization of developed technology related to PROCYSBI (acquired in October 2016).

Because inventory step-up expense is acquisition-related, will not continue indefinitely and has a significant effect on our gross profit, gross margin percentage and net income (loss) for all affected periods, we disclose balance sheet and income statement amounts related to inventory step-up within the Notes to the consolidated financial statements. The increase in inventory step-up expense of $48.0 million recorded to cost of goods sold during the year ended December 31, 2017 compared to the prior year was primarily due to KRYSTEXXA inventory step-up expense of $78.3 million (acquired in January 2016) and PROCYSBI and QUINSAIR inventory step-up expense of $40.8 million (acquired in October 2016) recorded during the year ended December 31, 2017, compared to $48.8 million recorded during the year ended December 31, 2016 related to KRYSTEXXA and MIGERGOT inventory step-up expense and $22.3 million recorded related to PROCYSBI and QUINSAIR inventory step-up expense.

Research and Development Expenses. Research and development expenses increased $164.3 million to $225.0 million during the year ended December 31, 2017, from $60.7 million during the year ended December 31, 2016. The increase was primarily attributable to $150.3 million related to the acquisition of River Vision during the year ended December 31, 2017. Pursuant to ASC 805, as amended by ASU No. 2017-01, we accounted for the River Vision acquisition as the purchase of an IPR&D asset and, pursuant to ASC 730, recorded the purchase price as a research and development expense during the year ended December 31, 2017. Additionally, during the year ended December 31, 2017, we entered into an agreement to license HZN-003 (formerly MEDI4945), a rheumatology pipeline program with the objective of enhancing our leadership position in the uncontrolled gout market, from MedImmune and we paid MedImmune an upfront cash payment of $12.0 million which we recorded as a "research and development" expense in the consolidated statement of comprehensive loss during the year ended December 31, 2017 and included in "accrued expenses" as of December 31, 2017. The upfront payment was subsequently paid in January 2018.

Selling, General and Administrative Expenses. Selling, general and administrative expenses increased $52.0 million to $655.1 million during the year ended December 31, 2017, from $603.1 million during the year ended December 31, 2016. The increase was primarily attributable to an increase of $22.9 million in employee costs related to our growth in headcount following the Raptor acquisition in October 2016 and an increase of $24.2 million in marketing program costs.

Impairment of Long-Lived Assets. Impairment of long-lived assets of $22.3 million during the year ended December 31, 2017 represents the impairment of a non-current asset recorded following payment to Boehringer Ingelheim International for the acquisition of certain rights to interferon gamma-1b. This was previously included within "selling, general and

administrative" expenses. Impairment of long-lived assets of $71.3 million during the year ended December 31, 2016, primarily relates to an impairment of $66.0 million to fully write off the fair value of the intangible asset following the discontinuation of the FA program on December 8, 2016. At the time of the merger of the businesses of Horizon Pharma, Inc., or HPI, and Therapeutics International Public Limited Company, or Vidara, on September 19, 2014, or the Vidara Merger, the impairment was considered separable from the business as the project could be sold to a third party, and we assigned a fair value of $66.0 million to an intangible asset. Following the announcement to discontinue the FA program on December 8, 2016, we determined that the impairment had no alternative use or economic value, and we recorded an impairment charge during the year ended December 31, 2016 to fully write off the value of the asset on our consolidated balance sheet. Additionally, $5.3 million represents the impairment of a non-current asset recorded during the year ended December 31, 2016, following the upfront payment to Boehringer Ingelheim International for the acquisition of certain rights to interferon gamma-1b. This was previously included within "selling, general and administrative" expenses.

Interest Expense, Net. Interest expense, net, increased $39.9 million to $126.5 million during the year ended December 31, 2017, from $86.6 million during the year ended December 31, 2016. The increase was primarily due to higher borrowings, including our $300.0 million aggregate principal amount of 8.75% Senior Notes due 2024, or the 2024 Senior Notes, in connection with our acquisition of Raptor in October 2016, and our $850.0 million principal amount of secured loans under our term loan facility, of which $375.0 million was in connection with our acquisition of Raptor, compared to the $397.0 million principal amount of secured loans from previous borrowings under our senior secured loan facility.

Gain on divestiture. During the year ended December 31, 2017, we completed the Chiesi divestiture for an upfront payment of $72.5 million, which reflects $3.1 million of cash divested, with additional potential milestone payments based on sales thresholds, and we recorded a gain of $6.3 million on the divestiture.

Foreign Exchange Loss. During the year ended December 31, 2017, we reported a foreign exchange loss of $0.3 million.

Loss on Debt Extinguishment. During the year ended December 31, 2017, we entered into two refinancing amendments for our term loans. We accounted for a portion of the repayments under these refinancing amendments as a debt extinguishment and recorded a loss on debt extinguishment of $1.0 million in the consolidated statements of comprehensive loss, which reflected the write-off of the unamortized portion of debt discount and deferred financing costs previously incurred and a one percent prepayment penalty fee.

Benefit for Income Taxes. During the year ended December 31, 2017, we recorded a benefit for income taxes of $102.7 million compared to $61.3 million during the year ended December 31, 2016. The increase in benefit for income taxes during the year ended December 31, 2017, compared to year ended December 31, 2016, was primarily due to a provisional $74.9 million net benefit recorded following the enactment in the United States of the Tax Act, in December 2017, which net benefit included a $134.2 million tax benefit from the revaluation of our U.S. net deferred tax liability based on the revised U.S. federal tax rate of 21 percent, partially offset by the write-off of the $59.2 million deferred tax asset related to our U.S. interest expense carryforwards under Section 163(j) of the Code. On April 2, 2018, we reinstated the deferred tax asset related to its U.S. interest expense carryforwards under Section 163(j) based on the revised U.S. federal tax rate of 21 percent. The impact of the deferred tax asset reinstatement in accordance with SAB 118 was a $37.4 million increase to our benefit for income taxes and a corresponding decrease to the U.S. group net deferred tax liability position. Additionally, during the year ended December 31, 2017, we recorded an increase in pre-tax losses which resulted in an increase in the benefit for income taxes during the year.

During the year ended December 31, 2017, the first of three tranches of our outstanding PSUs issued in 2015 expired without payout as the minimum total compounded annual shareholder rate of return was not achieved. As a result, we wrote off to income tax expense $16.4 million of deferred tax assets related to previously recognized share-based compensation. During the years ended December 31, 2017, 2016 and 2015, we recorded share-based compensation expense of $49.6 million, $48.6 million and $37.7 million, respectively, related to these PSUs.

Information by Segment

See Note 13, *Segment and Other Information,* of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K for a reconciliation of our segment operating income to our total loss before benefit for income taxes for the year ended December 31, 2017 and 2016.

Orphan and Rheumatology

The following table reflects our orphan and rheumatology net sales and segment operating income for the three years ended December 31, 2017 and 2016 (in thousands, except percentages).

	For the Year Ended December 31,			
	2017	2016	Change	% Change
Net sales	$ 680,886	$ 441,993	$ 238,893	54%
Segment operating income	241,135	124,779	116,356	93%

The increase in orphan and rheumatology net sales during the year ended December 31, 2017 is described in the *Consolidated Results* section above.

Segment operating income. Orphan and rheumatology segment operating income increased $116.3 million to $241.1 million during the year ended December 31, 2017, from $124.8 million during the year ended December 31, 2016. The increase was primarily attributable to an increase in net sales of $238.9 million as described above, partially offset by increased marketing program costs related to KRYSTEXXA.

Primary Care

The following table reflects our primary care net sales and segment operating income for the years ended December 31, 2017 and 2016 (in thousands, except percentages).

	For the Year Ended December 31,			
	2017	2016	Change	% Change
Net sales	$ 375,345	$ 604,127	$ (228,782)	(38)%
Segment operating income	149,133	347,968	(198,835)	(57)%

The decrease in primary care net sales during the year ended December 31, 2017 is described in the *Consolidated Results* section above.

Segment operating income. Primary care segment operating income decreased $198.8 million to $149.1 million during the year ended December 31, 2017, from $347.9 million during the year ended December 31, 2016. The decrease was primarily attributable to a decrease in net sales of $228.8 million as described above.

Non-GAAP Financial Measures

EBITDA, or earnings before interest, taxes, depreciation and amortization, adjusted EBITDA, non-GAAP net income and non-GAAP earnings per share are used and provided by us as non-GAAP financial measures. These non-GAAP financial measures are intended to provide additional information on our performance, operations and profitability. Adjustments to our GAAP figures as well as EBITDA exclude acquisition/divestiture-related costs, gain on sale of assets, gain on divestiture, upfront and milestone payments related to license agreements, drug substance harmonization costs, fees related to term loan refinancing, restructuring and realignment costs, litigation settlements and charges related to discontinuation of the FA program, as well as non-cash items such as share-based compensation, inventory step-up expense, depreciation and amortization, remeasurement of royalties for medicines acquired through business combinations, royalty accretion, non-cash interest expense, long-lived assets impairment charges, gain on divestiture, loss on debt extinguishment, reversal of pre-acquisition reserve upon signing of contract and other non-cash adjustments. Certain other special items or substantive events may also be included in the non-GAAP adjustments periodically when their magnitude is significant within the periods incurred. We maintain an established non-GAAP cost policy that guides the determination of what costs will be excluded in non-GAAP measures. We believe that these non-GAAP financial measures, when considered together with the GAAP figures, can enhance an overall understanding of our financial and operating performance. The non-GAAP financial measures are included with the intent of providing investors with a more complete understanding of our historical financial results and trends and to facilitate comparisons between periods. In addition, these non-GAAP financial measures are among the indicators our management uses for planning and forecasting purposes and measuring our performance. For example, adjusted EBITDA is used by us as one measure of management performance under certain incentive compensation arrangements. These non-GAAP financial measures should be considered in addition to, and not as a substitute for, or superior to, financial measures calculated in accordance with GAAP. The non-GAAP financial measures used by us may be calculated differently from, and therefore may not be comparable to, non-GAAP financial measures used by other companies.

Beginning in the second quarter of 2016, we modified the method of calculating non-GAAP income tax expense to align with guidance issued by the SEC on May 17, 2016. The modified methodology calculates the income tax component of non-GAAP net income for each period by adjusting the GAAP tax benefit for the estimated tax impact of each non-GAAP adjustment based on the statutory income tax rate of the applicable jurisdictions for each non-GAAP adjustment. This modified methodology does not reflect any use of net operating loss carryforwards that we potentially may have been able to use if our actual earnings for these periods had been the non-GAAP net income. Previously, we had calculated the income tax component of non-GAAP net income by using the estimated cash taxes that we expected to pay for the period. The non-GAAP net income and diluted net income per share amounts shown in the GAAP to non-GAAP reconciliation tables below are based on the modified methodology.

Reconciliations of reported GAAP net sales to non-GAAP adjusted net sales and reported GAAP net loss to EBITDA, adjusted EBITDA and non-GAAP net income, and the related per share amounts, are as follows (in thousands, except share and per share amounts):

	For the Years Ended December 31,		
	2018	2017	2016
GAAP net sales	**$ 1,207,570**	**$ 1,056,231**	**$ 981,120**
Litigation settlements (10)	—	—	65,000
Non-GAAP adjusted net sales	**$ 1,207,570**	**$ 1,056,231**	**$ 1,046,120**

	For the Years Ended December 31,		
	2018	2017	2016
GAAP net loss	**$ (74,187)**	**$ (401,585)**	**$ (165,563)**
Non-GAAP adjustments:			
Depreciation (1)	6,126	6,631	4,962
Amortization, accretion and inventory step-up:			
Intangible amortization expense (2)	269,603	276,613	216,703
Accretion of royalty liabilities (3)	59,565	51,263	40,616
Inventory step-up expense (4)	17,312	119,151	71,137
Amortization of debt discount and deferred financing costs (5)	22,752	21,619	18,546
Acquisition/divestiture-related costs (6)	7,717	177,035	52,874
Restructuring and realignment costs (7)	15,350	4,883	—
Share-based compensation (8)	114,860	121,553	114,144
Impairment of long-lived assets (9)	50,302	22,270	71,260
Litigation settlements (10)	5,750	—	65,000
Drug substance harmonization costs (11)	2,855	10,651	—
Fees related to term loan refinancings (12)	937	5,220	—
Upfront and milestone payments related to license agreements (13)	(10)	12,186	2,000
Charges relating to discontinuation of the Friedreich's ataxia program (14)	(1,464)	239	18,253
Remeasurement of royalties for medicines acquired through business combinations (3)	(3,383)	13,004	(713)
Gain on sale of assets (15)	(42,688)	—	—
Royalties for medicines acquired through business combinations (3)	(53,961)	(47,003)	(37,593)
Gain on divestiture (16)	—	(6,267)	—
Loss on debt extinguishment (17)	—	978	—
Reversal of pre-acquisition reserve upon signing of contract (18)	—	—	(6,900)
Total of pre-tax non-GAAP adjustments	**471,623**	**790,026**	**630,289**
Income tax effect of pre-tax non-GAAP adjustments (19)	(45,393)	(118,704)	(110,290)
Other non-GAAP income tax adjustments (20)	(37,392)	(74,939)	—
Total of non-GAAP adjustments	**388,838**	**596,383**	**519,999**
Non-GAAP Net Income	**$ 314,651**	**$ 194,798**	**$ 354,436**
Non-GAAP Earnings Per Share:			
Weighted average ordinary shares – Basic	**166,155,405**	**163,122,663**	**160,699,543**
Non-GAAP Earnings Per Share – Basic			
GAAP loss per share - Basic	**$ (0.45)**	**$ (2.46)**	**$ (1.03)**
Non-GAAP adjustments	2.34	3.65	3.24
Non-GAAP earnings per share – Basic	**$ 1.89**	**$ 1.19**	**$ 2.21**
Weighted average ordinary shares – Diluted			
Weighted average ordinary shares – Basic	166,155,405	163,122,663	160,699,543
Ordinary share equivalents	5,393,514	2,582,576	3,626,570
Weighted average ordinary shares – Diluted	**171,548,919**	**165,705,239**	**164,326,113**
Non-GAAP Earnings Per Share – Diluted			
GAAP loss per share – Diluted	**$ (0.45)**	**$ (2.46)**	**$ (1.03)**
Non-GAAP adjustments	2.34	3.65	3.24
Diluted earnings per share effect of ordinary share equivalents	(0.06)	(0.01)	(0.05)
Non-GAAP earnings per share – Diluted	**$ 1.83**	**$ 1.18**	**$ 2.16**

	For the Years Ended December 31,		
	2018	2017	2016
GAAP net loss	**$ (74,187)**	**$ (401,585)**	**$ (165,563)**
Depreciation (1)	6,126	6,631	4,962
Amortization, accretion and inventory step-up:			
Intangible amortization expense (2)	269,603	276,613	216,703
Accretion of royalty liabilities (3)	59,565	51,263	40,616
Amortization of deferred revenue	—	(860)	(836)
Inventory step-up expense (4)	17,312	119,151	71,137
Interest expense, net (including amortization of debt discount and deferred financing costs)	121,692	126,523	86,610
Benefit for income taxes	(44,959)	(102,749)	(61,251)
EBITDA	**355,152**	**74,987**	**192,378**
Other non-GAAP adjustments:			
Acquisition/divestiture-related costs (6)	7,717	177,035	52,874
Restructuring and realignment costs (7)	15,350	4,883	—
Share-based compensation (8)	114,860	121,553	114,144
Impairment of long-lived assets (9)	50,302	22,270	71,260
Litigation settlements (10)	5,750	—	65,000
Drug substance harmonization costs (11)	2,855	10,651	—
Fees related to term loan refinancings (12)	937	5,220	—
Upfront and milestone payments related to license agreements (13)	(10)	12,186	2,000
Charges relating to discontinuation of the Friedreich's ataxia program (14)	(1,464)	239	18,253
Remeasurement of royalties for medicines acquired through business combinations (3)	(3,383)	13,004	(713)
Gain on sale of assets (15)	(42,688)	—	—
Royalties for medicines acquired through business combinations (3)	(53,961)	(47,003)	(37,593)
Gain on divestiture (16)	—	(6,267)	—
Loss on debt extinguishment (17)	—	978	—
Reversal of pre-acquisition reserve upon signing of contract (18)	—	—	(6,900)
Total of other non-GAAP adjustments	**96,265**	**314,749**	**278,325**
Adjusted EBITDA	**$ 451,417**	**$ 389,736**	**$ 470,703**

(1) Represents depreciation expense related to our property, equipment, software and leasehold improvements.

(2) Intangible amortization expenses are associated with our intellectual property rights, developed technology and customer relationships related to ACTIMMUNE, BUPHENYL, KRYSTEXXA, LODOTRA, MIGERGOT, PENNSAID 2%, PROCYSBI, RAVICTI, RAYOS and VIMOVO.

(3) Our accrued contingent royalty liabilities consist of contingent third-party royalty obligations that we assume when we acquire the rights to medicines. At the time of each acquisition, we assign a fair value to the contingent liability for royalties. On a quarterly basis, we evaluate the carrying amount of the liability and we remeasure, or adjust, the liability when anticipated royalty payments materially change. Any remeasurements of the contingent royalty liabilities are recorded as an increase in or reduction to cost of goods sold during the period. In addition, accretion expense on the contingent royalty liability is recorded in cost of goods sold. When we prepare our non-GAAP financial measures, we exclude the ongoing impacts of acquisition-related contingent royalty liabilities. We do this by excluding the impact of any remeasurement of contingent royalty liabilities and the royalty accretion expense. However, since we recorded a liability for contingent royalties in purchase accounting, when we exclude the remeasurement and royalty accretion expense, our non-GAAP financial measures would not include any impact of the royalties we are obligated to pay based on our current period net sales. Therefore, we also add back in our non-GAAP financial measures the actual royalty amount incurred based on the periods' net sales for each of our medicines acquired through business combinations.

(4) During the year ended December 31, 2018, we recognized in cost of goods sold $17.3 million for inventory step-up expense primarily related to KRYSTEXXA inventory sold.

During the year ended December 31, 2017, we recognized in cost of goods sold $78.3 million for inventory step-up expense related to KRYSTEXXA and MIGERGOT inventory sold and $40.8 million for inventory step-up expense related to PROCYSBI and QUINSAIR inventory sold.

During the year ended December 31, 2016, we recognized in cost of goods sold $48.8 million for inventory step-up expense related to KRYSTEXXA and MIGERGOT inventory sold and $22.3 million for inventory step-up expense related to PROCYSBI and QUINSAIR inventory sold.

(5) Represents amortization of debt discount and deferred financing costs associated with our debt.

(6) Represents expenses, including legal and consulting fees, incurred in connection with our acquisitions and divestitures.

(7) Represents expenses, including severance costs and consulting fees, related to restructuring and realignment activities.

(8) Represents share-based compensation expense associated with our stock option, restricted stock unit and performance stock unit grants to our employees and non-employees, our previous cash-settled long-term incentive plan and our employee stock purchase plan.

(9) Impairment of long-lived assets during the year ended December 31, 2018, primarily relates to the write-off of the book value of developed technology related to PROCYSBI in Canada and Latin America and LODOTRA.

Impairment of long-lived assets during the year ended December 31, 2017 of $22.3 million relates to an impairment recorded following payment to Boehringer Ingelheim International for the acquisition of certain rights to interferon gamma-1b. This was presented in the "charges relating to the discontinuation of the Friedreich's ataxia program" line item in the reconciliation of GAAP to non-GAAP measures during the year ended December 31, 2017.

Impairment of long-lived assets during the year ended December 31, 2016 of $71.3 million relates to an impairment of in-process research and development of $66.0 million recorded following the discontinuation of the FA program in December 2016, or the FA discontinuation, and a $5.3 million impairment of a non-current asset. These amounts were presented in the "impairment of in-process research and development" and "charges relating to the discontinuation of the Friedreich's ataxia program" line items, respectively, in the reconciliation of GAAP to non-GAAP measures during the year ended December 31, 2016.

(10) We recorded $5.8 million of expense during the year ended December 31, 2018, for litigation settlements related to PENNSAID 2% and RAVICTI.

During the year ended December 31, 2016, we entered into a settlement agreement and mutual release with Express Scripts pursuant to which we and Express Scripts were released from any and all claims relating to our then ongoing litigation without admitting any fault or wrongdoing and we agreed to pay Express Scripts $65.0 million. This settlement was accounted for as a reduction of "net sales" in the consolidated statement of comprehensive loss for the year ended December 31, 2016.

(11) During the year ended December 31, 2016, we entered into a definitive agreement to acquire certain rights to interferon gamma-1b, marketed as IMUKIN in an estimated thirty countries primarily in Europe and the Middle East, or the IMUKIN purchase agreement. We already owned the rights to interferon gamma-1b marketed as ACTIMMUNE in the United States, Canada and Japan. In connection with the IMUKIN purchase agreement, we also committed to pay our contract manufacturer certain amounts related to the harmonization of the manufacturing processes for ACTIMMUNE and IMUKIN drug substance, or the harmonization program. At the time we entered into the IMUKIN purchase agreement and the harmonization program commitment was made, we had anticipated achieving certain benefits should the Phase 3 clinical trial evaluating ACTIMMUNE for the treatment of Friedreich's ataxia, or FA, be successful. If the study had been successful and if U.S. marketing approval had subsequently been obtained, we had forecasted significant increases in demand for the medicine and the harmonization program would have resulted in significant benefits for us. Following the FA discontinuation, we determined that certain assets, including an upfront payment related to the IMUKIN purchase agreement, were impaired, and the costs under the harmonization program would no longer have benefit to us and should be expensed as incurred.

(12) Represents arrangement and other fees relating to the refinancing of our term loans.

(13) During the year ended December 31, 2017, we incurred $12.2 million of upfront and milestone payments related to license agreements, primarily related to our agreement to license HZN-003 (formerly MEDI4945), a rheumatology pipeline program with the objective of enhancing our leadership position in the uncontrolled gout market, from MedImmune for an upfront cash payment of $12.0 million.

(14) During the year ended December 31, 2018, we recorded a reduction to previously incurred charges relating to the FA discontinuation of $1.5 million reflecting lower costs to discontinue the clinical trial than previously anticipated.

During the year ended December 31, 2017, we recorded charges relating to the FA discontinuation of $0.2 million.

During the year ended December 31, 2016, charges relating to the FA discontinuation included a $14.3 million loss on inventory purchase commitments and $4.0 million of clinical trial wind-down costs.

(15) During the year ended December 31, 2018, we sold our rights to interferon gamma-1b in all territories outside the United States, Canada and Japan to Clinigen for cash proceeds of $9.5 million, with a potential additional contingent consideration payment, and we recorded a gain of $12.3 million. Additionally, during the year ended December 31, 2018, we sold our rights to RAVICTI and AMMONAPS outside of North America and Japan to Medical Need Europe AB, and we recorded a gain of $30.4 million.

(16) During the year ended December 31, 2017, we completed the divestiture of a European subsidiary that owns the marketing rights to PROCYSBI and QUINSAIR in EMEA to Chiesi and in connection with this divestiture we recorded a gain of $6.3 million.

(17) During the year ended December 31, 2017, we entered into two refinancing amendments for our term loans. We accounted for a portion of the repayments under these refinancing amendments as a debt extinguishment and recorded a loss on debt extinguishment of $1.0 million in the consolidated statements of comprehensive loss, which reflected the write-off of the unamortized portion of debt discount and deferred financing costs previously incurred and a one percent prepayment penalty fee.

(18) During the year ended December 31, 2016, we recorded a release of a contingent liability of $6.9 million which was assumed as part of the Crealta acquisition.

(19) Income tax adjustments on pre-tax non-GAAP adjustments represent the estimated income tax impact of each pre-tax non-GAAP adjustment based on the statutory income tax rate of the applicable jurisdictions for each non-GAAP adjustment.

(20) Other non-GAAP income tax adjustments during the year ended December 31, 2017, reflect the provisional $74.9 million net benefit recorded following the enactment of the Tax Act, which net benefit included a $134.2 million tax benefit from the revaluation of our U.S. net deferred tax liability based on the revised U.S. federal tax rate of 21 percent, partially offset by the write-off of the $59.2 million deferred tax asset related to our U.S. interest expense carryforwards under Section 163(j) of the Code.

Following Notice 2018-28, that was issued by the U.S. Treasury Department and the U.S. Internal Revenue Service during the year ended December 31, 2018 and in accordance with the measurement period provisions under SAB 118, we reinstated the deferred tax asset related to our U.S. interest expense carry forwards under Section 163(j) based on the revised U.S. federal tax rate of 21 percent. The impact of the deferred tax asset reinstatement in accordance with SAB 118 was a $37.4 million increase to our benefit for income taxes and a corresponding decrease to the U.S. group net deferred tax liability position.

Liquidity, Financial Position and Capital Resources

We have incurred losses since our inception in June 2005 and, as of December 31, 2018, we had an accumulated deficit of $1,314.7 million. We expect that our sales and marketing expenses will continue to increase as a result of the commercialization of our medicines but we believe these cost increases will be more than offset by higher net sales and gross profits. Additionally, we expect that our research and development costs will increase as we acquire more development-stage medicine candidates and advance our candidates through the clinical development and regulatory approval processes.

We have financed our operations to date through equity financings, debt financings and the issuance of convertible notes, along with cash flows from operations during the last several years. As of December 31, 2018, we had $958.7 million in cash and cash equivalents and total debt with a book value of $1,896.7 million and face value of $1,993.0 million. We believe our existing cash and cash equivalents and our expected cash flows from our operations will be sufficient to fund our business needs for at least the next twelve months from the issuance of the financial statements in this Annual Report on Form 10-K. Part of our strategy is to expand and leverage our commercial capabilities and to develop a pipeline of rare disease medicine candidates by researching, developing and commercializing innovative medicines that address unmet treatment needs for rare and rheumatic diseases. To the extent we enter into transactions to acquire medicines or businesses in the future, we will most likely need to finance a significant portion of those acquisitions through additional debt, equity or convertible debt financings, or through the use of cash on hand.

On October 19, 2018, HPI, our wholly owned subsidiary, and Horizon Pharma USA, Inc., our wholly owned subsidiary, and together with HPI in such capacity, the Borrowers, borrowed approximately $818.0 million aggregate principal amount of loans, or the October 2018 Refinancing Loans, pursuant to an amendment to our Credit Agreement. The Borrowers used the proceeds of the October 2018 Refinancing Loans to repay the outstanding amounts under our prior term loans, which totaled approximately $818.0 million. For a description of our debt agreements, see Note 15, *Debt Agreements* of the Notes to Consolidated Financial Statements, included in Item 15 in this Annual Report on Form 10-K.

We were, as of December 31, 2018, and currently are in compliance with the Credit Agreement.

We have a significant amount of debt outstanding on a consolidated basis. This substantial level of debt could have important consequences to our business, including, but not limited to: making it more difficult for us to satisfy our obligations; requiring a substantial portion of our cash flows from operations to be dedicated to the payment of principal and interest on our indebtedness, therefore reducing our ability to use our cash flows to fund acquisitions, capital expenditures, and future business opportunities; limiting our ability to obtain additional financing, including borrowing additional funds; increasing our vulnerability to, and reducing our flexibility to respond to, general adverse economic and industry conditions; limiting our flexibility in planning for, or reacting to, changes in our business and the industry in which we operate; and placing us at a disadvantage as compared to our competitors, to the extent that they are not as highly leveraged. We may not be able to generate sufficient cash to service all of our indebtedness and may be forced to take other actions to satisfy our obligations under our indebtedness.

In addition, the indentures governing our $300.0 million aggregate principal amount of 8.750% Senior Notes due 2024 and $475.0 million aggregate principal amount of 6.625% Senior Notes due 2023 and our Credit Agreement impose various covenants that limit our ability and/or our restricted subsidiaries' ability to, among other things, pay dividends or distributions, repurchase equity, prepay junior debt and make certain investments, incur additional debt and issue certain preferred stock, incur liens on assets, engage in certain asset sales or merger transactions, enter into transactions with affiliates, designate subsidiaries as unrestricted subsidiaries; and allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to us.

We were, as of December 31, 2018, and currently are in compliance with the indentures governing the 2024 Senior Notes and 2023 Senior Notes.

During the year ended December 31, 2018, we issued an aggregate of 4.4 million of our ordinary shares in connection with stock option exercises, the vesting of restricted stock units and employee stock program purchases and we received a total net cash amount of $11.1 million in relation to these programs.

Sources and Uses of Cash

The following table provides a summary of our cash position and cash flows for the years ended December 31, 2018, 2017 and 2016 (in thousands):

	For the Years Ended December 31,		
	2018	2017	2016
Cash, cash equivalents and restricted cash	$ 962,117	$ 757,897	$ 516,150
Cash provided by (used in):			
Operating activities	194,543	284,340	369,456
Investing activities	27,653	(102,185)	(1,370,646)
Financing activities	(16,596)	54,276	657,074

Operating Cash Flows

During the years ended December 31, 2018, 2017 and 2016, net cash provided by operating activities was $194.5 million, $284.3 million and $369.5 million, respectively.

Net cash provided by operating activities during the year ended December 31, 2018 was primarily attributable to cash collections from net sales, net of operating expenses. Operating cash flow was also used to fund interest on outstanding debt of $112.5 million and income taxes of $53.1 million.

Net cash provided by operating activities during the year ended December 31, 2017 was primarily attributable to cash collections from net sales. Cash provided by operating activities was negatively impacted during the year ended December 31, 2017 by cash payments of $113.8 million for interest, $32.5 million outlay for the remaining fifty percent of the litigation settlement amount with Express Scripts, cash payments of $54.0 million for acquisition/divestiture-related costs, cash payments relating to term loan refinancing of $9.1 million, cash payments related to the discontinuation of the FA program of $7.2 million, cash payments relating to our drug substance harmonization program of $5.2 million and cash payments related to our restructuring and realignment activities of $4.7 million.

Net cash provided by operating activities during the year ended December 31, 2016, was primarily attributable to cash collections from net sales. Cash provided by operating activities was negatively impacted during the year ended December 31, 2016 by a $32.5 million outlay for fifty percent of the litigation settlement amount with Express Scripts, cash payments of $48.9 million for acquisition-related expenses and $60.8 million for interest payments made on our term loan facility, 2023 Senior Notes and Exchangeable Senior Notes.

Investing Cash Flows

During the year ended December 31, 2018, net cash provided by investing activities was $27.7 million. During the years ended December 31, 2017 and 2016, net cash used in investing activities was $102.2 million and $1,370.6 million, respectively.

Net cash provided by investing activities during the year ended December 31, 2018, was primarily attributable to proceeds from the sale of assets during the year, including cash proceeds of $35.0 million following the sale of rights to RAVICTI and AMMONAPS outside of North America and Japan to Immedica and cash proceeds of $9.5 million following the IMUKIN sale. This was partially offset by $12.0 million we paid to MedImmune to license HZN-003 (formerly MEDI4945).

Net cash used in investing activities during the year ended December 31, 2017, was primarily associated with $144.9 million of payments for the acquisition of River Vision, net of cash acquired, and associated transaction costs, and $22.3 million relating to the payment for certain rights for interferon gamma-1b. This was partially offset by $69.4 million of proceeds received from the Chiesi divestiture, net of cash divested.

Net cash used in investing activities during the year ended December 31, 2016, was primarily related to $835.9 million of payments for the acquisition of Raptor, net of cash acquired, $514.8 million of payments for the acquisition of Crealta, net of cash acquired, a $5.6 million (€5.0 million) initial payment for certain non-U.S. intellectual property rights to interferon gamma-1b and $15.7 million of payments for purchases of property and equipment.

Financing Cash Flows

During the year ended December 31, 2018, net cash used in financing activities was $16.6 million. During the years ended December 31, 2017 and 2016, net cash provided by financing activities was $54.3 million and $657.1 million, respectively.

Net cash used in financing activities during the year ended December 31, 2018, was primarily attributable to the repayment of term loans of $845.7 million, partially offset by $818.0 million in net proceeds from term loans. In June 2018, we made a mandatory prepayment of $23.5 million under our term loan facility. In October 2018, we refinanced our term loans without changing the principal amount outstanding.

Net cash provided by financing activities during the year ended December 31, 2017, was primarily attributable to the net proceeds of $1,693.5 million from term loans, offset in part by repayment of term loans of $1,622.8 million. We refinanced our term loans during March 2017 and October 2017. The March 2017 refinancing loans replaced the $394.0 million 2015 term loan facility and the $375.0 million 2016 incremental loan facility and the October 2017 Refinancing Loans replaced the October 2017 Refinanced Loans. The March 2017 Credit Agreement resulted in an increase of $81.0 million of principal amount of our outstanding debt and the October 2017 Refinancing Loans did not result in any changes to the principal amount outstanding. Additionally, during the year ended December 31, 2017, we paid $20.0 million relating to milestones in connection with a contingent consideration liability assumed in our acquisition of Raptor.

Net cash provided by financing activities during the year ended December 31, 2016, was primarily related to $364.3 million of net proceeds received from borrowings under our term loan facility and $291.9 million of net proceeds received from borrowings under our 2024 Senior Notes.

Financial Condition as of December 31, 2018 compared to December 31, 2017

Accounts receivable, net. Accounts receivable, net, increased $59.5 million, from $405.2 million as of December 31, 2017 to $464.7 million as of December 31, 2018. The increase was due to growth in gross sales of our medicines.

Inventories, net. Inventories, net, decreased $10.9 million, from $61.7 million as of December 31, 2017 to $50.8 million as of December 31, 2018. The decrease was primarily due to $17.0 million of inventory step-up expense recorded during the year ended December 31, 2018, related to KRYSTEXXA, partially offset by an increase in medicine inventory levels.

Prepaid expenses and other current assets. Prepaid expenses and other current assets increased $27.4 million, from $43.4 million as of December 31, 2017 to $70.8 million as of December 31, 2018. The increase was primarily due to an increase in deferred charges on intra-company profit of $21.2 million and an increase in prepaid income taxes of $5.9 million.

Developed technology, net. Developed technology, net, decreased $321.7 million, from $2,442.3 million as of December 31, 2017 to $2,120.6 million as of December 31, 2018. The decrease was due to the amortization of developed technology of $268.8 million during the year ended December 31, 2018, the recording of an impairment of $48.5 million during the year ended December 31, 2018, to fully write off the book value of developed technology related to PROCYSBI in Canada and Latin America and LODOTRA and the disposal of developed technology with a net book value of $4.4 million as a result of the Immedica transaction.

Long-term debt - current portion. Long-term debt - current portion, decreased $10.6 million from $10.6 million as of December 31, 2017 to zero as of December 31, 2018. Following the mandatory prepayment of $23.5 million under our term loan facility in June 2018, we are not required to pay any further quarterly installments under our term loan facility until June 30, 2020. See Note 15 of the Notes to consolidated financial statements, included in Item 15 of this Annual Report on Form 10-K, for details of our October 2018 Refinancing Loans.

Accrued expenses. Accrued expenses increased $29.9 million, from $175.7 million as of December 31, 2017 to $205.6 million as of December 31, 2018. This was primarily due to an increase in payroll-related expenses of $22.2 million.

Accrued trade discounts and rebates. Accrued trade discounts and rebates decreased $44.0 million, from $501.8 million as of December 31, 2017 to $457.8 million as of December 31, 2018. This was primarily due to a $51.1 million decrease in accrued co-pay and other patient assistance costs and a $37.1 million decrease in accrued commercial rebates and wholesaler fees, offset partially by a $44.2 million increase in accrued government rebates and chargebacks.

Long-term debt, net of current. Long-term debt, net of current decreased $12.2 million from $1,576.7 million as of December 31, 2017 to $1,564.5 million as of December 31, 2018. The decrease was primarily related to the mandatory prepayment of $23.5 million in June 2018, under our term loan facility, of which $17.1 million had been included in long-term debt, net of current, at December 31, 2017. See Note 15 of the Notes to consolidated financial statements, included in Item 15 of this Annual Report on Form 10-K, for details of our October 2018 Refinancing Loans.

Deferred revenues, net of current. Deferred revenues, net of current, decreased $9.7 million, from $9.7 million as of December 31, 2017 to zero as of December 31, 2018. Upon adoption of Accounting Standards Update No. 2014-09, Revenue from Contracts with Customers on January 1, 2018, we reclassified $9.7 million of deferred revenues, net of current, directly to retained earnings.

Deferred tax liabilities, net. Deferred tax liabilities, net, net of deferred tax assets, decreased $64.0 million, from $154.5 million as of December 31, 2017 to $90.5 million as of December 31, 2018. This was primarily due to the measurement period adjustment which reinstated $37.4 million of the deferred tax asset related to our U.S. interest expense carryforwards under Section 163(j) of the Code, to reflect the guidance in Notice 2018-28 that was issued by the U.S. Treasury Department and the U.S. Internal Revenue Service in April 2018 and the decrease in net deferred tax liabilities of $15.3 million relating to U.S. interest expense disallowed under Section 163(j) of the Code relating to the year ended December 31, 2018. Further, decrease in net deferred tax liabilities related to the deferred tax impact of amounts recorded during the year ended December 31, 2018, including amortization of intangible assets of $32.5 million, amortization of debt discount of $4.6 million and changes in accruals, reserves, royalties and inventories. The decrease in net deferred tax liabilities was partially offset by utilization of net operating loss carryforwards in various jurisdictions of $14.4 million, and the write off $23.3 million of deferred tax assets relating to previously recognized share-based compensation on outstanding PSUs, which expired without payout.

Contractual Obligations

As of December 31, 2018, minimum future cash payments due under contractual obligations, including, among others, our debt agreements, minimum purchase agreements and non-cancelable operating lease agreements, were as follows (in thousands):

	2019	2020	2021	2022	2023	2024 & Thereafter	Total
Debt agreements – principal (1)	$ —	$ 5,080	$ 6,774	$ 406,774	$ 481,774	$1,092,624	$1,993,026
Debt agreements - interest (1)	110,819	115,185	114,437	109,038	83,736	40,464	573,679
Purchase commitments (2)	54,531	10,705	10,329	10,264	10,259	17,126	113,214
Operating lease obligations (3)	6,228	6,680	5,788	4,565	4,442	36,696	64,399
Total contractual cash obligations	**$ 171,578**	**$ 137,650**	**$ 137,328**	**$ 530,641**	**$ 580,211**	**$1,186,910**	**$2,744,318**

(1) Represents the minimum contractual obligation due under the following debt agreements:

- $818.0 million under the October 2018 Refinancing Loans, which includes estimated quarterly interest payments based on the applicable interest rate at December 31, 2018 of 5.56% and quarterly payments of 0.25% of the principal, and repayment of the remaining principal in March 2024. In June 2018, we repaid $23.5 million under the mandatory prepayment provisions of our Credit Agreement. Following the mandatory prepayment in June 2018, we are not required to pay any further quarterly installments until June 30, 2020.
- $475.0 million 2023 Senior Notes, which includes bi-annual interest payments and repayment of the principal in May 2023.
- $400.0 million Exchangeable Senior Notes, which includes bi-annual interest payments and repayment of the principal in March 2022.
- $300.0 million 2024 Senior Notes, which includes bi-annual interest payments and repayment of the principal in November 2024.

(2) These amounts reflect the following purchase commitments with our third-party manufacturers:

- Purchase commitment for RAVICTI through 2020.
- Purchase commitment for PROCYSBI and QUINSAIR through December 2020.
- Minimum annual order quantities required to be placed with Boehringer Ingelheim for final packaged ACTIMMUNE through July 2024 and additional units we also committed to purchase which were intended to cover anticipated demand if the results of the FA program of ACTIMMUNE for the treatment of FA had been successful. As of December 31, 2018, the minimum binding purchase commitment to Boehringer Ingelheim Biopharmaceuticals GmbH, or Boehringer Ingelheim Biopharmaceuticals, was $25.7 million (converted using a Dollar-to-Euro exchange rate of 1.1466) through July 2024.
- A commitment to spend $1.1 million with Boehringer Ingelheim related to the harmonization of the manufacturing process for ACTIMMUNE drug substance.
- Purchase commitment for BUPHENYL through 2020.
- Minimum purchase commitment for KRYSTEXXA through 2026.
- Minimum purchase commitment for RAYOS tablets from Jagotec AG through December 2023 (the end of the minimum term), which was the firm commitment term under the contract as of December 31, 2018. Effective January 1, 2019, we amended our license and supply agreements with Jagotec AG and Skyepharma AG, which are affiliates of Vectura. Under these amendments, from the earlier of the completion of certain transfer activities or January 1, 2020, we will no longer be subject to a minimum purchase commitment in respect of the supply agreement with Jagotec AG. At December 31, 2018, the minimum purchase commitment based on tablet pricing in effect under the agreement was $4.8 million through December 2023. Purchase commitment for final packaged PENNSAID 2% from Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.) through March 2019.
- Purchase commitment for final packaged DUEXIS tablets from Sanofi-Aventis U.S. through May 2019.
- Minimum purchase commitment for VIMOVO tablets from Patheon Pharmaceuticals Inc. through March 2019.
- Purchase commitments for process validation activities for teprotumumab through 2019.

(3) These amounts reflect payments due under our operating leases, which are principally for our facilities. For further details regarding these properties, see Item 2 of Part I, *Properties,* of this Annual Report on Form 10-K.

As of December 31, 2018, our contingent liability for uncertain tax positions amounted to $26.3 million (excluding interest and penalties). Due to the nature and timing of the ultimate outcome of these uncertain tax positions, we cannot make a reasonably reliable estimate of the amount and period of related future payments, if any. Therefore, our contingent liability has been excluded from the above contractual obligations table. We do not expect a significant tax payment related to these obligations within the next year.

In addition to the obligations set out in the above table, we have assumed material obligations to make royalty and milestone payments to certain third parties on net sales of certain of our medicines. See Note 17 of the Notes to consolidated financial statements, included in Item 15 of this Annual Report on Form 10-K, for details of these material obligations.

Off-Balance Sheet Arrangements

Since our inception, we have not engaged in any off-balance sheet arrangements, including the use of structured finance, special purpose entities or variable interest entities, other than the indemnification agreements discussed in Note 17 in the Notes to our consolidated financial statements included in this report.

Critical Accounting Policies and Significant Judgments and Estimates

The methods, estimates and judgments that we use in applying our critical accounting policies have a significant impact on the results that we report in our financial statements. Some of our accounting policies require us to make difficult and subjective judgments, often as a result of the need to make estimates regarding matters that are inherently uncertain.

We have identified the accounting policies and estimates listed below as those that we believe require management's most subjective and complex judgments in estimating the effect of inherent uncertainties. This section should also be read in conjunction with Note 2 in the Notes to our consolidated financial statements included in this report, which includes a discussion of these and other significant accounting policies.

Revenue Recognition

In the United States, we sell our medicines primarily to wholesale distributors, specialty distributors and specialty pharmacy providers. In other countries, we sell our medicines primarily to wholesale distributors and other third-party distribution partners. These customers subsequently resell our medicines to health care providers and patients. In addition, we enter into arrangements with health care providers and payers that provide for government-mandated or privately negotiated discounts and allowances related to our medicines. Revenue is recognized when performance obligations under the terms of a contract with a customer are satisfied. The majority of our contracts have a single performance obligation to transfer medicines. Accordingly, revenues from medicine sales are recognized when the customer obtains control of our medicines, which occurs at a point in time, typically upon delivery to the customer. Revenue is measured as the amount of consideration we expect to receive in exchange for transferring medicines and is generally based upon a list or fixed price less allowances for medicine returns, rebates and discounts. We sell our medicines to wholesale pharmaceutical distributors and pharmacies under agreements with payment terms typically less than 90 days. Our process for estimating reserves established for these variable consideration components does not differ materially from our historical practices.

Medicine Sales Discounts and Allowances

The nature of our contracts gives rise to variable consideration because of allowances for medicine returns, rebates and discounts. Allowances for medicine returns, rebates and discounts are recorded at the time of sale to wholesale pharmaceutical distributors and pharmacies. We apply significant judgments and estimates in determining some of these allowances. If actual results differ from our estimates, we will be required to make adjustments to these allowances in the future. Our adjustments to gross sales are discussed further below.

Commercial Rebates

We participate in certain commercial rebate programs. Under these rebate programs, we pay a rebate to the commercial entity or third-party administrator of the program. We calculate accrued commercial rebate estimates using the expected value method. We accrue estimated rebates based on contract prices, estimated percentages of medicine that will be prescribed to qualified patients and estimated levels of inventory in the distribution channel and record the rebate as a reduction of revenue. Accrued commercial rebates are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Distribution Service Fees

We include distribution service fees paid to our wholesalers for distribution and inventory management services as a reduction of revenue. We calculate accrued distribution service fee estimates using the most likely amount method. We accrue estimated distribution fees based on contractually determined amounts, typically as a percentage of revenue. Accrued distribution service fees are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Patient Access Programs

We offer discount card and other programs such as our HorizonCares program to patients under which the patient receives a discount on his or her prescription. In certain circumstances when a patient's prescription is rejected by a managed care vendor, we will pay for the full cost of the prescription. We reimburse pharmacies for this discount through third-party vendors. We reduce gross sales by the amount of actual co-pay and other patient assistance in the period based on invoices received. We also record an accrual to reduce gross sales for estimated co-pay and other patient assistance on units sold to distributors that have not yet been prescribed/dispensed to a patient. We calculate accrued co-pay and other patient assistance fee estimates using the expected value method. The estimate is based on contract prices, estimated percentages of medicine that will be prescribed to qualified patients, average assistance paid based on reporting from the third-party vendors and estimated levels of inventory in the distribution channel. Accrued co-pay and other patient assistance fees are included in "accrued trade discounts and rebates" on the consolidated balance sheet. Patient access programs include both co-pay assistance and fully bought down prescriptions.

Sales Returns

Consistent with industry practice, we maintain a return policy that allows customers to return medicines within a specified period prior to and subsequent to the medicine expiration date. Generally, medicines may be returned for a period beginning six months prior to its expiration date and up to one year after its expiration date. The right of return expires on the earlier of one year after the medicine expiration date or the time that the medicine is dispensed to the patient. The majority of medicine returns result from medicine dating, which falls within the range set by our policy, and are settled through the issuance of a credit to the customer. We calculate sales returns using the expected value method. The estimate of the provision for returns is based upon our historical experience with actual returns. The return period is known to us based on the shelf life of medicines at the time of shipment. We record sales returns in "accrued expenses" and as a reduction of revenue.

Prompt Pay Discounts

As an incentive for prompt payment, we offer a 2% cash discount to most customers. We calculate accrued prompt pay discounts using the most likely amount method. We expect that all eligible customers will comply with the contractual terms to earn the discount. We record the discount as an allowance against "accounts receivable, net" and a reduction of revenue.

Government Rebates

We participate in certain federal government rebate programs such as Medicare Coverage Gap and Medicaid. We calculate accrued government rebate estimates using the expected value method. We accrue estimated rebates based on percentages of medicine sold to qualified patients, estimated rebate percentages and estimated levels of inventory in the distribution channel that will be prescribed to qualified patients and record the rebates as a reduction of revenue. Accrued government rebates are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Government Chargebacks

We provide discounts to federal government qualified entities with whom we have contracted. These federal entities purchase medicines from the wholesale pharmaceutical distributors at a discounted price and the wholesale pharmaceutical distributors then charge back to us the difference between the current retail price and the contracted price that the federal entities paid for the medicines. We calculate accrued government chargeback estimates using the expected value method. We accrue estimated chargebacks based on contract prices, sell-through sales data obtained from third-party information and estimated levels of inventory in the distribution channel and record the chargeback as a reduction of revenue. Accrued government chargebacks are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Bad Debt Expense

Our medicines are sold to wholesale pharmaceutical distributors and pharmacies. We monitor our accounts receivable balances to determine the impact, if any, of such factors as changes in customer concentration, credit risk and the realizability of our accounts receivable and records a bad debt reserve when applicable.

Cost of Goods Sold

We recognize cost of goods sold in connection with our sales of each of our distributed medicines. Cost of goods sold includes all costs directly related to the acquisition of our medicines from our third-party manufacturers, including freight charges and other direct expenses such as insurance and supply chain costs. Cost of goods sold also includes amortization of intellectual property as described in the intangible assets and goodwill accounting policy below, inventory step-up expense, royalty payments to third parties, royalty accretion expense, changes in estimates associated with the contingent royalty liability as described in the accrued contingent royalty accounting policy below and loss on inventory purchase commitments.

Intangible Assets

Definite-lived intangible assets are amortized over their estimated useful lives. We review our intangible assets when events or circumstances may indicate that the carrying value of these assets is not recoverable and exceeds their fair value. We measure fair value based on the estimated future discounted cash flows associated with our assets in addition to other assumptions and projections that we deem to be reasonable and supportable. The estimated useful lives, from the date of acquisition, for all identified intangible assets that are subject to amortization are between five and thirteen years.

Indefinite-lived intangible assets consist of capitalized IPR&D. IPR&D assets represent capitalized incomplete research projects that we acquired through business combinations. Such assets are initially measured at their acquisition date fair values and are tested for impairment, until completion or abandonment of research and development efforts associated with the projects. An IPR&D asset is considered abandoned when research and development efforts associated with the asset have ceased, and there are no plans to sell or license the asset or derive value from the asset. At that point, the asset is considered to be impaired and is written off. Upon successful completion of each project, we will make a determination about the then remaining useful life of the intangible asset and begin amortization. We test our indefinite-lived intangibles, including IPR&D assets, for impairment annually during the fourth quarter and more frequently if events or changes in circumstances indicate that it is more likely than not that the asset is impaired.

Business Combinations

We account for business combinations in accordance with the guidance in ASC 805, under which acquired assets and liabilities are measured at their respective estimated fair values as of the acquisition date. We may be required, as in the case of intangible assets or contingent royalties, to determine the fair value associated with these amounts by estimating the fair value using an income approach under the discounted cash flow method, which may include revenue projections and other assumptions made by us to determine the fair value.

Goodwill

Goodwill represents the excess of the purchase price of acquired businesses over the estimated fair value of the identifiable net assets acquired. Goodwill is not amortized but is tested for impairment at least annually at the reporting unit level or more frequently if events or changes in circumstances indicate that the asset might be impaired. Impairment loss, if any, is recognized based on a comparison of the fair value of the asset to its carrying value, without consideration of any recoverability. We test goodwill for impairment annually during the fourth quarter and whenever indicators of impairment exist by first assessing qualitative factors to determine whether it is more likely than not that the fair value is less than its carrying amount. If we conclude it is more likely than not that the fair value of a reporting unit is less than its carrying amount, a quantitative impairment test is performed. If we conclude that goodwill is impaired, we will record an impairment charge in our consolidated statement of comprehensive loss.

Provision for Income Taxes

We account for income taxes based upon an asset and liability approach. Deferred tax assets and liabilities represent the future tax consequences of the differences between the financial statement carrying amounts of assets and liabilities versus the tax basis of assets and liabilities. Under this method, deferred tax assets are recognized for deductible temporary differences, and operating loss and tax credit carryforwards. Deferred tax liabilities are recognized for taxable temporary differences. Deferred tax assets are reduced by a valuation allowance when, in the opinion of management, it is more likely than not that some portion or all of the deferred tax assets will not be realized. The impact of tax rate changes on deferred tax assets and liabilities is recognized in the year that the change is enacted. We also account for the uncertainty in income taxes by utilizing a comprehensive model for the recognition, measurement, presentation and disclosure in financial statements of any uncertain tax positions that have been taken or are expected to be taken on an income tax return. Deferred tax assets and deferred tax liabilities are netted by jurisdiction in our consolidated balance sheets.

On December 22, 2017, the SAB 118, which provided guidance on accounting for the tax effects of the Tax Act. SAB 118 provided a measurement period that should not extend beyond one year from the date of enactment for companies to complete the accounting under ASC 740, *Income Taxes*. In accordance with SAB 118, we reflected the income tax effects of those aspects of the Tax Act for which the accounting under ASC 740 was complete. To the extent that our accounting for certain income tax effects of the Tax Act was incomplete but we could determine a reasonable estimate, we recorded a provisional estimate in the consolidated financial statements. As of December 31, 2017, we had not completed our accounting for the effects of the Tax Act. However, we made reasonable estimates of the effects on our income tax provision with respect to certain items, primarily the revaluation of our existing U.S. deferred tax balances and the write-off of our U.S. deferred tax assets resulting from interest expense carryforwards under Section 163(j) of the Code. In other cases, we were not been able to make reasonable estimates and continued to account for those items based on our existing accounting under the provisions of the tax laws that were in effect prior to enactment. We recognized a net income tax benefit of $74.9 million for the year ended December 31, 2017, associated with the items we could reasonably estimate; refer to Note 22 of the Notes to consolidated financial statements. This benefit reflects the revaluation of our U.S. net deferred tax liability based on the new U.S. federal tax rate of 21 percent, partially offset by the write-off of the deferred tax asset related to our U.S. interest expense carryforwards.

On April 2, 2018, the U.S. Treasury Department and the U.S. Internal Revenue Service issued Notice 2018-28, or the Notice, which provides guidance for computing the business interest expense limitation under the Tax Act and clarifies the treatment of interest disallowed and carried forward under Section 163(j) of the Code, prior to enactment of the Tax Act. In accordance with the measurement period provisions under SAB 118 and the guidance in the Notice the Company reinstated the deferred tax asset related to its U.S. interest expense carryforwards under Section 163(j) based on the new U.S. federal tax rate of 21 percent plus applicable state tax rates. The impact of the deferred tax asset reinstatement in accordance with SAB 118 was a $37.4 million increase to the Company's benefit for income taxes and a corresponding decrease to the U.S. group net deferred tax liability position. The impact of this reinstatement has been recognized as a discrete tax adjustment during the year ended December 31, 2018 and resulted in a 31.4% increase in our effective tax rate during the period. Other than the reinstatement of our U.S interest expense carryforwards under Section 163(j), as described previously, in the fourth quarter of 2018, we completed our analysis to determine the effect of the Tax Act and recorded immaterial adjustments as of December 31, 2018, which related to return to provision adjustments which impacted our U.S. net deferred tax liabilities.

Share-Based Compensation

We account for employee share-based compensation by measuring and recognizing compensation expense for all share-based payments based on estimated grant date fair values. We use the straight-line method to allocate compensation cost to reporting periods over each awardee's requisite service period, which is generally the vesting period. We adopted ASU No. 2016-09 on January 1, 2017 and elected to retain a forfeiture rate after adoption.

Accrued Contingent Royalties

Our accrued contingent royalties consist of the contingent royalty obligations assumed by us related to our acquisitions of rights to certain of our medicines. At the time of each acquisition, we assigned a fair value to the liability for royalties. The royalty liability was based on anticipated revenue streams utilizing the income approach under the discounted cash flow method. The estimated liability for royalties is increased or decreased over time to reflect the change in its present value, and accretion expense is recorded as part of cost of goods sold. We evaluate the adequacy of the estimated contingent royalty liability at least annually in the fourth quarter, or whenever events or changes in circumstances indicate that an evaluation of the estimate is necessary. As part of our evaluation, we adjust the carrying value of the liability to the present value of the revised estimated cash flows using the original discount rate.

Any adjustment to the liability is recorded as an increase or reduction in cost of goods sold. The royalty liability is included in current and long-term accrued royalties on the consolidated balance sheets.

New Accounting Pronouncements Impacting Critical Accounting Policies

Refer to Note 2 in the Notes to our consolidated financial statements included in this report, which includes a discussion of the new accounting pronouncements impacting critical accounting policies.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

We are exposed to various market risks, which include potential losses arising from adverse changes in market rates and prices, such as interest rates and foreign exchange fluctuations. We do not enter into derivatives or other financial instruments for trading or speculative purposes.

Interest Rate Risk. We are subject to interest rate fluctuation exposure through our borrowings under the Credit Agreement and our investment in money market accounts which bear a variable interest rate. Loans under the Credit Agreement bear interest, at our option, at a rate equal to either the London Inter-Bank Offered Rate, or LIBOR, plus an applicable margin of 3.00% per annum (subject to a 1.00% LIBOR floor), or the adjusted base rate plus 2.00%. The adjusted base rate is defined as the greatest of (a) LIBOR (using one-month interest period) plus 1.00%, (b) the prime rate, (c) the federal funds rate plus 0.50% and (d) 2.00%. Our approximately $818.0 million of October 2018 Refinancing Loans are based on LIBOR. The one month LIBOR rate as of January 24, 2019, which was the most recent date the interest rate on the term loan was fixed, was 2.56%, and as a result, the interest rate on our borrowings is currently 5.56% per annum. Because the United Kingdom Financial Conduct Authority, which regulates LIBOR, intends to phase out the use of LIBOR by the end of 2021, future borrowings under our Credit Agreement could be subject to reference rates other than LIBOR.

An increase of 100 basis points (1.00%) in the interest rate on our outstanding loans at the date of filing of this Annual Report on Form 10-K would increase our interest expense related to the Credit Agreement by $8.2 million per year.

The goals of our investment policy are associated with the preservation of capital, fulfillment of liquidity needs and fiduciary control of cash. To achieve our goal of maximizing income without assuming significant market risk, we maintain our excess cash and cash equivalents in money market funds. Because of the short-term maturities of our cash equivalents, we do not believe that a decrease in interest rates would have any material negative impact on the fair value of our cash equivalents.

Foreign Currency Risk. Our purchase cost of ACTIMMUNE are principally denominated in Euros and are subject to foreign currency risk. We have contracts relating to RAVICTI, QUINSAIR and PROCYSBI for sales in Canada which sales are subject to foreign currency risk. We also incur certain operating expenses in currencies other than the U.S. dollar in relation to our Irish operations and foreign subsidiaries. Therefore, we are subject to volatility in cash flows due to fluctuations in foreign currency exchange rates, particularly changes in the Euro and the Canadian dollar.

Inflation Risk. We do not believe that inflation has had a material impact on our business or results of operations during the periods for which the consolidated financial statements are presented in this report.

Credit Risk. Historically, our accounts receivable balances have been highly concentrated with a select number of customers, consisting primarily of large wholesale pharmaceutical distributors who, in turn, sell the medicines to pharmacies, hospitals and other customers. As of December 31, 2018, and 2017, our top four customers accounted for approximately 85% and 74%, respectively, of our total outstanding accounts receivable balances, after the reclassification adjustments as described in Note 2, *Summary of Significant Accounting Policies*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K.

Item 8. Financial Statements and Supplementary Data

The financial information required by Item 8 is contained in Part IV, Item 15 of this Annual Report on Form 10-K.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our Chief Executive Officer and Chief Financial Officer, after evaluating the effectiveness of our "disclosure controls and procedures" (as defined in Rule 13a-15(e) promulgated under the Securities Exchange Act of 1934, as amended, or the Exchange Act), have concluded that, as of December 31, 2018, our disclosure controls and procedures were effective to provide reasonable assurance that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the Securities and Exchange Commission's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by an issuer in the reports that it files or submits under the Exchange Act is accumulated and communicated to the issuer's management, including its principal executive officer or officers and principal financial officer or officers, or persons performing similar functions, as appropriate to allow timely decisions regarding required disclosure.

Management's Report on Internal Control over Financial Reporting

Our management, under the supervision of our chief executive officer and our chief financial officer, is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined under Rule 13a-15(f) of the Exchange Act. Internal control over financial reporting is designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate. Therefore, even those systems determined to be effective can provide only reasonable assurance with respect to financial statement preparation and presentation.

Our management has assessed the effectiveness of our internal control over financial reporting as of December 31, 2018. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in *Internal Control – Integrated Framework (2013).* Management's assessment included an evaluation of the design of our internal control over financial reporting and testing of the operational effectiveness of our internal control over financial reporting. Based on management's assessment, management has concluded that, as of December 31, 2018, our internal control over financial reporting was effective based on those criteria.

The effectiveness of our internal control over financial reporting as of December 31, 2018, has been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm, as stated in their report which appears herein.

Changes in Internal Control Over Financial Reporting

There have been no material changes to our internal control over financial reporting, as defined in Exchange Act Rules 13a-15(f) and 15d-15(f), during the three months ended December 31, 2018, that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The information required by this item is incorporated herein by reference to our definitive Proxy Statement to be filed in connection with our 2019 Annual General Meeting of Shareholders, or our 2019 Proxy Statement, which will be filed with the Securities and Exchange Commission within 120 days after December 31, 2018.

We have adopted a written Code of Business Conduct and Ethics, or Ethics Code, that applies to all officers, directors and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. The Ethics Code is available on our website at www.horizonpharma.com. If we make any substantive amendments to the Ethics Code or grant any waiver from a provision of the Ethics Code to any executive officer or director, we will promptly disclose the nature of the amendment or waiver on our website or in a Current Report on Form 8-K.

Item 11. Executive Compensation

The information required by this item is incorporated herein by reference to our 2019 Proxy Statement.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this item is incorporated herein by reference to our 2019 Proxy Statement.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this item is incorporated herein by reference to our 2019 Proxy Statement.

Item 14. Principal Accounting Fees and Services

The information required by this item is incorporated herein by reference to our 2019 Proxy Statement.

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a) Documents filed as part of this report.

1. Financial Statements

The financial statements listed on the Index to Consolidated Financial Statements F-1 to F-58 are filed as part of this Annual Report on Form 10-K.

2. Financial Statement Schedules

Schedule II – Valuation and Qualifying Accounts and Reserves for each of the three fiscal years ended December 31, 2018, 2017 and 2016 appearing on page F-59. Other financial statement schedules have been omitted because the required information is included in the consolidated financial statements or notes thereto or because they are not applicable or not required.

3. Exhibits

INDEX TO EXHIBITS

Exhibit Number	Description of Document
3.1	Memorandum and Articles of Association of Horizon Pharma Public Limited Company, as amended (incorporated by reference to Exhibit 3.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on May 4, 2017).
4.1	Indenture, dated March 13, 2015, by and among Horizon Pharma Public Limited Company, Horizon Pharma Investment Limited and U.S. Bank National Association (incorporated by reference to Exhibit 4.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on March 13, 2015).
4.2	Form of 2.50% Exchangeable Senior Note due 2022 (incorporated by reference to Exhibit 4.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on March 13, 2015).
4.3	Indenture, dated April 29, 2015, by and between Horizon Pharma Financing Inc. and U.S. Bank National Association (incorporated by reference to Exhibit 4.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on April 29, 2015).
4.4	Form of 6.625% Senior Note due 2023 (incorporated by reference to Exhibit 4.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on April 29, 2015).
4.5	First Supplemental Indenture, dated May 7, 2015, by and among Horizon Pharma Public Limited Company, certain subsidiaries of Horizon Pharma Public Limited Company and U.S. Bank National Association (incorporated by reference to Exhibit 10.2 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on May 11, 2015).
4.6	Indenture, dated October 25, 2016, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and U.S. Bank National Association, as trustee (incorporated by reference to Exhibit 4.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on October 25, 2016).
4.7	Form of 8.75% Senior Note due 2024 (incorporated by reference to Exhibit 4.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on October 25, 2016).

4.8	First Supplemental Indenture, dated October 23, 2017, by and between Horizon Pharma Tepro, Inc. and U.S. Bank National Association (incorporated by reference to Exhibit 4.8 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on November 7, 2018).
4.9	Second Supplemental Indenture, dated October 19, 2018, by and between Horizon Pharma Services LLC and U.S. Bank National Association (incorporated by reference to Exhibit 4.9 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on November 7, 2018).
4.10	Second Supplemental Indenture, dated May 10, 2016, by and between Horizon Pharma Rheumatology LLC and U.S. Bank National Association (incorporated by reference to Exhibit 4.10 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on November 7, 2018).
4.11	Third Supplemental Indenture, dated October 25, 2016, by and among Horizon Pharmaceutical LLC, Horizon Orphan LLC and U.S. Bank National Association (incorporated by reference to Exhibit 4.11 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on November 7, 2018).
4.12	Fourth Supplemental Indenture, dated October 23, 2017, by and between Horizon Pharma Tepro, Inc. and U.S. Bank National Association (incorporated by reference to Exhibit 4.12 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on November 7, 2018).
4.13	Fifth Supplemental Indenture, dated October 19, 2018, by and between Horizon Pharma Services LLC and U.S. Bank National Association (incorporated by reference to Exhibit 4.13 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on November 7, 2018).
4.14	Sixth Supplemental Indenture, dated October 31, 2018, by and between Horizon Pharma USA, Inc. and U.S. Bank National Association (incorporated by reference to Exhibit 4.14 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on November 7, 2018).
4.15	Third Supplemental Indenture, dated November 15, 2018, by and between Horizon Medicines LLC and U.S. Bank National Association.
4.16	Seventh Supplemental Indenture, dated November 15, 2018, by and between Horizon Medicines LLC and U.S. Bank National Association.
10.1+	Form of Indemnification Agreement entered into by and between Horizon Pharma Public Limited Company and certain of its directors, officers and employees (incorporated by reference to Exhibit 10.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on September 19, 2014).
10.2+	Form of Indemnification Agreement entered into by and between Horizon Pharma, Inc. and certain directors, officers and employees of Horizon Pharma Public Limited Company (incorporated by reference to Exhibit 10.2 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on September 19, 2014).
10.3+	Horizon Pharma Public Limited Company Non-Employee Director Compensation Policy, as amended.
10.4+**	Horizon Pharma, Inc. 2005 Stock Plan and Form of Stock Option Agreement thereunder (incorporated by reference to Exhibit 10.2 to Horizon Pharma, Inc.'s Registration Statement on Form S-1 (No. 333-168504), as amended).
10.5+**	Horizon Pharma, Inc. 2011 Equity Incentive Plan, as amended, and Form of Option Agreement and Form of Stock Option Grant Notice thereunder (incorporated by reference to Exhibit 99.1 to Horizon Pharma, Inc.'s Current Report on Form 8-K, filed on July 2, 2014).
10.6+	Horizon Pharma Public Limited Company 2014 Equity Incentive Plan, as amended, and Form of Option Agreement, Form of Stock Option Grant Notice, Forms of Restricted Stock Unit Agreement and Forms of Restricted Stock Unit Grant Notice thereunder (incorporated by reference to Exhibit 99.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on May 7, 2018).
10.7+	Horizon Pharma Public Limited Company 2014 Non-Employee Equity Plan, as amended, and Form of Option Agreement, Form of Stock Option Grant Notice, Form of Restricted Stock Unit Agreement and Form of Restricted Stock Unit Grant Notice thereunder (incorporated by reference to Exhibit 99.3 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on May 4, 2016).

10.8+	Horizon Pharma Public Limited Company 2014 Employee Share Purchase Plan, as amended (incorporated by reference to Exhibit 99.2 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on May 4, 2016).
10.9+	Form of Employee Proprietary Information and Inventions Agreement (incorporated by reference to Exhibit 10.15 to Horizon Pharma, Inc.'s Registration Statement on Form S-1 (No. 333-168504), as amended).
10.10+	Amended and Restated Executive Employment Agreement, dated July 27, 2010, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Timothy P. Walbert (incorporated by reference to Exhibit 10.22 to Horizon Pharma, Inc.'s Registration Statement on Form S-1 (No. 333-168504), as amended).
10.11*	Manufacturing and Supply Agreement, dated May 25, 2011, by and between Horizon Pharma USA, Inc. and Sanofi-Aventis U.S. LLC (incorporated by reference to Exhibit 10.35 to Horizon Pharma, Inc.'s Registration Statement on Form S-1 (No. 333-168504), as amended).
10.12*	Amendment to Manufacturing and Supply Agreement, effective as of September 25, 2013, by and between Horizon Pharma USA, Inc. and Sanofi-Aventis U.S. LLC (incorporated by reference to Exhibit 10.3 to Horizon Pharma, Inc.'s Quarterly Report on Form 10-Q, filed on November 8, 2013).
10.13+	First Amendment to Amended and Restated Executive Employment Agreement, dated January 16, 2014, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Timothy P. Walbert (incorporated by reference to Exhibit 99.1 to Horizon Pharma, Inc.'s Current Report on Form 8-K, filed on January 16, 2014).
10.14+	Executive Employment Agreement, effective as of March 5, 2014, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Robert F. Carey (incorporated by reference to Exhibit 10.56 to Horizon Pharma, Inc.'s Annual Report on Form 10-K, filed on March 13, 2014).
10.15+	Executive Employment Agreement, effective as of June 23, 2014, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Paul W. Hoelscher (incorporated by reference to Exhibit 99.4 to Horizon Pharma, Inc.'s Current Report on Form 8-K, filed on June 18, 2014).
10.16*	Supply Agreement, dated October 17, 2014, by and between Horizon Pharma Ireland Limited and Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.) (incorporated by reference to Exhibit 10.57 to Horizon Pharma Public Limited Company's Amendment No. 2 to Annual Report on Form 10-K, filed on April 10, 2015).
10.17	Lease, dated November 4, 2014, by and among Horizon Pharma Public Limited Company, Horizon Pharma Services Limited and John Ronan and Castle Cove Property Developments Limited (incorporated by reference to Exhibit 10.58 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).
10.18*	License Agreement for Interferon Gamma, dated May 5, 1998, by and between Genentech, Inc. and Connetics Corporation (incorporated by reference to Exhibit 10.62 to Horizon Pharma Public Limited Company's Amendment No. 3 to Annual Report on Form 10-K, filed on May 26, 2017).
10.19	Amendment No. 1 to License Agreement for Interferon Gamma, dated December 28, 1998, by and between Genentech, Inc. and Connetics Corporation (incorporated by reference to Exhibit 10.63 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).
10.20*	Amendment No. 2 to License Agreement for Interferon Gamma, dated January 15, 1999, by and between Genentech, Inc. and Connetics Corporation (incorporated by reference to Exhibit 10.64 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).
10.21*	Amendment No. 3 to License Agreement for Interferon Gamma, dated April 27, 1999, by and between Genentech, Inc. and Connetics Corporation (incorporated by reference to Exhibit 10.65 to Horizon Pharma Public Limited Company's Amendment No. 3 to Annual Report on Form 10-K, filed on May 26, 2017).
10.22	Consent to Assignment Agreement, dated June 23, 2000 (Amendment No. 4), by and among Genentech, Inc., Connetics Corporation and InterMune Pharmaceuticals, Inc. (incorporated by reference to Exhibit 10.66 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).
10.23	Amendment No. 5 to License Agreement for Interferon Gamma, dated January 25, 2001, by and between Genentech, Inc. and InterMune Pharmaceuticals, Inc. (incorporated by reference to Exhibit 10.67 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).

10.24*	Amendment No. 6 to License Agreement for Interferon Gamma, dated February 27, 2006, by and between Genentech, Inc. and InterMune, Inc. (incorporated by reference to Exhibit 10.68 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).
10.25*	Amendment No. 7 to License Agreement for Interferon Gamma, dated December 17, 2013, by and between Genentech, Inc. and Vidara Therapeutics International Public Limited Company (incorporated by reference to Exhibit 10.69 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).
10.26+	Executive Employment Agreement, effective as of September 18, 2014, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Barry Moze (incorporated by reference to Exhibit 10.74 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).
10.27+	Horizon Pharma, Inc. Deferred Compensation Plan (incorporated by reference to Exhibit 10.30 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 28, 2018).
10.28+	Horizon Pharma Public Limited Company Equity Long-Term Incentive Program (incorporated by reference to Exhibit 10.2 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on May 8, 2015).
10.29+	Executive Employment Agreement, dated May 7, 2015, by and among Horizon Pharma Inc., Horizon Pharma USA, Inc. and Brian Beeler (incorporated by reference to Exhibit 10.4 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on May 8, 2015).
10.30	Credit Agreement, dated May 7, 2015, by and among Horizon Pharma, Inc., as borrower, Horizon Pharma Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 10.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on May 11, 2015).
10.31*	License Agreement, dated April 16, 1999, by and among Saul Brusilow, M.D., Brusilow Enterprises, Inc. and Medicis Pharmaceutical Corporation (incorporated by reference to Exhibit 10.8 to Horizon Pharma Public Limited Company's Amendment No. 2 to Quarterly Report on Form 10-Q, filed on May 26, 2017).
10.32*	Settlement Agreement and First Amendment to License Agreement, dated August 21, 2007, by and among Saul Brusilow, M.D., Brusilow Enterprises, Inc., Medicis Pharmaceutical Corporation and Bausch Health Companies Inc. (formerly Ucyclyd Pharma, Inc.) (incorporated by reference to Exhibit 10.22 to Hyperion Therapeutics, Inc.'s Amendment No. 1 to the Registration Statement on Form S-1, filed on May 24, 2012).
10.33+	Horizon Pharma Public Limited Company Share Clog Program Trust Deed, as amended, and Form of Clog Letter (incorporated by reference to Exhibit 10.6 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on August 8, 2016).
10.34*	License Agreement, dated August 12, 1998, by and among Mountain View Pharmaceuticals, Inc., Duke University and Crealta Pharmaceuticals LLC (as successor in interest to Bio-Technology General Corporation), as amended November 12, 2001, August 30, 2010, March 12, 2014 and July 16, 2015 (incorporated by reference to Exhibit 10.61 to Horizon Pharma Public Limited Company's Amendment No. 1 to Annual Report on Form 10-K, filed on May 26, 2017).
10.35*	Commercial Supply Agreement, dated March 20, 2007, by and between Crealta Pharmaceuticals LLC (as successor in interest to Savient Pharmaceuticals, Inc.) and Bio-Technology General (Israel) Ltd., as amended September 24, 2007, January 24, 2009, July 1, 2010 and March 21, 2012 (incorporated by reference to Exhibit 10.62 to Horizon Pharma Public Limited Company's Amendment No. 1 to Annual Report on Form 10-K, filed on May 26, 2017).
10.36*	Supply Agreement, dated August 3, 2015, by and between NOF Corporation and Crealta Pharmaceuticals LLC (incorporated by reference to Exhibit 10.63 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 29, 2016).

10.37	Sublease, dated August 21, 2015, by and between Solo Cup Operating Corporation and Horizon Pharma USA, Inc. and Sublease Consent and Recognition Agreement, dated October 2, 2015, by and among Lake Forest Landmark II, LLC, Solo Cup Operating Corporation and Horizon Pharma USA, Inc. (incorporated by reference to Exhibit 10.64 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 29, 2016).
10.38*	Asset Purchase Agreement, dated March 22, 2012, by and between Hyperion Therapeutics, Inc. and Bausch Health Companies Inc. (formerly Ucyclyd Pharma, Inc.) (incorporated by reference to Exhibit 2.1 to Hyperion Therapeutics, Inc.'s Amendment No. 1 to the Registration Statement on Form S-1, filed on May 24, 2012).
10.39*	Amendment No. 1 to Supply Agreement, dated February 4, 2016, by and between Horizon Pharma Ireland Limited and Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.) (incorporated by reference to Exhibit 10.66 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 29, 2016).
10.40*	Commercial Supply Agreement, dated October 16, 2008, by and between Exelead, Inc. (formerly known as Sigma-Tau PharmaSource, Inc. (as successor in interest to Enzon Pharmaceuticals, Inc.)) and Crealta Pharmaceuticals LLC (as successor in interest to Savient Pharmaceuticals, Inc.), as amended October 5, 2009, October 22, 2009 and July 29, 2014 (incorporated by reference to Exhibit 10.68 to Horizon Pharma Public Limited Company's Amendment No. 1 to Annual Report on Form 10-K, filed on May 26, 2017).
10.41*	Fifth Amendment to Commercial Supply Agreement, effective as of August 31, 2016, by and between Horizon Pharma Ireland Limited and Bio-Technology General (Israel) Ltd. (incorporated by reference to Exhibit 10.1 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on November 7, 2016).
10.42	Amendment No. 1, dated October 25, 2016, to Credit Agreement, dated May 7, 2015, by and among Horizon Pharma, Inc., as borrower, Horizon Pharma Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 99.1 to Horizon Pharma Public Limited Company's Amendment No. 1 to Current Report on Form 8-K, filed on October 25, 2016).
10.43*	API Supply Agreement, dated November 3, 2010, by and among Cambrex Profarmaco Milano, Horizon Orphan LLC (as successor in interest to Raptor Therapeutics Inc.) and Horizon Pharma Europe B.V. (as successor in interest to Raptor Pharmaceuticals Europe B.V.), as amended April 9, 2013 (incorporated by reference to Exhibit 10.4 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on November 7, 2016).
10.44*	Manufacturing Services Agreement, dated November 15, 2010, by and among Patheon Pharmaceuticals Inc., Horizon Orphan LLC (as successor in interest to Raptor Therapeutics Inc.) and Horizon Pharma Europe B.V. (as successor in interest to Raptor Pharmaceuticals Europe B.V.), as amended April 5, 2012 and June 21, 2013 (incorporated by reference to Exhibit 10.5 to Horizon Pharma Public Limited Company's Amendment No. 1 to Quarterly Report on Form 10-Q, filed on May 26, 2017).
10.45+	Horizon Pharma Public Limited Company Equity Long-Term Incentive Program (incorporated by reference to Exhibit 99.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on January 11, 2018).
10.46+	Horizon Pharma Public Limited Company Cash Incentive Program (incorporated by reference to Exhibit 99.2 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on January 11, 2018).
10.47+	Horizon Pharma Public Limited Company Incentive Compensation Recoupment Policy (incorporated by reference to Exhibit 99.4 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on January 11, 2018).
10.48+	Executive Employment Agreement, effective as of January 4, 2018, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Shao-Lee Lin, M.D., Ph.D. (incorporated by reference to Exhibit 10.53 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 28, 2018).

10.49+	Executive Employment Agreement, effective as of September 11, 2017, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Irina Konstantinovsky (incorporated by reference to Exhibit 10.2 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on November 6, 2017).
10.50	Amendment No. 2, dated March 29, 2017, to Credit Agreement, dated May 7, 2015, by and among Horizon Pharma, Inc., as Borrower, Horizon Pharma USA, Inc., as an Additional Borrower, Horizon Pharma Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 99.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on March 30, 2017).
10.51	Amendment No. 3, dated October 23, 2017, to Credit Agreement, dated May 7, 2015, by and among Horizon Pharma, Inc., as Borrower, Horizon Pharma USA, Inc., as an Additional Borrower, Horizon Pharma Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 99.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on October 23, 2017).
10.52*	Global Supply Agreement, dated June 30, 2017, by and between Horizon Pharma Ireland Limited and Boehringer Ingelheim Biopharmaceuticals GmbH (incorporated by reference to Exhibit 10.3 to Horizon Pharma Public Limited Company's Amendment No. 1 to Quarterly Report on Form 10-Q, filed on September 28, 2017).
10.53*	Amended and Restated License Agreement, dated May 31, 2017, by and between Horizon Orphan LLC and The Regents of the University of California (incorporated by reference to Exhibit 10.4 to Horizon Pharma Public Limited Company's Amendment No. 1 to Quarterly Report on Form 10-Q, filed on September 28, 2017).
10.54+	Amended and Restated Executive Employment Agreement, effective as of March 1, 2018, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Vikram Karnani (incorporated by reference to Exhibit 10.10 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on May 9, 2018).
10.55+	First Amendment to Executive Employment Agreement, dated May 4, 2017, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Paul W. Hoelscher (incorporated by reference to Exhibit 10.7 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2017).
10.56+	First Amendment to Executive Employment Agreement, dated May 4, 2017, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Barry Moze (incorporated by reference to Exhibit 10.8 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2017).
10.57+	First Amendment to Executive Employment Agreement, dated May 4, 2017, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Brian Beeler (incorporated by reference to Exhibit 10.9 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2017).
10.58+	First Amendment to Executive Employment Agreement, dated May 4, 2017, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Robert F. Carey (incorporated by reference to Exhibit 10.12 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2017).
10.59+	Second Amendment to Amended and Restated Executive Employment Agreement, dated May 4, 2017, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Timothy P. Walbert (incorporated by reference to Exhibit 10.13 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2017).
10.60+	Executive Employment Agreement, effective as of February 16, 2017, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Michael DesJardin (incorporated by reference to Exhibit 10.68 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 28, 2018).
10.61+	First Amendment to Executive Employment Agreement, dated May 4, 2017, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Michael DesJardin (incorporated by reference to Exhibit 10.69 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 28, 2018).

10.62*	Second Amendment to Supply Agreement, dated January 1, 2017, by and between Horizon Pharma Ireland Limited and Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.) (incorporated by reference to Exhibit 10.71 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 28, 2018).
10.63*	Third Amendment to Supply Agreement, dated February 16, 2018, by and between Horizon Pharma Ireland Limited and Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.) (incorporated by reference to Exhibit 10.72 to Horizon Pharma Public Limited Company's Annual Report on Form 10-K, filed on February 28, 2018).
10.64*	Confidential Settlement and License Agreement, effective as of June 27, 2018, by and among Horizon Therapeutics, LLC, Lupin Ltd. and Lupin Pharmaceuticals, Inc. (incorporated by reference to Exhibit 10.1 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on August 8, 2018).
10.65*	Letter Agreement, dated May 1, 2018, by and between Horizon Pharma USA, Inc. and Sanofi US Services, Inc. (incorporated by reference to Exhibit 10.2 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on August 8, 2018).
10.66*	Confidential Settlement and License Agreement, effective as of September 17, 2018, by and between Horizon Therapeutics, LLC and Par Pharmaceutical, Inc. (incorporated by reference to Exhibit 10.1 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on November 7, 2018).
10.67	Amendment No. 4, dated October 19, 2018, to Credit Agreement, dated May 7, 2015 (as amended by Amendment No. 1, dated October 25, 2016, Amendment No. 2, dated March 29, 2017 and Amendment No. 3, dated October 23, 2017), by and among Horizon Pharma, Inc., as Borrower, Horizon Pharma USA, Inc., as an Additional Borrower, Horizon Pharma Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 99.1 to Horizon Pharma Public Limited Company's Current Report on Form 8-K, filed on October 19, 2018).
10.68*	Amendment No. 1 to Amended and Restated License Agreement, dated September 11, 2018, by and between Horizon Orphan LLC and The Regents of the University of California (incorporated by reference to Exhibit 10.3 to Horizon Pharma Public Limited Company's Quarterly Report on Form 10-Q, filed on November 7, 2018).
10.69+	Amended and Restated Executive Employment Agreement, effective as of August 1, 2018, by and among Horizon Pharma, Inc., Horizon Pharma USA, Inc. and Geoffrey M. Curtis.
21.1	Subsidiaries of Horizon Pharma Public Limited Company.
23.1	Consent of PricewaterhouseCoopers LLP, independent registered public accounting firm.
24.1	Power of Attorney. Reference is made to the signature page hereto.
31.1	Certification of Principal Executive Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Exchange Act.
31.2	Certification of Principal Financial Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Exchange Act.
32.1	Certification of Principal Executive Officer pursuant to Rule 13a-14(b) or 15d-14(b) of the Exchange Act and 18 U.S.C. Section 1350.
32.2	Certification of Principal Financial Officer pursuant to Rule 13a-14(b) or 15d-14(b) of the Exchange Act and 18 U.S.C. Section 1350.
101.INS	XBRL Instance Document
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	XBRL Taxonomy Extension Label Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document

+ Indicates management contract or compensatory plan.

* Confidential treatment has been granted with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.

** Indicates an instrument, agreement or compensatory arrangement or plan assumed by Horizon Pharma Public Limited Company in the merger with Vidara and no longer binding on Horizon Pharma, Inc.

Item 16. Form 10-K Summary

None.

HORIZON PHARMA PLC

Index to Consolidated Financial Statements

Report of Independent Registered Public Accounting Firm

To the Board of Directors and Shareholders of Horizon Pharma plc

Opinions on the Financial Statements and Internal Control over Financial Reporting

We have audited the accompanying consolidated balance sheets of Horizon Pharma plc and its subsidiaries (the "Company") as of December 31, 2018 and 2017, and the related consolidated statements of comprehensive loss, shareholders' equity, and cash flows for each of the three years in the period ended December 31, 2018, including the related notes and financial statement schedule listed in the index appearing under Item 15(a)(2) (collectively referred to as the "consolidated financial statements"). We also have audited the Company's internal control over financial reporting as of December 31, 2018, based on criteria established in *Internal Control - Integrated Framework* (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO).

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of the Company as of December 31, 2018 and 2017, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2018 in conformity with accounting principles generally accepted in the United States of America. Also in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2018, based on criteria established in *Internal Control - Integrated Framework* (2013) issued by the COSO.

Basis for Opinions

The Company's management is responsible for these consolidated financial statements, for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting, included in Management's Report on Internal Control over Financial Reporting appearing under Item 9A. Our responsibility is to express opinions on the Company's consolidated financial statements and on the Company's internal control over financial reporting based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) ("PCAOB") and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud, and whether effective internal control over financial reporting was maintained in all material respects.

Our audits of the consolidated financial statements included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audits also included performing such other procedures as we considered necessary in the circumstances. We believe that our audits provide a reasonable basis for our opinions.

Definition and Limitations of Internal Control over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the

company; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ PricewaterhouseCoopers LLP
Chicago, Illinois
February 27, 2019

We have served as the Company's auditor since 2009.

HORIZON PHARMA PLC

CONSOLIDATED BALANCE SHEETS
(In thousands, except share data)

	As of December 31, 2018	As of December 31, 2017
ASSETS		
CURRENT ASSETS:		
Cash and cash equivalents	$ 958,712	$ 751,368
Restricted cash	3,405	6,529
Accounts receivable, net	464,730	405,214
Inventories, net	50,751	61,655
Prepaid expenses and other current assets	70,828	43,402
Total current assets	**1,548,426**	**1,268,168**
Property and equipment, net	20,101	20,405
Developed technology, net	2,120,596	2,442,292
Other intangible assets, net	4,630	5,441
Goodwill	426,441	426,441
Deferred tax assets, net	3,148	3,470
Other assets	23,029	36,081
Total assets	**$ 4,146,371**	**$ 4,202,298**
LIABILITIES AND SHAREHOLDERS' EQUITY		
CURRENT LIABILITIES:		
Long-term debt—current portion	$ —	$ 10,625
Accounts payable	30,284	34,681
Accrued expenses	205,593	175,697
Accrued trade discounts and rebates	457,763	501,753
Accrued royalties—current portion	63,363	65,328
Deferred revenues—current portion	4,901	6,885
Total current liabilities	**761,904**	**794,969**
LONG-TERM LIABILITIES:		
Exchangeable notes, net	332,199	314,384
Long-term debt, net of current	1,564,485	1,576,646
Accrued royalties, net of current	285,374	279,316
Deferred revenues, net of current	—	9,713
Deferred tax liabilities, net	93,630	157,945
Other long-term liabilities	54,622	68,015
Total long-term liabilities	**2,330,310**	**2,406,019**
COMMITMENTS AND CONTINGENCIES		
SHAREHOLDERS' EQUITY:		
Ordinary shares, $0.0001 nominal value; 300,000,000 shares authorized; 169,244,520 and 164,785,083 shares issued at December 31, 2018 and December 31, 2017, respectively, and 168,860,154 and 164,400,717 shares outstanding at December 31, 2018 and December 31, 2017, respectively	17	16
Treasury stock, 384,366 ordinary shares at December 31, 2018 and December 31, 2017	(4,585)	(4,585)
Additional paid-in capital	2,374,966	2,248,979
Accumulated other comprehensive loss	(1,523)	(983)
Accumulated deficit	(1,314,718)	(1,242,117)
Total shareholders' equity	**1,054,157**	**1,001,310**
Total liabilities and shareholders' equity	**$ 4,146,371**	**$ 4,202,298**

The accompanying notes are an integral part of these consolidated financial statements.

HORIZON PHARMA PLC

CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS
(In thousands, except share and per share data)

	For the Years Ended December 31,		
	2018	**2017**	**2016**
Net sales	$ 1,207,570	$ 1,056,231	$ 981,120
Cost of goods sold	422,317	537,334	392,001
Gross profit	**785,253**	**518,897**	**589,119**
OPERATING EXPENSES:			
Research and development	82,762	224,962	60,707
Selling, general and administrative	692,485	655,093	603,048
Impairment of long-lived assets	50,302	22,270	71,260
Gain on sale of assets	(42,688)	—	—
Total operating expenses	**782,861**	**902,325**	**735,015**
Operating income (loss)	**2,392**	**(383,428)**	**(145,896)**
OTHER EXPENSE, NET:			
Interest expense, net	(121,692)	(126,523)	(86,610)
Foreign exchange loss	(192)	(260)	(1,005)
Gain on divestiture	—	6,267	—
Loss on debt extinguishment	—	(978)	—
Other income, net	346	588	6,697
Total other expense, net	**(121,538)**	**(120,906)**	**(80,918)**
Loss before benefit for income taxes	**(119,146)**	**(504,334)**	**(226,814)**
Benefit for income taxes	(44,959)	(102,749)	(61,251)
Net loss	**$ (74,187)**	**$ (401,585)**	**$ (165,563)**
Net loss per ordinary share—basic and diluted	$ (0.45)	$ (2.46)	$ (1.03)
Weighted average ordinary shares outstanding—basic and diluted	166,155,405	163,122,663	160,699,543
OTHER COMPREHENSIVE (LOSS) INCOME, NET OF TAX			
Foreign currency translation adjustments	$ (826)	$ 2,067	$ (302)
Pension remeasurements	286	36	(133)
Other comprehensive (loss) income	(540)	2,103	(435)
Comprehensive loss	**$ (74,727)**	**$ (399,482)**	**$ (165,998)**

The accompanying notes are an integral part of these consolidated financial statements.

HORIZON PHARMA PLC

CONSOLIDATED STATEMENTS OF SHAREHOLDERS' EQUITY
(In thousands, except share data)

	Ordinary Shares		Treasury Stock		Additional Paid-in	Accumulated Other Comprehensive	Accumulated	Total Shareholders'
	Shares	Amount	Shares	Amount	Capital	Loss	Deficit	Equity
Balances at December 31, 2015	**160,069,067**	**$ 16**	**384,366**	**$ (4,585)**	**$ 2,001,552**	**$ (2,651)**	**$ (681,187)**	**$ 1,313,145**
Issuance of ordinary shares in conjunction with vesting of restricted stock units and stock option exercises	1,245,637	—	—	—	3,875	—	—	3,875
Ordinary shares withheld for payment of employees' withholding tax liability	—	—	—	—	(5,539)	—	—	(5,539)
Issuance of ordinary shares in conjunction with ESPP purchases	513,659	—	—	—	6,540	—	—	6,540
Issuance of ordinary shares in conjunction with PSU vesting	13,584	—	—	—	—	—	—	—
Share-based compensation	—	—	—	—	113,019	—	—	113,019
Issuance of ordinary shares in conjunction with warrant exercises	163,009	—	—	—	8	—	—	8
Currency translation adjustment	—	—	—	—	—	(302)	—	(302)
Pension remeasurements	—	—	—	—	—	(133)	—	(133)
Net loss	—	—	—	—	—	—	(165,563)	(165,563)
Balances at December 31, 2016	**162,004,956**	**$ 16**	**384,366**	**$ (4,585)**	**$ 2,119,455**	**$ (3,086)**	**$ (846,750)**	**$ 1,265,050**
Cumulative effect adjustment from adoption of ASU 2016-09	—	—	—	—	—	—	7,210	7,210
Issuance of ordinary shares in conjunction with vesting of restricted stock units and stock option exercises	1,117,876	—	—	—	2,167	—	—	2,167
Ordinary shares withheld for payment of employees' withholding tax liability	—	—	—	—	(6,533)	—	—	(6,533)
Issuance of ordinary shares in conjunction with ESPP purchases	822,231	—	—	—	7,082	—	—	7,082
Issuance of ordinary shares in conjunction with PSU vesting	25,000	—	—	—	—	—	—	—
Share-based compensation	—	—	—	—	125,019	—	—	125,019
Issuance of ordinary shares in conjunction with warrant exercises	915,020	—	—	—	1,789	—	—	1,789
Shares repurchased	(100,000)	—	—	—	—	—	(992)	(992)
Currency translation adjustment	—	—	—	—	—	2,067	—	2,067
Pension remeasurements	—	—	—	—	—	36	—	36
Net loss	—	—	—	—	—	—	(401,585)	(401,585)
Balances at December 31, 2017	**164,785,083**	**$ 16**	**384,366**	**$ (4,585)**	**$ 2,248,979**	**$ (983)**	**$ (1,242,117)**	**$ 1,001,310**
Cumulative effect adjustments from adoption of ASUs 2014-09 and 2016-16	—	—	—	—	—	—	1,586	1,586
Issuance of ordinary shares in conjunction with vesting of restricted stock units and stock option exercises	3,541,933	1	—	—	16,972	—	—	16,973
Ordinary shares withheld for payment of employees' withholding tax liability	—	—	—	—	(14,455)	—	—	(14,455)
Issuance of ordinary shares in conjunction with ESPP purchases	917,504	—	—	—	8,610	—	—	8,610
Share-based compensation	—	—	—	—	114,860	—	—	114,860
Currency translation adjustment	—	—	—	—	—	(826)	—	(826)
Pension remeasurements	—	—	—	—	—	286	—	286
Net loss	—	—	—	—	—	—	(74,187)	(74,187)
Balances at December 31, 2018	**169,244,520**	**$ 17**	**384,366**	**$ (4,585)**	**$ 2,374,966**	**$ (1,523)**	**$ (1,314,718)**	**$ 1,054,157**

The accompanying notes are an integral part of these consolidated financial statements.

HORIZON PHARMA PLC

CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	For the Years Ended December 31,		
	2018	**2017**	**2016**
CASH FLOWS FROM OPERATING ACTIVITIES:			
Net loss	$ (74,187)	$ (401,585)	$ (165,563)
Adjustments to reconcile net (loss) income to net cash provided by operating activities:			
Depreciation and amortization expense	275,729	283,244	221,665
Equity-settled share-based compensation	114,860	125,019	113,019
Royalty accretion	59,476	51,263	40,616
Impairment of long-lived assets	50,302	22,270	71,260
Amortization of debt discount and deferred financing costs	22,751	21,619	18,546
Deferred income taxes	(64,491)	(132,231)	(65,561)
Gain on sale of assets	(42,688)	—	—
Royalty liability remeasurement	(3,383)	13,004	(713)
Gain on divestiture	—	(2,934)	—
Acquired in-process research and development expense	—	159,171	—
Loss on debt extinguishment	—	978	—
Foreign exchange and other adjustments	332	(1,466)	420
Changes in operating assets and liabilities:			
Accounts receivable	(59,697)	(84,444)	(68,271)
Inventories	10,280	108,371	67,633
Prepaid expenses and other current assets	(25,313)	5,110	(28,239)
Accounts payable	(4,593)	(16,521)	32,065
Accrued trade discounts and rebates	(44,028)	205,487	112,381
Accrued expenses and accrued royalties	(9,972)	(82,203)	14,629
Deferred revenues	(395)	4,468	1,114
Other non-current assets and liabilities	(10,440)	5,720	4,455
Net cash provided by operating activities	**194,543**	**284,340**	**369,456**
CASH FLOWS FROM INVESTING ACTIVITIES:			
Proceeds from sale of assets	44,424	—	—
Payment related to license agreements	(12,000)	—	—
Purchases of property and equipment	(4,771)	(4,336)	(15,725)
Payments for acquisitions, net of cash acquired	—	(167,220)	(1,354,921)
Proceeds from divestiture, net of cash divested	—	69,371	—
Net cash provided by (used in) investing activities	**27,653**	**(102,185)**	**(1,370,646)**
CASH FLOWS FROM FINANCING ACTIVITIES:			
Net proceeds from term loans	818,026	1,693,512	364,297
Repayment of term loans	(845,749)	(1,622,749)	(4,000)
Payment of contingent consideration	—	(20,000)	—
Repurchase of ordinary shares	—	(992)	—
Proceeds from the issuance of ordinary shares in connection with warrant exercises	—	1,789	8
Proceeds from the issuance of ordinary shares through an employee stock purchase plan	8,610	7,082	6,540
Proceeds from the issuance of ordinary shares in connection with stock option exercises	16,972	2,167	3,875
Payment of employee withholding taxes relating to share-based awards	(14,455)	(6,533)	(5,539)
Net proceeds from issuance of 2024 Senior Notes	—	—	291,893
Net cash (used in) provided by financing activities	**(16,596)**	**54,276**	**657,074**
Effect of foreign exchange rate changes on cash, cash equivalents and restricted cash	(1,380)	5,316	(1,210)
Net increase (decrease) in cash, cash equivalents and restricted cash	204,220	241,747	(345,326)
Cash, cash equivalents and restricted cash, beginning of the year	757,897	516,150	861,476
Cash, cash equivalents and restricted cash, end of the year	**$ 962,117**	**$ 757,897**	**$ 516,150**

HORIZON PHARMA PLC

CONSOLIDATED STATEMENTS OF CASH FLOWS (CONTINUED)
(In thousands)

	For the Years Ended December 31,		
	2018	**2017**	**2016**
Supplemental cash flow information:			
Cash paid for interest	$ 112,468	$ 113,790	$ 60,817
Cash paid for income taxes	53,058	2,548	22,339
Cash paid for debt extinguishment	—	145	—
Supplemental non-cash flow information:			
Purchases of property and equipment included in accounts payable and accrued expenses	1,101	—	700
Purchases of acquired in-process research and development included in accounts payable and accrued expenses	—	12,000	—

The accompanying notes are an integral part of these consolidated financial statements.

NOTE 1 – BASIS OF PRESENTATION

Unless otherwise indicated or the context otherwise requires, references to the "Company", "we", "us" and "our" refer to Horizon Pharma plc and its consolidated subsidiaries.

Overview

The Company is focused on researching, developing and commercializing innovative medicines that address unmet treatment needs for rare and rheumatic diseases. By expanding its growing pipeline of medicines in development and exploring all potential uses for currently marketed medicines, the Company strives to make a powerful difference for patients, their caregivers and physicians. The Company has two reportable segments, referred to as the "orphan and rheumatology segment" and the "primary care segment". The Company currently markets eleven medicines in the areas of orphan diseases, rheumatology and primary care.

The Company's currently marketed medicines are:

Orphan and Rheumatology
KRYSTEXXA® (pegloticase injection), for intravenous infusion
RAVICTI® (glycerol phenylbutyrate) oral liquid
PROCYSBI® (cysteamine bitartrate) delayed-release capsules, for oral use
ACTIMMUNE® (interferon gamma-1b) injection, for subcutaneous use
RAYOS® (prednisone) delayed-release tablets
BUPHENYL® (sodium phenylbutyrate) Tablets and Powder
QUINSAIR™ (levofloxacin) solution for inhalation
Primary Care
PENNSAID® (diclofenac sodium topical solution) 2% w/w, ("PENNSAID 2%"), for topical use
DUEXIS® (ibuprofen/famotidine) tablets, for oral use
VIMOVO® (naproxen/esomeprazole magnesium) delayed-release tablets, for oral use
MIGERGOT® (ergotamine tartrate & caffeine suppositories), for rectal use

Revision of Prior Period Financial Statements

During the course of preparing the Company's consolidated financial statements for the year ended December 31, 2018, the Company identified an error in the measurement of the contingent royalty liability calculation pertaining to the royalty end date for one of its medicines. The royalty end date for KRYSTEXXA is approximately two and one half years earlier than the date originally assumed in the calculations. As a result of the error, accrued royalties, net of current, and cost of goods sold had been overstated and shareholders' equity had been understated. The Company concluded that the amounts were not material to any of its previously issued consolidated financial statements. The Company has revised the accompanying consolidated balance sheet as at December 31, 2017, and the consolidated statements of comprehensive (loss) income and of cash flows for the years ended December 31, 2017 and 2016. Total shareholders' equity at December 31, 2016, was understated by $1.3 million. The impact on the consolidated statements of cash flows consisted of adjustments to reconcile net (loss) income to net cash provided by operating activities and changes in operating assets and liabilities for all periods presented. There was no impact on total operating, investing or financing cash flows for any prior period. See Note 23 for revisions to the Company's unaudited quarterly financial information. The following are selected line items from the Company's annual consolidated financial statements illustrating the effect of the revisions:

	Consolidated Balance Sheet as of December 31, 2017		
	As Previously Reported	Revision	As Revised
Developed technology, net	$ 2,443,949	$ (1,657)	$ 2,442,292
Total assets	4,203,955	(1,657)	4,202,298
Accrued royalties, net of current	291,185	(11,869)	279,316
Total long-term liabilities	2,417,888	(11,869)	2,406,019
Accumulated deficit	(1,252,329)	10,212	(1,242,117)
Total shareholders' equity	991,098	10,212	1,001,310
Total liabilities and shareholders' equity	4,203,955	(1,657)	4,202,298

	Consolidated Statements of Comprehensive Loss					
	For the Twelve Months Ended December 31, 2017			For the Twelve Months Ended December 31, 2016		
	As Previously Reported	Revision	As Revised	As Previously Reported	Revision	As Revised
Cost of goods sold	$ 546,275	$ (8,941)	$ 537,334	$ 393,272	$ (1,271)	$ 392,001
Gross profit	509,956	8,941	518,897	587,848	1,271	589,119
Operating loss	(392,369)	8,941	(383,428)	(147,167)	1,271	(145,896)
Loss before benefit for income taxes	(513,275)	8,941	(504,334)	(228,085)	1,271	(226,814)
Net loss	(410,526)	8,941	(401,585)	(166,834)	1,271	(165,563)
Net loss per ordinary share—basic	(2.52)	0.06	(2.46)	(1.04)	0.01	(1.03)
Net loss per ordinary share—diluted	(2.52)	0.06	(2.46)	(1.04)	0.01	(1.03)
Comprehensive loss	(408,423)	8,941	(399,482)	(167,269)	1,271	(165,998)

NOTE 2 – SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Basis of Presentation

The accompanying consolidated financial statements have been prepared in accordance with the accounting principles generally accepted in the United States of America ("GAAP").

The impairment recorded during the year ended December 31, 2017 of $22.3 million of the asset recognized in connection with the acquisition of certain rights to interferon gamma-1b, as further described in Note 4, was previously included within "selling, general and administrative" expenses. Additionally, during the year ended December 31, 2016, an impairment of a non-current asset of $5.3 million was included within "selling, general and administrative" expenses, and an impairment of in-process research and development expenses was included on an "impairment of in-process research and development" line item. For prior-period comparisons, the Company now includes these amounts in the "impairment of long-lived assets" line in its consolidated statement of comprehensive loss.

Principles of Consolidation

The consolidated financial statements include the Company's accounts and those of its wholly owned subsidiaries. All intercompany accounts and transactions have been eliminated.

Segment Information

Effective as of the second quarter of 2018, management realigned the Company's reportable segments to reflect changes in the manner in which the chief operating decision maker ("CODM") assesses financial information for decision-making purposes. See Note 13 for further details. The Company determined that it operates in two reportable segments, an orphan and rheumatology segment and a primary care segment. The Company's reportable segments are reported in a manner consistent with the internal reporting provided to the CODM. The Company's CODM has been identified as its chief executive officer. The Company has no transactions between reportable segments.

Use of Estimates

The preparation of the accompanying consolidated financial statements in conformity with GAAP requires management to make certain estimates and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent liabilities at the date of the financial statements and reported amounts of revenues and expenses during the reporting period. Actual results could differ from those estimates.

Foreign Currency Translation and Transactions

The reporting currency of the Company and its subsidiaries is the U.S. dollar.

The U.S. dollar is the functional currency for the Company's Ireland and United States-based businesses and the majority of its subsidiaries. The Company has foreign subsidiaries that have the Euro and the Canadian Dollar as their functional currency. Foreign currency-denominated assets and liabilities of these subsidiaries are translated into U.S. dollars based on exchange rates prevailing at the end of the period, revenues and expenses are translated at average exchange rates prevailing during the corresponding period, and shareholders' equity accounts are translated at historical exchange rates as of the date of any equity transaction. The effects of foreign exchange gains and losses arising from the translation of assets and liabilities of those entities where the functional currency is not the U.S. dollar are included as a component of accumulated other comprehensive (loss) income.

Gains and losses resulting from foreign currency transactions are reflected within the Company's results of operations.

Revenue Recognition

On January 1, 2018, the Company adopted ASU 2014-09, Revenue from Contracts with Customers, and subsequent amendments (ASC 606 or new guidance), using the modified retrospective method. The Company applied the new guidance to all contracts with customers within the scope of the standard that were in effect on January 1, 2018 and recognized the cumulative effect of initially applying the new guidance as an adjustment to the opening balance of retained earnings. Comparative information for prior periods has not been restated and continues to be reported under the accounting standards in effect for those periods. In the United States, the Company sells its medicines primarily to wholesale distributors and specialty pharmacy providers. In other countries, the Company sells its medicines primarily to wholesale distributors and other third-party distribution partners. These customers subsequently resell the Company's medicines to health care providers and patients. In addition, the Company enters into arrangements with health care providers and payers that provide for government-mandated or privately negotiated discounts and allowances related to the Company's medicines. Revenue is recognized when performance obligations under the terms of a contract with a customer are satisfied. The majority of the Company's contracts have a single performance obligation to transfer medicines. Accordingly, revenues from medicine sales are recognized when the customer obtains control of the Company's medicines, which occurs at a point in time, typically upon delivery to the customer. Revenue is measured as the amount of consideration the Company expects to receive in exchange for transferring medicines and is generally based upon a list or fixed price less allowances for medicine returns, rebates and discounts. The Company sells its medicines to wholesale pharmaceutical distributors and pharmacies under agreements with payment terms typically less than 90 days. The Company's process for estimating reserves established for these variable consideration components does not differ materially from the Company's historical practices.

Medicine Sales Discounts and Allowances

The nature of the Company's contracts gives rise to variable consideration because of allowances for medicine returns, rebates and discounts. Allowances for medicine returns, rebates and discounts are recorded at the time of sale to wholesale pharmaceutical distributors and pharmacies. The Company applies significant judgments and estimates in determining some of these allowances. If actual results differ from its estimates, the Company will be required to make adjustments to these allowances in the future. The Company's adjustments to gross sales are discussed further below.

Commercial Rebates

The Company participates in certain commercial rebate programs. Under these rebate programs, the Company pays a rebate to the commercial entity or third-party administrator of the program. The Company calculates accrued commercial rebate estimates using the expected value method. The Company accrues estimated rebates based on contract prices, estimated percentages of medicine that will be prescribed to qualified patients and estimated levels of inventory in the distribution channel and records the rebate as a reduction of revenue. Accrued commercial rebates are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Distribution Service Fees

The Company includes distribution service fees paid to its wholesalers for distribution and inventory management services as a reduction to revenue. The Company calculates accrued distribution service fee estimates using the most likely amount method. The Company accrues estimated distribution fees based on contractually determined amounts, typically as a percentage of revenue. Accrued distribution service fees are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Patient Access Programs

The Company offers discount card and other programs such as its HorizonCares program to patients under which the patient receives a discount on his or her prescription. In certain circumstances when a patient's prescription is rejected by a managed care vendor, the Company will pay for the full cost of the prescription. The Company reimburses pharmacies for this discount through third-party vendors. The Company reduces gross sales by the amount of actual co-pay and other patient assistance in the period based on invoices received. The Company also records an accrual to reduce gross sales for estimated co-pay and other patient assistance on units sold to distributors that have not yet been prescribed/dispensed to a patient. The Company calculates accrued co-pay and other patient assistance fee estimates using the expected value method. The estimate is based on contract prices, estimated percentages of medicine that will be prescribed to qualified patients, average assistance paid based on reporting from the third-party vendors and estimated levels of inventory in the distribution channel. Accrued co-pay and other patient assistance fees are included in "accrued trade discounts and rebates" on the consolidated balance sheet. Patient access programs include both co-pay assistance and fully bought down prescriptions.

Sales Returns

Consistent with industry practice, the Company maintains a return policy that allows customers to return medicines within a specified period prior to and subsequent to the medicine expiration date. Generally, medicines may be returned for a period beginning six months prior to its expiration date and up to one year after its expiration date. The right of return expires on the earlier of one year after the medicine expiration date or the time that the medicine is dispensed to the patient. The majority of medicine returns result from medicine dating, which falls within the range set by the Company's policy, and are settled through the issuance of a credit to the customer. The Company calculates sales returns using the expected value method. The estimate of the provision for returns is based upon the Company's historical experience with actual returns. The return period is known to the Company based on the shelf life of medicines at the time of shipment. The Company records sales returns in "accrued expenses" and as a reduction of revenue.

Prompt Pay Discounts

As an incentive for prompt payment, the Company offers a 2% cash discount to most customers. The Company calculates accrued prompt pay discounts using the most likely amount method. The Company expects that all eligible customers will comply with the contractual terms to earn the discount. The Company records the discount as an allowance against "accounts receivable, net" and a reduction of revenue.

Government Rebates

The Company participates in certain federal government rebate programs such as Medicare Coverage Gap and Medicaid. The Company calculates accrued government rebate estimates using the expected value method. The Company accrues estimated rebates based on percentages of medicine sold to qualified patients, estimated rebate percentages and estimated levels of inventory in the distribution channel that will be prescribed to qualified patients and records the rebates as a reduction of revenue. Accrued government rebates are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Government Chargebacks

The Company provides discounts to federal government qualified entities with whom the Company has contracted. These federal entities purchase medicines from the wholesale pharmaceutical distributors at a discounted price and the wholesale pharmaceutical distributors then charge back to the Company the difference between the current retail price and the contracted price that the federal entities paid for the medicines. The Company calculates accrued government chargeback estimates using the expected value method. The Company accrues estimated chargebacks based on contract prices, sell-through sales data obtained from third-party information and estimated levels of inventory in the distribution channel and records the chargeback as a reduction of revenue. Accrued government chargebacks are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Bad Debt Expense

The Company's medicines are sold to wholesale pharmaceutical distributors and pharmacies. The Company monitors its accounts receivable balances to determine the impact, if any, of such factors as changes in customer concentration, credit risk and the realizability of its accounts receivable, and records a bad debt reserve when applicable.

Inventories

Inventories are stated at the lower of cost or net realizable value, using the first-in, first-out convention. Inventories consist of raw materials, work-in-process and finished goods. The Company has entered into manufacturing and supply agreements for the manufacture or purchase of raw materials and production supplies. The Company's inventories include the direct purchase cost of materials and supplies and manufacturing overhead costs. The Company reviews its inventory balance and purchase obligations to assess if it has obsolete or excess inventory and records a charge to "cost of goods sold" when applicable.

Inventories acquired in business combinations are recorded at their estimated fair values. "Step-up" represents the write-up of inventory from the lower of cost or net realizable value (the historical book value as previously recorded on the acquired company's balance sheet) to fair market value at the acquisition date. Inventory step-up expense is recorded in the consolidated statement of comprehensive loss based on actual sales, or usage, using the first-in, first-out convention.

Inventories exclude medicine sample inventory, which is included in other current assets and is expensed as a component of "selling, general and administrative" expense when shipped to sales representatives.

Cost of Goods Sold

The Company recognizes cost of goods sold in connection with its sales of each of its distributed medicines. Cost of goods sold includes all costs directly related to the acquisition of the Company's medicines from its third-party manufacturers, including freight charges and other direct expenses such as insurance and supply chain costs. Cost of goods sold also includes amortization of intellectual property as described in the intangible assets accounting policy below, inventory step-up expense, drug substance harmonization costs, share-based compensation, charges relating to discontinuation of clinical trials, royalty payments to third parties, royalty accretion expense, changes in estimates associated with the contingent royalty liability as described in the accrued contingent royalty accounting policy below and loss on inventory purchase commitments.

Pre-clinical Studies and Clinical Trial Accruals

The Company's pre-clinical studies and clinical trials have historically been conducted by third-party contract research organizations and other vendors. Pre-clinical study and clinical trial expenses are based on the services received from these contract research organizations and vendors. Payments depend on factors such as the milestones accomplished, successful enrollment of certain numbers of patients and site initiation. In accruing service fees, the Company estimates the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from the estimate, the Company adjusts the accrual accordingly.

Net (Loss) Income Per Share

Basic net (loss) income per share is computed by dividing net (loss) income by the weighted-average number of ordinary shares outstanding during the period. Diluted earnings per share ("EPS") reflects the potential dilution beyond shares for basic EPS that could occur if securities or other contracts to issue ordinary shares were exercised, converted into ordinary shares, or resulted in the issuance of ordinary shares that would have shared in the Company's earnings.

Cash and Cash Equivalents

The Company considers all highly liquid investments, readily convertible to cash, that mature within three months or less from date of purchase to be cash equivalents. Cash and cash equivalents primarily consist of cash balances and money market funds. The Company generally invests excess cash in money market funds and other financial instruments with short-term durations, based upon operating requirements.

Restricted Cash

Restricted cash consists primarily of balances in interest-bearing money market accounts required by a vendor for the Company's sponsored employee business credit card program and collateral for a letter of credit.

Fair Value of Financial Instruments

The carrying amounts of the Company's financial instruments, including cash and cash equivalents, restricted cash, accounts receivable, accounts payable and accrued expenses, approximate their fair values due to their short maturities.

Business Combinations

The Company accounts for business combinations in accordance with the guidance in Accounting Standards Codification Topic 805*, Business Combinations* ("ASC 805") under which acquired assets and liabilities are measured at their respective estimated fair values as of the acquisition date. The Company may be required, as in the case of intangible assets, contingent royalties or derivatives, to determine the fair value associated with these amounts by estimating the fair value using an income approach under the discounted cash flow method, which may include revenue projections and other assumptions made by the Company to determine the fair value.

Provision for Income Taxes

The Company accounts for income taxes based upon an asset and liability approach. Deferred tax assets and liabilities represent the future tax consequences of the differences between the financial statement carrying amounts of assets and liabilities versus the tax basis of assets and liabilities. Under this method, deferred tax assets are recognized for deductible temporary differences, and operating loss and tax credit carryforwards. Deferred tax liabilities are recognized for taxable temporary differences. Deferred tax assets are reduced by a valuation allowance when, in the opinion of management, it is more likely than not that some portion or all of the deferred tax assets will not be realized. The impact of tax rate changes on deferred tax assets and liabilities is recognized in the year that the change is enacted. The Company also accounts for the uncertainty in income taxes by utilizing a comprehensive model for the recognition, measurement, presentation and disclosure in financial statements of any uncertain tax positions that have been taken or are expected to be taken on an income tax return. Deferred tax assets and deferred tax liabilities are netted by jurisdiction on the Company's consolidated balance sheets.

On December 22, 2017, the SEC staff issued Staff Accounting Bulletin No. 118, ("SAB 118"), which provided guidance on accounting for the tax effects of the Tax Act. SAB 118 provided a measurement period that should not extend beyond one year from the date of enactment for companies to complete the accounting under ASC 740, *Income Taxes*. In accordance with SAB 118, we reflected the income tax effects of those aspects of the Tax Act for which the accounting under ASC 740 was complete. To the extent that our accounting for certain income tax effects of the Tax Act was incomplete but we could determine a reasonable estimate, we recorded a provisional estimate in the consolidated financial statements. As of December 31, 2017, we had not completed our accounting for the effects of the Tax Act. However, we made reasonable estimates of the effects on our income tax provision with respect to certain items, primarily the revaluation of our existing U.S. deferred tax balances and the write-off of our U.S. deferred tax assets resulting from interest expense carryforwards under Section 163(j) of the Internal Revenue Code, as amended of the Code ("Section 163(j)"). In other cases, we were not been able to make reasonable estimates and continued to account for those items based on our existing accounting under the provisions of the tax laws that were in effect prior to enactment. We recognized a net income tax benefit of $74.9 million for the year ended December 31, 2017, associated with the items we could reasonably estimate; refer to Note 21 of the Notes to consolidated financial statements. This benefit reflects the revaluation of our U.S. net deferred tax liability based on the new U.S. federal tax rate of 21 percent, partially offset by the write-off of the deferred tax asset related to our U.S. interest expense carryforwards.

On April 2, 2018, the U.S. Treasury Department and the U.S. Internal Revenue Service issued Notice 2018-28 ("the Notice") which provides guidance for computing the business interest expense limitation under the Tax Act and clarifies the treatment of interest disallowed and carried forward under Section 163(j) of the Tax Act. In accordance with the measurement period provisions under SAB 118 and the guidance in the Notice the Company reinstated the deferred tax asset related to its U.S. interest expense carryforwards under Section 163(j) based on the new U.S. federal tax rate of 21 percent plus applicable state tax rates. The impact of the deferred tax asset reinstatement in accordance with SAB 118 was a $37.4 million increase to the Company's benefit for income taxes and a corresponding decrease to the U.S. group net deferred tax liability position. The impact of this reinstatement has been recognized as a discrete tax adjustment during the year ended December 31, 2018 and resulted in a 31.4% increase in the Company's effective tax rate during the period. Other than the reinstatement of the Company's U.S interest expense carryforwards under Section 163(j), as described previously, in the fourth quarter of 2018, the Company completed our analysis to determine the effect of the Tax Act and recorded immaterial adjustments as of December 31, 2018 which related to return to provision adjustments which impacted the Company's U.S. net deferred tax liabilities.

Property and Equipment, Net

Property and equipment are stated at cost less accumulated depreciation. Depreciation is recognized using the straight-line method over the estimated useful lives of the related assets for financial reporting purposes and an accelerated method for income tax reporting purposes. Upon retirement or sale of an asset, the cost and related accumulated depreciation and amortization are removed from the balance sheet and the resulting gain or loss is reflected in operations. Repair and maintenance costs are charged to expenses as incurred and improvements are capitalized.

Leasehold improvements are amortized on a straight-line basis over the term of the applicable lease, or the useful life of the assets, whichever is shorter.

Depreciation and amortization periods for the Company's property and equipment are as follows:

Machinery and equipment	5 to 7 years
Furniture and fixtures	3 to 5 years
Computer equipment	3 years
Software	3 years
Trade show equipment	3 years

The Company capitalizes software development costs associated with internal use software, including external direct costs of materials and services and payroll costs for employees devoting time to a software project. Costs incurred during the preliminary project stage, as well as costs for maintenance and training, are expensed as incurred.

Software includes internal-use software acquired and modified to meet the Company's internal requirements. Amortization commences when the software is ready for its intended use.

Intangible Assets

Definite-lived intangible assets are amortized over their estimated useful lives. The Company reviews its intangible assets when events or circumstances may indicate that the carrying value of these assets is not recoverable and exceeds their fair value. The Company measures fair value based on the estimated future discounted cash flows associated with these assets in addition to other assumptions and projections that the Company deems to be reasonable and supportable. The estimated useful lives, from the date of acquisition, for all identified intangible assets that are subject to amortization are between five and thirteen years.

Indefinite-lived intangible assets consist of capitalized in-process research and development ("IPR&D"). IPR&D assets represent capitalized incomplete research projects that the Company acquired through business combinations. Such assets are initially measured at their acquisition date fair values and are tested for impairment, until completion or abandonment of research and development efforts associated with the projects. An IPR&D asset is considered abandoned when research and development efforts associated with the asset have ceased, and there are no plans to sell or license the asset or derive value from the asset. At that point, the asset is considered to be impaired and is written off. Upon successful completion of each project, the Company will make a determination about the then remaining useful life of the intangible asset and begin amortization. The Company tests its indefinite-lived intangibles, including IPR&D assets, for impairment annually during the fourth quarter and more frequently if events or changes in circumstances indicate that it is more likely than not that the asset is impaired.

Goodwill

Goodwill represents the excess of the purchase price of acquired businesses over the estimated fair value of the identifiable net assets acquired. Goodwill is not amortized but is tested for impairment at least annually at the reporting unit level or more frequently if events or changes in circumstances indicate that the asset might be impaired. Impairment loss, if any, is recognized based on a comparison of the fair value of the asset to its carrying value, without consideration of any recoverability. The Company tests goodwill for impairment annually during the fourth quarter and whenever indicators of impairment exist by first assessing qualitative factors to determine whether it is more likely than not that the fair value is less than its carrying amount. If the Company concludes it is more likely than not that the fair value of a reporting unit is less than its carrying amount, a quantitative impairment test is performed. If the Company concludes that goodwill is impaired, it will record an impairment charge in its consolidated statement of comprehensive loss.

Research and Development Expenses

Research and development expenses include, but are not limited to, payroll and other personnel expenses, consultant expenses, expenses incurred under agreements with contract research organizations to conduct clinical trials, expenses incurred to manufacture clinical trial materials and acquired IPR&D assets. Research and development expenses were $82.8 million, $225.0 million and $60.7 million for the years ended December 31, 2018, 2017 and 2016, respectively.

Advertising Expenses

We expense the costs of advertising as incurred. Advertising expenses were $21.6 million, $19.2 million and $14.4 million for the years ended December 31, 2018, 2017 and 2016, respectively.

Deferred Financing Costs

Costs incurred in connection with debt financings have been capitalized to "Long-term debt, net of current" and "Exchangeable notes, net" in the Company's consolidated balance sheets as deferred financing costs, and are charged to interest expense using the effective interest method over the terms of the related debt agreements. These costs include document preparation costs, commissions, fees and expenses of investment bankers and underwriters, and accounting and legal fees.

Concentration of Credit Risk and Other Risks and Uncertainties

Financial instruments that potentially subject the Company to concentrations of credit risk consist of cash, cash equivalents and investments. The Company's investment policy permits investments in U.S. federal government and federal agency securities, corporate bonds or commercial paper, money market instruments, certain qualifying money market mutual funds, certain repurchase agreements, and tax-exempt obligations of municipalities and places restrictions on credit ratings, maturities, and concentration by type and issuer. The Company is exposed to credit risk in the event of a default by the financial institutions holding the Company's cash, cash equivalents and investments to the extent recorded on the balance sheet.

The purchase cost of ACTIMMUNE is denominated in Euros and is subject to foreign currency risk. The Company has contracts relating to RAVICTI, QUINSAIR and PROCYSBI for sales in Canada which sales are denominated in Canadian dollars and are subject to foreign currency risk. The Company also incurs certain operating expenses in currencies other than the U.S. dollar in relation to its Irish operations and foreign subsidiaries. Therefore, the Company is subject to volatility in cash flows due to fluctuations in foreign currency exchange rates, particularly changes in the Euro and the Canadian dollar.

Historically, the Company's accounts receivable balances have been highly concentrated with a select number of customers consisting primarily of large wholesale pharmaceutical distributors who, in turn, sell the medicines to pharmacies, hospitals and other customers. As of December 31, 2018 and 2017, the Company's top four customers accounted for approximately 85% and 74%, respectively, of the Company's total outstanding accounts receivable balances, after the reclassification adjustments as described in this Note 2.

The Company depends on single-source suppliers and manufacturers for certain of its medicines, medicine candidates and their active pharmaceutical ingredients.

Comprehensive Loss

Comprehensive loss is composed of net loss and other comprehensive loss ("OCI"). OCI includes certain changes in shareholders' equity that are excluded from net loss, which consist of foreign currency translation adjustments and pension remeasurements. The Company reports the effect of significant reclassifications out of accumulated OCI on the respective line items in net loss if the amount being reclassified is required under GAAP to be reclassified in its entirety to net loss. For other amounts that are not required under GAAP to be reclassified in their entirety to net loss in the same reporting period, the Company cross-references other disclosures required under GAAP that provide additional detail about those amounts.

Share-Based Compensation

The Company accounts for employee share-based compensation by measuring and recognizing compensation expense for all share-based payments based on estimated grant date fair values. The Company uses the straight-line method to allocate compensation cost to reporting periods over each awardee's requisite service period, which is generally the vesting period. The Company adopted ASU No. 2016-09, *Improvements to Employee Share-Based Payment Accounting* ("ASU No. 2016-09") on January 1, 2017 and has elected to retain a forfeiture rate after adoption.

Accrued Contingent Royalties

The Company's accrued contingent royalties consist of the contingent royalty obligations assumed by the Company related to the Company's acquisitions of rights to certain of its medicines. At the time of each acquisition, the Company assigned an estimated fair value to its contingent liability for royalties. The estimated royalty liability is based on anticipated revenue streams utilizing the income approach under the discounted cash flow method. The estimated liability for royalties is increased or decreased over time to reflect the change in its present value and accretion expense is recorded as part of cost of goods sold. The Company evaluates the adequacy of the estimated contingent royalty liability at least annually in the fourth quarter, or whenever events or changes in circumstances indicate that an evaluation of the estimate is necessary. As part of its evaluation, the Company adjusts the carrying value of the liability to the present value of the revised estimated cash flows using the original discount rate. Any adjustment to the liability is recorded as an increase or reduction in cost of goods sold. The royalty liability is included in current and long-term accrued royalties on the consolidated balance sheets.

Contingencies

From time to time, the Company may become involved in claims and other legal matters arising in the ordinary course of business. The Company records accruals for loss contingencies to the extent that it concludes that it is probable that a liability has been incurred and the amount of the related loss can be reasonably estimated. Legal fees and other expenses related to litigation are expensed as incurred and included in "selling, general and administrative" expenses.

Recent Accounting Pronouncements

From time to time, the Company adopts new accounting pronouncements issued by the Financial Accounting Standards Board ("FASB") or other standard-setting bodies.

Effective January 1, 2018, the Company adopted Accounting Standards Update ("ASU") No. 2014-09, *Revenue from Contracts with Customers* ("ASU No. 2014-09"). The standard aims to achieve a consistent application of revenue recognition, resulting in a single revenue model to be applied by reporting companies under GAAP. Under this model, recognition of revenue occurs when a customer obtains control of promised goods or services in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. In addition, the new standard requires that reporting companies disclose the nature, amount, timing and uncertainty of revenue and cash flows arising from contracts with customers. The standard is required to be applied retrospectively to each prior reporting period presented or modified retrospectively with the cumulative effect of initially applying it recognized at the date of initial application. The Company elected to utilize the modified retrospective method. The performance obligations identified by the Company under Accounting Standards Codification ("ASC") Topic 606, Revenue From Contracts With Customers, are similar to the unit of account and performance obligation determination under ASC Topic 605, *Revenue Recognition*. The implementation of this guidance did not have a material impact on the Company's consolidated financial statements as the timing of revenue recognition for its primary revenue stream, product sales, did not significantly change. Certain of the Company's contracts for sales outside the United States include variable consideration that the Company was precluded from recognizing because the amounts were contingent. The Company concluded that this standard required a cumulative-effect adjustment of certain deferred revenues under these contracts that were originally expected to be recognized in the future. Upon adoption on January 1, 2018, the Company reclassified $11.3 million of deferred revenue directly to retained earnings. Following this reclassification, no amounts remained in deferred revenue relating to these contracts. In addition, as a result of the adoption of ASU No. 2014-09, the Company now presents all allowances for medicine returns in accrued expenses on the consolidated balance sheet. This resulted in a reclassification of $37.9 million of allowances for medicine returns from "accounts receivable, net" to "accrued expenses" in the consolidated balance sheet at December 31, 2017, and a reclassification of $22.6 million and $0.8 million between the "accounts receivable" and "accrued expenses and accrued royalties" line items within the changes in operating assets and liabilities section of the consolidated statement of cash flow for the years ended December 31, 2017 and December 31, 2016, respectively.

Effective January 1, 2018, the Company adopted ASU No. 2016-16, *Income Taxes (Topic 740): Intra-Entity Transfers of Assets Other Than Inventory* ("ASU No. 2016-16"). ASU No. 2016-16 was issued to improve the accounting for the income tax consequences of intra-entity transfers of assets other than inventory. Previously, GAAP prohibited the recognition of current and deferred income taxes for an intra-entity asset transfer until the asset has been sold to an outside party which has resulted in diversity in practice and increased complexity within financial reporting. ASU No. 2016-16 requires an entity to recognize the income tax consequences of an intra-entity transfer of an asset other than inventory when the transfer occurs and does not require new disclosures. Upon adoption, the Company applied the modified retrospective basis through a cumulative-effect adjustment to retained earnings and the Company reclassified $9.3 million of unrecognized deferred charges directly to retained earnings.

Effective January 1, 2018, the Company adopted ASU No. 2017-09, *Compensation-Stock Compensation (Topic 718): Scope of Modification Accounting* ("ASU No. 2017-09"). The amendment amends the scope of modification accounting for share-based payment arrangements, provides guidance on the types of changes to the terms or conditions of share-based payment awards to which an entity would be required to apply modification accounting under ASC Topic 718, *Compensation- Stock Compensation*. Upon adoption, the Company applied the prospective method and will account for future modifications, if any, under this guidance. The adoption of ASU No. 2017-09 did not have a material impact on the Company's consolidated financial statements.

Effective January 1, 2018, the Company adopted ASU No. 2016-18, *Statement of Cash Flows (Topic 230): Restricted Cash* ("ASU No. 2016-18"). ASU No. 2016-18 addresses diversity in practice related to the classification and presentation of changes in restricted cash on the statement of cash flows. ASU No. 2016-18 requires that a statement of cash flows explain the change during the period in the total of cash, cash equivalents and amounts generally described as restricted cash or restricted cash equivalents. Therefore, amounts generally described as restricted cash and restricted cash equivalents should be included with cash and cash equivalents when reconciling the beginning-of-period and end-of-period total amounts shown on the statement of cash flows.

Effective January 1, 2018, the Company adopted ASU No. 2016-15, *Statement of Cash Flows (Topic 230): Classification of Certain Cash Receipts and Cash Payments* ("ASU No. 2016-15"). ASU No. 2016-15 provides guidance on the following eight specific cash flow classification issues: (1) debt prepayment or debt extinguishment costs; (2) settlement of zero-coupon debt instruments or other debt instruments with coupon interest rates that are insignificant in relation to the effective interest rate of the borrowing; (3) contingent consideration payments made after a business combination; (4) proceeds from the settlement of insurance claims; (5) proceeds from the settlement of corporate-owned life insurance policies, including bank-owned life insurance policies; (6) distributions received from equity method investees; (7) beneficial interests in securitization transactions; and (8) separately identifiable cash flows and application of the predominance principle.

The following table summarizes the adjustments made to conform prior period classifications as a result of the adoption of ASU No. 2016-18 and ASU No. 2016-15 (in thousands):

	For the Year Ended December 31, 2017			
	As filed	ASU No. 2016-18 Reclassification (2)	ASU No. 2016-15 Reclassification (3)	As adjusted
Net cash provided by operating activities	$ 280,208	$ —	$ 4,132	$ 284,340
Net cash used in investing activities	(101,619)	(566)	—	(102,185)
Net cash provided by financing activities	58,408	—	(4,132)	54,276
Cash, cash equivalents and restricted cash, beginning of the period (1)	509,055	7,095	—	516,150
Cash, cash equivalents and restricted cash, end of the period (1)	751,368	6,529	—	757,897

	For the Year Ended December 31, 2016			
	As filed	ASU No. 2016-18 Reclassification (2)	ASU No. 2016-15 Reclassification (3)	As adjusted
Net cash provided by operating activities	$ 369,456	$ —	$ —	$ 369,456
Net cash used in investing activities	(1,375,881)	5,235	—	(1,370,646)
Net cash provided by financing activities	657,074	—	—	657,074
Cash, cash equivalents and restricted cash, beginning of the period (1)	859,616	1,860	—	861,476
Cash, cash equivalents and restricted cash, end of the period (1)	509,055	7,095	—	516,150

(1) Cash, cash equivalents and restricted cash, beginning of the period and end of the period presented in the "As filed" column in the table above excludes restricted cash.
(2) $1.9 million, $7.1 million and $6.5 million in the tables above represent the Company's restricted cash balance at December 31, 2015, 2016 and 2017, respectively.
(3) Upon adoption of ASU No. 2016-15, the Company reclassified prepayment penalties and debt extinguishment costs of $3.8 million and $0.3 million, respectively, from operating activities to financing activities.

Effective January 1, 2018, the Company adopted ASU No. 2017-04, *Intangibles - Goodwill and Other (Topic 350): Simplifying the Test for Goodwill Impairment* ("ASU No. 2017-04"), to eliminate the second step of the goodwill impairment test. ASU No. 2017-04 requires an entity to measure a goodwill impairment loss as the amount by which the carrying value of a reporting unit exceeds its fair value. Additionally, an entity should include the income tax effects from any tax deductible goodwill on the carrying value of the reporting unit when measuring a goodwill impairment loss, if applicable. The adoption of ASU No. 2017-04 did not have a material impact on the Company's consolidated financial statements and related disclosures.

In February 2016, the FASB issued ASU No. 2016-02, *Leases (Topic 842) ("ASU No. 2016-02").* Under ASU No. 2016-02, an entity is required to recognize right-of-use assets and lease liabilities on its balance sheet and disclose key information about leasing arrangements. For leases with a term of twelve months or less, the lessee is permitted to make an accounting policy election not to recognize lease assets and lease liabilities by class of underlying assets. ASU No. 2016-02 becomes effective for the Company beginning in the first quarter of 2019. The guidance can be applied using either a modified retrospective approach at the beginning of the earliest period presented, or at the beginning of the period in which it is adopted. The Company will adopt this standard in the first quarter of 2019, using a modified retrospective approach at the adoption date through a cumulative-effect adjustment to retained earnings. The Company does not expect the adoption will have a material impact on its consolidated statement of comprehensive loss. However, the new standard requires the Company to establish approximately $38.0 million of liabilities and corresponding right-of-use assets of $36.0 million on its consolidated balance sheet for leases, primarily related to operating leases on rented office properties, that existed as of the January 1, 2019, adoption date. The Company also expects to elect to not recognize lease assets and liabilities for leases with a term of twelve months or less.

In June 2018, the FASB issued ASU No. 2018-07, *Compensation—Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting* ("ASU No. 2018-07"). ASU No. 2018-07 largely aligns the accounting for share-based payment awards issued to employees and non-employees. The Company will adopt ASU No. 2018-07 in the first quarter of 2019, and it does not expect the adoption of ASU No. 2018-07 to have a material impact on the Company's consolidated financial statements and related disclosures.

In June 2018, the FASB issued ASU No. 2018-08, *Clarifying the Scope and the Accounting Guidance for Contributions Received and Contributions Made* ("ASU No. 2018-08"). The new guidance applies to all entities that receive or make contributions, including business entities. The Company will adopt the standard in the first quarter of 2019, using prospective application to any new agreements entered into after the effective date. The Company does not expect the adoption of ASU No. 2018-08 to have a material impact on the Company's consolidated financial statements and related disclosures.

Other recent authoritative guidance issued by the FASB (including technical corrections to the ASC), the American Institute of Certified Public Accountants, and the Securities and Exchange Commission ("SEC") did not, or are not expected to, have a material impact on the Company's consolidated financial statements and related disclosures.

NOTE 3 – NET LOSS PER SHARE

The following table presents basic and diluted net loss per share for the years ended December 31, 2018, 2017 and 2016 (in thousands, except share and per share data):

	For the Years Ended December 31,		
	2018	**2017**	**2016**
Basic and diluted loss per share calculation:			
Net loss	$ (74,187)	$ (401,585)	$ (165,563)
Weighted average of ordinary shares outstanding	166,155,405	163,122,663	160,699,543
Basic and diluted net loss per share	**$ (0.45)**	**$ (2.46)**	**$ (1.03)**

Basic net loss per share is computed by dividing net loss by the weighted-average number of ordinary shares outstanding during the period. Diluted net loss per share reflects the potential dilution beyond shares for basic net loss per share that could occur if securities or other contracts to issue ordinary shares were exercised, converted into ordinary shares, or resulted in the issuance of ordinary shares that would have shared in the Company's earnings.

The outstanding securities listed in the table below were excluded from the computation of diluted loss per ordinary share for the years ended December 31, 2018, 2017 and 2016 due to being anti-dilutive:

	For the Years Ended December 31,		
	2018	2017	2016
Stock options	6,406,914	12,887,595	7,515,297
Restricted stock units	2,299,254	1,095,768	492,030
Performance stock units	1,248,632	2,742,301	5,247,987
Employee stock purchase plan shares	265,886	63,445	56,805
Warrants	—	388,841	1,123,737
	10,220,686	**17,177,950**	**14,435,856**

The potentially dilutive impact of the March 2015 private placement of $400.0 million aggregate principal amount of 2.50% Exchangeable Senior Notes due 2022 (the "Exchangeable Senior Notes") by Horizon Pharma Investment Limited ("Horizon Investment"), a wholly owned subsidiary of the Company, is determined using a method similar to the treasury stock method. Under this method, no numerator or denominator adjustments arise from the principal and interest components of the Exchangeable Senior Notes because the Company has the intent and ability to settle the Exchangeable Senior Notes' principal and interest in cash. Instead, the Company is required to increase the diluted net (loss) income per share denominator by the variable number of shares that would be issued upon conversion if it settled the conversion spread obligation with shares. For diluted net (loss) income per share purposes, the conversion spread obligation is calculated based on whether the average market price of the Company's ordinary shares over the reporting period is in excess of the exchange price of the Exchangeable Senior Notes. There was no calculated spread added to the denominator for the years ended December 31, 2018, 2017 and 2016.

NOTE 4 –ACQUISITIONS, DIVESTITURES AND OTHER ARRANGEMENTS

Sale of RAVICTI and AMMONAPS Rights outside of North America and Japan

On December 28, 2018, the Company sold its rights to RAVICTI and AMMONAPS (known as BUPHENYL in the United States) outside of North America and Japan to Medical Need Europe AB, part of the Immedica Group, for $35.0 million (the "Immedica transaction"). The Company previously distributed RAVICTI and AMMONAPS through a commercial partner in Europe and other non-U.S. markets. The Company has retained the rights to RAVICTI and BUPHENYL in North America and Japan.

Pursuant to ASC 805 (as amended by ASU No. 2017-01, *Business Combinations (Topic 805): Clarifying the Definition of a Business* ("ASU No. 2017-01")), the Company accounted for the Immedica transaction as a sale of assets, specifically a sale of intellectual property rights.

The gain on sale of assets recorded to the consolidated statement of comprehensive loss during the year ended December 31, 2018, was determined as follows (in thousands):

Cash proceeds	$	35,000
Less net assets sold:		
Developed technology		(4,443)
Transaction costs		(197)
Gain on sale of assets	**$**	**30,360**

Acquisition and Subsequent Sale of Additional Rights to Interferon Gamma-1b

On June 30, 2017, the Company completed its acquisition of certain rights to interferon gamma-1b from Boehringer Ingelheim International GmbH ("Boehringer Ingelheim International") in all territories outside of the United States, Canada and Japan and in connection therewith, paid Boehringer Ingelheim International €19.5 million ($22.3 million when converted using a Euro-to-Dollar exchange rate at date of payment of 1.1406). Boehringer Ingelheim International commercialized interferon gamma-1b as IMUKIN in an estimated thirty countries, primarily in Europe and the Middle East. Upon closing, during the year ended December 31, 2017, the Company accounted for the payment as the acquisition of an asset which was immediately impaired as projections for future net sales of IMUKIN in these territories did not exceed the related costs, and included the payment in the "impairment of long-lived assets" line item in its consolidated statement of comprehensive loss.

On July 24, 2018, the Company sold its rights to interferon gamma-1b in all territories outside the United States, Canada and Japan to Clinigen Group plc ("Clinigen") for an upfront payment of €7.5 million ($8.8 million when converted using a Euro-to-Dollar exchange rate at date of payment of 1.1683) and a potential additional contingent consideration payment of €3.0 million ($3.5 million when converted using a Euro-to-Dollar exchange rate of 1.1673) (the "IMUKIN sale"). The Company continues to market interferon gamma-1b as ACTIMMUNE in the United States.

Pursuant to ASC No. 2017-01, the Company accounted for the IMUKIN sale as a sale of assets, specifically a sale of intellectual property rights and a sale of inventory.

The gain on sale of assets recorded to the consolidated statement of comprehensive loss during the year ended December 31, 2018, was determined as follows (in thousands):

Cash proceeds including $715 for inventory	$	9,477
Contingent consideration receivable		3,502
Less net assets sold:		
Inventory		(623)
Transaction costs		(28)
Gain on sale of assets	**$**	**12,328**

Acquisition of River Vision

On May 8, 2017, the Company acquired 100% of the equity interests in River Vision Development Corp. ("River Vision") for upfront cash payments totaling approximately $150.3 million, including cash acquired of $6.3 million, with additional potential future milestone and royalty payments contingent on the satisfaction of certain regulatory milestones and sales thresholds. Pursuant to ASU No. 2017-01, the Company accounted for the River Vision acquisition as the purchase of an IPR&D asset and, pursuant to ASC Topic 730, *Research and Development,* recorded the purchase price as research and development expense during the year ended December 31, 2017. Further, the Company recognized approximately $32.4 million of federal net operating losses, $2.2 million of state net operating losses and $9.5 million of federal tax credits. The acquired tax attributes were set up as deferred tax assets which were further netted within the net deferred tax liabilities of the U.S. group, offset by a deferred credit recorded in long-term liabilities. The deferred tax assets were further netted with the net deferred tax liabilities of the U.S. group.

Under the agreement for the acquisition of River Vision, the Company is required to pay up to $325.0 million upon the attainment of various milestones related to U.S. Food and Drug Administration ("FDA") approval and net sales thresholds for teprotumumab. The agreement also includes a royalty payment of three percent of the portion of annual worldwide net sales exceeding $300.0 million (if any). Under separate agreements, the Company is also required to pay up to CHF103.0 million ($104.9 million when converted using a CHF-to-Dollar exchange rate at December 31, 2018 of 1.0185) upon the attainment of various milestones related to approval, filing and net sales thresholds for teprotumumab. During the year ended December 31, 2017, CHF2.0 million ($2.0 million when converted using a CHF-to-Dollar exchange rate at the date of payment of 1.0169) was paid in relation to these milestones. The separate agreement also includes a royalty payment of between nine percent and twelve percent of a portion of annual worldwide net sales.

Divestiture of PROCYSBI and QUINSAIR rights in EMEA Regions

On June 23, 2017, the Company completed the sale of its European subsidiary that owned the marketing rights to PROCYSBI and QUINSAIR in Europe, the Middle East and Africa ("EMEA") regions (the "Chiesi divestiture") to Chiesi Farmaceutici S.p.A. ("Chiesi") for an upfront payment of $72.5 million, which reflects $3.1 million of cash divested, with additional potential milestone payments based on sales thresholds.

Pursuant to ASU No. 2017-01, the Company accounted for the Chiesi divestiture as a sale of a business. The Company determined that the sale of the business and its assets in connection with the Chiesi divestiture did not constitute a strategic shift and that it did not and will not have a major effect on its operations and financial results. Accordingly, the operations associated with the Chiesi divestiture are not reported in discontinued operations.

The gain on divestiture recorded during the year ended December 31, 2017 was determined as follows (in thousands):

Cash proceeds	$	72,462
Add reimbursement of royalties		27,101
Less net assets sold:		
Developed technology		(47,261)
Goodwill		(16,285)
Other		(24,482)
Transaction and other costs		(5,268)
Gain on divestiture	**$**	**6,267**

Under the terms of its agreement with Chiesi, the Company will continue to pay third parties for the royalties on sales of PROCYSBI and QUINSAIR in the EMEA regions, and Chiesi will reimburse the Company for those royalties. At the date of divestiture, the Company recorded an asset of $27.1 million to "other assets", which represented the estimated amounts that are expected to be reimbursed from Chiesi for the PROCYSBI and QUINSAIR royalties. These estimated royalties are accrued in "accrued expenses" and "other long-term liabilities".

Transaction and other costs primarily relate to professional and license fees attributable to the divestiture.

Licensing Agreement

On December 12, 2017, the Company entered into an agreement to license HZN-003 (formerly MEDI4945), a potential next-generation biologic for uncontrolled gout, from MedImmune LLC ("MedImmune"), the global biologics research and development arm of the AstraZeneca Group. HZN-003 is a pre-clinical, genetically engineered uricase derivative with optimized uricase and optimized PEGylation technology that has the potential to improve the response rate to the biologic as well as the potential for subcutaneous dosing. Under the terms of the agreement, the Company agreed to pay MedImmune an upfront cash payment of $12.0 million with additional potential future milestone payments of up to $153.5 million contingent on the satisfaction of certain development and sales thresholds. The $12.0 million upfront payment was accounted for as the acquisition of an asset and was recorded as "research and development" expenses in the consolidated statement of comprehensive loss during the year ended December 31, 2017 and included in "accrued expenses" as of December 31, 2017. The upfront payment was subsequently paid in January 2018.

NOTE 5 – INVENTORIES

Inventories are stated at the lower of cost or net realizable value. Inventories consist of raw materials, work-in-process and finished goods. The Company has entered into manufacturing and supply agreements for the manufacture of finished goods or the purchase of raw materials and production supplies. The Company's inventories include the direct purchase cost of materials and supplies and manufacturing overhead costs.

The components of inventories as of December 31, 2018 and 2017 consisted of the following (in thousands):

	As of December 31,	
	2018	2017
Raw materials	$ 5,092	$ 4,553
Work-in-process	27,068	27,589
Finished goods	18,591	29,513
Inventories, net	**$ 50,751**	**$ 61,655**

Finished goods at December 31, 2017 included $17.0 million of stepped-up KRYSTEXXA inventory. During the year ended December 31, 2018, the Company recorded the remaining $17.0 million of KRYSTEXXA inventory step-up expense to cost of goods sold. During the year ended December 31, 2017, the Company recorded $78.3 million of KRYSTEXXA inventory step-up expense, and $40.8 million of PROCYSBI and QUINSAIR inventory step-up expense. In addition, during the year ended December 31, 2017, the Company recorded $3.2 million of inventory step-up expense to "gain on divestiture" relating to PROCYSBI and QUINSAIR in connection with the Chiesi divestiture in June 2017.

KRYSTEXXA inventory step-up was fully expensed by March 31, 2018. As a result, the costs of goods sold related to KRYSTEXXA have decreased significantly beginning with the second quarter of 2018 to levels consistent with the historical costs of goods sold before the Company's acquisition of Crealta Holdings LLC.

Because inventory step-up expense is acquisition-related, will not continue indefinitely and has a significant effect on the Company's gross profit, gross margin percentage and net income (loss) for all affected periods, the Company discloses balance sheet and income statement amounts related to inventory step-up within the notes to the consolidated financial statements.

NOTE 6 – PREPAID EXPENSES AND OTHER CURRENT ASSETS

Prepaid expenses and other current assets as of December 31, 2018 and 2017 consisted of the following (in thousands):

	As of December 31,	
	2018	2017
Deferred charge for taxes on intra-company profit	$ 21,734	$ 535
Rabbi trust assets	8,203	6,490
Prepaid income taxes	5,899	8
Medicine samples inventory	4,539	11,415
Other prepaid expenses and other current assets	30,453	24,954
Prepaid expenses and other current assets	**$ 70,828**	**$ 43,402**

NOTE 7 – PROPERTY AND EQUIPMENT

Property and equipment as of December 31, 2018 and 2017 consisted of the following (in thousands):

	As of December 31,	
	2018	2017
Software	$ 14,843	$ 14,956
Leasehold improvements	9,982	9,415
Machinery and equipment	4,800	4,819
Computer equipment	2,485	2,235
Other	2,501	2,508
	34,611	**33,933**
Less accumulated depreciation	(19,197)	(13,672)
Construction in process	4,687	144
Property and equipment, net	**$ 20,101**	**$ 20,405**

Depreciation expense for the years ended December 31, 2018, 2017 and 2016 was $6.1 million, $6.6 million and $5.0 million, respectively.

NOTE 8 – GOODWILL AND INTANGIBLE ASSETS

Goodwill

The gross carrying amount of goodwill as of December 31, 2018 and 2017 was as follows (in thousands):

Balance at December 31, 2016	$	445,579
Goodwill derecognized on Chiesi divestiture		(16,285)
Adjustment relating to the acquisition of Raptor in 2016		(2,853)
Balance at December 31, 2017 and 2018		**426,441**

During the year ended December 31, 2017, in connection with the Chiesi divestiture, the Company recorded a reduction to goodwill of $16.3 million. See Note 4 for further details.

During the year ended December 31, 2017, the Company recorded measurement period adjustments in connection with the acquisition of Raptor Pharmaceutical Corp. ("Raptor") related to deferred tax liabilities, accrued trade discounts and rebates and accrued expenses, which resulted in a net decrease in goodwill of $2.9 million.

As of December 31, 2018, there were no accumulated goodwill impairment losses.

As discussed in Note 13, during the second quarter of 2018, management realigned the Company's reportable segments to reflect changes in the manner in which the CODM assesses financial information for decision-making purposes. This resulted in a change in the Company's operating segment and reporting units. The Company allocated goodwill to its new reporting units using a relative fair value approach. In addition, the Company completed an assessment of any potential goodwill impairment for all reporting units immediately prior to the allocation and determined that no impairment existed. The table below presents goodwill for the Company's reportable segments as of December 31, 2018 (in thousands):

	Orphan and Rheumatology	Primary Care	Total
Goodwill	$ 371,883	$ 54,558	**$ 426,441**

Intangible Assets

As of December 31, 2018, the Company's finite-lived intangible assets consisted of developed technology related to ACTIMMUNE, BUPHENYL/AMMOMAPS, KRYSTEXXA, LODOTRA, MIGERGOT, PENNSAID 2%, PROCYSBI, RAVICTI, RAYOS and VIMOVO, as well as customer relationships for ACTIMMUNE.

During the year ended December 31, 2018, in connection with the Immedica transaction, the Company recorded a reduction in the net book value of developed technology related to RAVICTI and AMMONAPS of $4.4 million. See Note 4 for further details.

During the year ended December 31, 2017, in connection with the Chiesi divestiture, the Company recorded a reduction in the net book value of developed technology related to PROCYSBI of $47.3 million. See Note 4 for further details.

The Company tests its intangible assets for impairment when events or circumstances may indicate that the carrying value of these assets exceeds their fair value. During the year ended December 31, 2018, the Company recorded an impairment of $37.9 million to fully write off the book value of developed technology related to PROCYSBI in Canada and Latin America due primarily to lower anticipated future net sales based on a Patented Medicine Prices Review Board review. The fair value of developed technology was determined using an income approach.

The Company also recorded an impairment of $10.6 million during the year ended December 31, 2018, to fully write off the book value of developed technology related to LODOTRA as result of amendments to its license and supply agreements with Jagotec AG and Skyepharma AG, which are affiliates of Vectura. Under these amendments, effective January 1, 2019, the Company agreed to transfer all economic benefits of LODOTRA in Europe to Vectura during an initial transition period, with full rights transferring to Vectura when certain transfer activities have been completed. The Company will no longer record LODOTRA revenue from January 1, 2019. The fair value of developed technology was determined using an income approach.

During the course of preparing the consolidated financial statements for the year ended December 31, 2018, the Company identified an error in the measurement of the contingent royalty liability calculation pertaining to the royalty end date for one of its medicines. The revision resulted in certain adjustments to the consolidated financial statements as of and for the years ended December 31, 2017 and December 31, 2016, and the revised amounts are presented below. See Note 1 for further details of this error and the related revisions.

Intangible assets as of December 31, 2018 and December 31, 2017 consisted of the following (in thousands):

	As of December 31,						
	2018				2017		
	Cost Basis	Impairment	Accumulated Amortization	Net Book Value	Cost Basis	Accumulated Amortization	Net Book Value
Developed technology	$ 3,104,468	$ (48,451)	$ (935,421)	$ 2,120,596	$ 3,113,695	$ (671,403)	$ 2,442,292
Customer relationships	8,100	—	(3,470)	4,630	8,100	(2,659)	5,441
Total intangible assets	**$ 3,112,568**	**$ (48,451)**	**$ (938,891)**	**$ 2,125,226**	**$ 3,121,795**	**$ (674,062)**	**$ 2,447,733**

Amortization expense for the years ended December 31, 2018, 2017 and 2016 was $269.6 million, $276.6 million and $216.7 million, respectively. As of December 31, 2018, estimated future amortization expense was as follows (in thousands):

2019	$ 251,901
2020	251,205
2021	243,699
2022	242,428
2023	241,775
Thereafter	894,218
Total	**$ 2,125,226**

NOTE 9 - OTHER ASSETS

Included in other assets at December 31, 2018 and 2017, was $17.4 million and $24.6 million, respectively, which represents the long-term portion of the estimated amounts that are expected to be reimbursed from Chiesi for PROCYSBI and QUINSAIR royalties.

NOTE 10 – ACCRUED EXPENSES

Accrued expenses as of December 31, 2018 and 2017 consisted of the following (in thousands):

	As of December 31,	
	2018	2017
Payroll-related expenses	$ 78,555	$ 56,338
Allowances for returns	39,041	37,863
Consulting and professional services	35,799	27,542
Accrued interest	13,196	14,127
Accrued upfront payment related to license agreement	—	12,000
Accrued other	39,002	27,827
Accrued expenses	**$ 205,593**	**$ 175,697**

During the year ended December 31, 2017, the Company entered into an agreement to license HZN-003 from MedImmune. Under the terms of the agreement, the Company agreed to pay MedImmune an upfront cash payment of $12.0 million, which was recorded as "research and development" expenses in the consolidated statement of comprehensive loss during the year ended December 31, 2017 and was included in "accrued expenses" as of December 31, 2017.

Accrued other as of December 31, 2018 and 2017 included $1.7 million and $2.1 million, respectively, related to a loss on inventory purchase commitments.

NOTE 11 – ACCRUED TRADE DISCOUNTS AND REBATES

Accrued trade discounts and rebates as of December 31, 2018 and 2017 consisted of the following (in thousands):

	As of December 31,	
	2018	2017
Accrued commercial rebates and wholesaler fees	$ 153,083	$ 190,215
Accrued co-pay and other patient assistance	179,463	230,533
Accrued government rebates and chargebacks	125,217	81,005
Accrued trade discounts and rebates	**$ 457,763**	**$ 501,753**
Invoiced commercial rebates and wholesaler fees, co-pay and other patient assistance, and government rebates and chargebacks in accounts payable	3,666	15,042
Total customer-related accruals and allowances	**$ 461,429**	**$ 516,795**

The following table summarizes changes in the Company's customer-related accruals and allowances during the years ended December 31, 2018 and 2017 (in thousands):

	Wholesaler Fees and Commercial Rebates	Co-Pay and Other Patient Assistance	Government Rebates and Chargebacks	Total
Balance at December 31, 2016	**$ 47,651**	**$ 205,143**	**$ 61,592**	**$ 314,386**
Measurement period adjustment	—	—	(1,350)	**(1,350)**
Current provisions relating to sales during the year ended December 31, 2017	635,919	1,907,669	331,559	**2,875,147**
Adjustments relating to prior-year sales	5,580	(59)	(4,905)	**616**
Payments relating to sales during the year ended December 31, 2017	(445,621)	(1,675,344)	(237,574)	**(2,358,539)**
Payments relating to prior-year sales	(53,044)	(205,084)	(55,337)	**(313,465)**
Balance at December 31, 2017	**$ 190,485**	**$ 232,325**	**$ 93,985**	**$ 516,795**
Current provisions relating to sales during the year ended December 31, 2018	590,316	1,970,714	411,449	**2,972,479**
Adjustments relating to prior-year sales	(667)	(374)	(14,787)	**(15,828)**
Payments relating to sales during the year ended December 31, 2018	(436,871)	(1,791,252)	(283,124)	**(2,511,247)**
Payments relating to prior-year sales	(189,818)	(231,951)	(79,001)	**(500,770)**
Balance at December 31, 2018	**$ 153,445**	**$ 179,462**	**$ 128,522**	**$ 461,429**

NOTE 12 – ACCRUED ROYALTIES

Changes to the liability for royalties for medicines acquired through business combinations during the years ended December 31, 2018 and 2017 consisted of the following (in thousands):

Balance as of December 31, 2016	$ 331,175
Accrued royalties - current portion as of December 31, 2016	61,981
Accrued royalties, net of current as of December 31, 2016	269,194
Reclassification to other long-term liabilities	(5,233)
Remeasurement of royalty liabilities	13,004
Royalty payments	(45,739)
Accretion expense	51,127
Other royalty expense	310
Balance as of December 31, 2017	**$ 344,644**
Accrued royalties - current portion as of December 31, 2017	65,328
Accrued royalties, net of current as of December 31, 2017	279,316
Remeasurement of royalty liabilities	(3,383)
Royalty payments	(51,873)
Accretion expense	59,282
Other royalty expense	67
Balance as of December 31, 2018	**$ 348,737**
Accrued royalties - current portion as of December 31, 2018	63,363
Accrued royalties, net of current as of December 31, 2018	**$ 285,374**

During the year ended December 31, 2018, the Company recorded a reduction of $3.4 million to "cost of goods sold" related to the remeasurement of contingent royalty liabilities. This was composed of a reduction of $20.8 million related to certain of its other medicines as a result of updated estimates of future sales of these medicines (primarily composed of $16.9 million, $2.0 million and $1.9 million related to RAVICTI, PROCYSBI and ACTIMMUNE, respectively) and a reduction of $1.9 million to "selling, general and administrative" expenses related to MIGERGOT as a result of updated estimates of future sales of this medicine, partially offset by a charge of $19.3 million based on higher estimated future sales of KRYSTEXXA versus the Company's previous expectations.

During the year ended December 31, 2017, based on higher sales of certain of the Company's medicines versus its previous expectations and estimates for future sales of these medicines, the Company recorded total charges of $55.9 million and $0.6 million to "cost of goods sold" and "selling, general and administrative" expenses, respectively, (primarily composed of $31.7 million and $24.2 million related to KRYSTEXXA and RAVICTI, respectively). The Company also recorded a reduction of $43.5 million to cost of goods sold related to certain of its other medicines as a result of updated estimates of future sales of these medicines (primarily composed of $23.2 million, $11.7 million and $7.0 million related to PROCYSBI, VIMOVO and ACTIMMUNE, respectively).

During the course of preparing the consolidated financial statements for the year ended December 31, 2018, the Company identified an error in the measurement of the contingent royalty liability calculation pertaining to the royalty end date for one of its medicines. The revision resulted in certain adjustments to the consolidated financial statements as of and for the years ended December 31, 2017 and December 31, 2016, and the revised amounts are presented above. See Note 1 for further details of this error and the related revisions.

NOTE 13 – SEGMENT AND OTHER INFORMATION

Effective as of the second quarter of 2018, management realigned the Company's reportable segments to reflect changes in the manner in which the CODM assesses financial information for decision-making purposes. This realignment resulted in the Company changing its reporting from one operating segment to two operating segments. All prior year amounts have been presented using the Company's current reporting structure.

The Company has two reportable segments, the orphan and rheumatology segment and the primary care segment, and the Company reports net sales and segment operating income for each segment.

The orphan and rheumatology segment includes the marketed medicines ACTIMMUNE, BUPHENYL/AMMONAPS, KRYSTEXXA, PROCYSBI, QUINSAIR, RAVICTI and RAYOS/LODOTRA. The primary care segment consists of four marketed medicines, including DUEXIS, MIGERGOT, PENNSAID 2% and VIMOVO.

Management structured the business into two segments to improve operating and resource allocation decisions to align with the Company's long-term strategic goal of transforming into a leading rare disease medicine company.

The Company's CODM evaluates the financial performance of the Company's segments based upon segment operating income. Segment operating income is defined as income (loss) before (expense) benefit for income taxes adjusted for the items set forth in the reconciliation below. Items below income from operations are not reported by segment, since they are excluded from the measure of segment profitability reviewed by the Company's CODM. Additionally, certain expenses are not allocated to a segment. The Company does not report balance sheet information by segment as no balance sheet by segment is reviewed by the Company's CODM. The accounting policy for the Company's segments is described in Note 2.

The following table reflects net sales by medicine for the Company's reportable segments (in thousands):

	Year Ended December 31,		
	2018	2017	2016
KRYSTEXXA	$ 258,920	$ 156,483	$ 91,102
RAVICTI	226,650	193,918	151,532
PROCYSBI	154,895	137,740	25,268
ACTIMMUNE	105,563	110,993	104,624
RAYOS	61,067	52,125	47,356
BUPHENYL	21,810	20,792	16,879
LODOTRA	2,067	5,393	4,193
QUINSAIR	504	3,442	1,039
Orphan and Rheumatology segment net sales	**$ 831,476**	**$ 680,886**	**$ 441,993**
PENNSAID 2%	190,206	191,050	304,433
DUEXIS	114,672	121,161	173,728
VIMOVO	67,646	57,666	121,315
MIGERGOT	3,570	5,468	4,651
Primary Care segment net sales	**$ 376,094**	**$ 375,345**	**$ 604,127**
Litigation settlement	—	—	(65,000)
Total net sales	**$ 1,207,570**	**$ 1,056,231**	**$ 981,120**

The table below provides reconciliations of the Company's segment operating income to the Company's total loss before benefit for income taxes (in thousands):

	Year Ended December 31,		
	2018	2017	2016
Segment operating income:			
Orphan and Rheumatology	$ 290,014	$ 241,135	$ 124,779
Primary Care	160,447	149,133	347,968
Reconciling items:			
Amortization, accretion and step-up:			
Intangible amortization expense	(269,603)	(276,613)	(216,703)
Accretion of royalty liabilities	(59,565)	(51,263)	(40,616)
Inventory step-up expense	(17,312)	(119,151)	(71,137)
Interest expense, net	(121,692)	(126,523)	(86,610)
Share-based compensation	(114,860)	(121,553)	(114,144)
Impairment of long-lived assets	(50,302)	(22,270)	(71,260)
Restructuring and realignment costs	(15,350)	(4,883)	—
Acquisition/divestiture-related costs	(6,815)	(177,035)	(52,874)
Depreciation	(6,126)	(6,631)	(4,962)
Litigation settlements	(5,750)	—	(65,000)
Drug substance harmonization costs	(2,855)	(10,651)	—
Fees relating to term loan refinancing	(937)	(5,220)	—
Foreign exchange loss	(192)	(260)	(1,005)
Upfront and milestone payments related to license agreements	(90)	(12,186)	(2,000)
Gain on divestiture	—	6,267	—
Loss on debt extinguishment	—	(978)	—
Other income, net	346	588	6,697
Charges relating to discontinuation of Friedreich's ataxia program	1,464	(239)	(18,253)
Remeasurement of royalties for medicines acquired through business combinations	3,383	(13,004)	713
Gain on sale of assets	42,688	—	—
Royalties for medicines acquired through business combinations	53,961	47,003	37,593
Loss before benefit for income taxes	**$ (119,146)**	**$ (504,334)**	**$ (226,814)**

The following table presents the amount and percentage of gross sales from customers that represented more than 10% of the Company's gross sales included in its two reportable segments, and all other customers as a group (in thousands, except percentages):

	Year ended December 31,					
	2018		2017		2016	
	Amount	% of Gross Sales	Amount	% of Gross Sales	Amount	% of Gross Sales
Customer A	$ 1,553,333	36%	$ 1,165,591	29%	$ 667,031	20%
Customer B	1,011,996	24%	1,205,268	30%	1,413,774	44%
Customer C	526,398	12%	567,583	14%	355,920	11%
Customer D	458,074	11%	16,304	0%	—	0%
Other Customers	714,652	17%	1,103,093	27%	797,463	25%
Gross Sales	**$ 4,264,453**	**100%**	**$ 4,057,839**	**100%**	**$ 3,234,188**	**100%**

Geographic revenues are determined based on the country in which the Company's customers are located. The following table presents a summary of net sales attributed to geographic sources (in thousands, except percentages):

	Year Ended December 31, 2018		Year Ended December 31, 2017		Year Ended December 31, 2016	
	Amount	% of Total Net Sales	Amount	% of Total Net Sales	Amount	% of Total Net Sales
United States	$ 1,186,519	98%	$ 1,026,527	97%	$ 964,041	98%
Rest of world	21,051	2%	29,704	3%	17,079	2%
Total net sales	**$ 1,207,570**		**$ 1,056,231**		**$ 981,120**	

The following table presents total tangible long-lived assets by location (in thousands):

	As of December 31,	
	2018	2017
United States	$ 17,107	$ 17,089
Other	2,994	3,316
Total long-lived assets (1)	**$ 20,101**	**$ 20,405**

(1) Long-lived assets consist of property and equipment.

NOTE 14 – FAIR VALUE MEASUREMENTS

The following tables and paragraphs set forth the Company's financial instruments that are measured at fair value on a recurring basis within the fair value hierarchy. Assets and liabilities measured at fair value are classified in their entirety based on the lowest level of input that is significant to the fair value measurement. The Company's assessment of the significance of a particular input to the fair value measurement in its entirety requires management to make judgments and consider factors specific to the asset or liability. The following describes three levels of inputs that may be used to measure fair value:

Level 1—Observable inputs such as quoted prices in active markets for identical assets or liabilities.

Level 2—Observable inputs other than Level 1 prices such as quoted prices for similar assets or liabilities, quoted prices in markets that are not active, or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.

Level 3—Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

The Company utilizes the market approach to measure fair value for its money market funds. The market approach uses prices and other relevant information generated by market transactions involving identical or comparable assets or liabilities.

As of December 31, 2017, the Company's restricted cash included bank time deposits which were measured at fair value using Level 2 inputs and their carrying values were approximately equal to their fair values. Level 2 inputs, obtained from various third-party data providers, represent quoted prices for similar assets in active markets, or these inputs were derived from observable market data, or if not directly observable, were derived from or corroborated by other observable market data.

Other current assets and other long-term liabilities recorded at fair value on a recurring basis are composed of investments held in a rabbi trust and the related deferred liability for deferred compensation arrangements. Quoted prices for this investment, primarily in mutual funds, are available in active markets. Thus, the Company's investments related to deferred compensation arrangements and the related long-term liability are classified as Level 1 measurements in the fair value hierarchy.

Assets and liabilities measured at fair value on a recurring basis

The following tables set forth the Company's financial assets and liabilities at fair value on a recurring basis as of December 31, 2018 and 2017 (in thousands):

	December 31, 2018			
	Level 1	Level 2	Level 3	Total
Assets:				
Bank time deposits	$ —	$ 6,500	$ —	$ 6,500
Money market funds	915,800	—	—	915,800
Other current assets	8,203	—	—	8,203
Total assets at fair value	**$ 924,003**	**$ 6,500**	**$ —**	**$ 930,503**
Liabilities:				
Other long-term liabilities	(8,203)	—	—	(8,203)
Total liabilities at fair value	**$ (8,203)**	**$ —**	**$ —**	**$ (8,203)**

	December 31, 2017			
	Level 1	Level 2	Level 3	Total
Assets:				
Bank time deposits	$ —	$ 3,000	$ —	$ 3,000
Money market funds	687,000	—	—	687,000
Other current assets	6,490	—	—	6,490
Total assets at fair value	**$ 693,490**	**$ 3,000**	**$ —**	**$ 696,490**
Liabilities:				
Other long-term liabilities	(6,490)	—	—	(6,490)
Total liabilities at fair value	**$ (6,490)**	**$ —**	**$ —**	**$ (6,490)**

NOTE 15 – DEBT AGREEMENTS

The Company's outstanding debt balances as of December 31, 2018 and 2017 consisted of the following (in thousands):

	As of December 31,	
	2018	2017
Term Loan Facility	$ 818,026	$ 845,750
2023 Senior Notes	475,000	475,000
2024 Senior Notes	300,000	300,000
Exchangeable Senior Notes	400,000	400,000
Total face value	**1,993,026**	**2,020,750**
Debt discount	(87,038)	(108,054)
Deferred financing fees	(9,304)	(11,041)
Total long-term debt	**1,896,684**	**1,901,655**
Less: long-term debt - current portion	—	(10,625)
Long-term debt, net of current portion	**$ 1,896,684**	**$ 1,891,030**

Scheduled maturities with respect to the Company's long-term debt are as follows (in thousands):

2019	$ —
2020	5,080
2021	6,774
2022	406,774
2023	481,774
Thereafter	1,092,624
Total	**$ 1,993,026**

Term Loan Facility

On October 19, 2018, Horizon Pharma, Inc. ("HPI") and Horizon Pharma USA, Inc. ("HPUSA" and, together with HPI, in such capacity, the "Borrowers"), wholly owned subsidiaries of the Company, borrowed approximately $818.0 million aggregate principal amount of loans (the "October 2018 Refinancing Loans") pursuant to an amendment (the "October 2018 Refinancing Amendment") to the credit agreement, dated as of May 7, 2015, by and among the Borrowers, the Company and certain of its subsidiaries as guarantors, the lenders party thereto from time to time and Citibank, N.A., as administrative agent and collateral agent, as amended by Amendment No. 1, dated as of October 25, 2016, Amendment No. 2, dated March 29, 2017 (the "March 2017 Credit Agreement") and Amendment No. 3, dated October 23, 2017 (the "October 2017 Credit Agreement") (the "2018 Term Loan Facility"). On October 31, 2018, HPI merged with and into HPUSA, and as a result, HPUSA became sole borrower under the Credit Agreement. As used herein, all references to the "Credit Agreement" are references to the October 2017 Credit Agreement, as amended by the October 2018 Refinancing Amendment.

The October 2018 Refinancing Loans were incurred as a separate new class of term loans under the Credit Agreement with substantially the same terms as the previously outstanding senior secured term loans incurred on October 23, 2017 under the October 2017 Credit Agreement (the "October 2017 Refinancing Loans") to effectuate a repricing of the October 2017 Refinancing Loans. The Borrowers used the proceeds of the October 2018 Refinancing Loans to repay the October 2017 Refinancing Loans, which totaled approximately $818.0 million. The October 2018 Refinancing Loans bear interest, at HPUSA's option, at a rate equal to either the London Inter-Bank Offered Rate ("LIBOR") plus an applicable margin of 3.00% per year (subject to a LIBOR floor of 1.00%), or the adjusted base rate plus 2.00% per year. The adjusted base rate is defined as the greatest of (a) LIBOR (using one-month interest period) plus 1.00%, (b) the prime rate, (c) the federal funds rate plus 0.50%, and (d) 2.00%. The applicable margins will be reduced by 0.25% if the Company's leverage ratio is less than or equal to 3.50 to 1.00. The Credit Agreement provides for (i) the October 2018 Refinancing Loans, (ii) one or more uncommitted additional incremental loan facilities subject to the satisfaction of certain financial and other conditions, and (iii) one or more uncommitted refinancing loan facilities with respect to loans thereunder. The Credit Agreement allows for the Company and certain of its subsidiaries to become borrowers under incremental or refinancing facilities.

The obligations under the Credit Agreement (including obligations in respect of the October 2018 Refinancing Loans) and any swap obligations and cash management obligations owing to a lender (or an affiliate of a lender) thereunder are guaranteed by the Company and each of the Company's existing and subsequently acquired or formed direct and indirect subsidiaries (other than certain immaterial subsidiaries, subsidiaries whose guarantee would result in material adverse tax consequences and subsidiaries whose guarantee is prohibited by applicable law). The obligations under the Credit Agreement (including obligations in respect of the October 2018 Refinancing Loans) and any such swap and cash management obligations are secured, subject to customary permitted liens and other agreed upon exceptions, by a perfected security interest in (i) all tangible and intangible assets of HPUSA and the guarantors, except for certain customary excluded assets, and (ii) all of the capital stock owned by HPUSA and guarantors thereunder (limited, in the case of the stock of certain non-U.S. subsidiaries of HPUSA, to 65% of the capital stock of such subsidiaries). HPUSA and the guarantors under the Credit Agreement are individually and collectively referred to herein as a "Loan Party" and the "Loan Parties," as applicable.

The Company elected to exercise its reinvestment rights under the mandatory prepayment provisions of the March 2017 Credit Agreement with respect to the net proceeds from the Chiesi divestiture. To the extent the Company had not applied such net proceeds to permitted acquisitions (including the acquisition of rights to products and products lines) and/or the acquisition of capital assets within 365 days of the receipt thereof (or committed to so apply and then applied within 180 days after the end of such 365-day period), the Company was required to make a mandatory prepayment under the March 2017 Credit Agreement in an amount equal to the unapplied net proceeds. In June 2018, the Company repaid $23.5 million under the mandatory prepayment provisions of the March 2017 Credit Agreement.

Additionally, the Company elected to exercise its reinvestment rights under the mandatory prepayment provisions of the Credit Agreement with respect to the net proceeds from the IMUKIN sale and the Immedica transaction. To the extent the Company does not apply such net proceeds to permitted acquisitions (including the acquisition of rights to products and products lines) and/or the acquisition of capital assets within 365 days of the receipt of proceeds from the Immedica transaction (or commit to so apply and then apply within 180 days after the end of such 365-day period), the Borrowers under the Credit Agreement would be required to make a mandatory prepayment under the Credit Agreement in an amount equal to the unapplied net proceeds. Until such time, the net proceeds are not legally restricted for use.

HPUSA is permitted to make voluntary prepayments of the loans under the Credit Agreement at any time without payment of a premium, except that with respect to the October 2018 Refinancing Loans, a 1.00% premium will apply to a repayment of the October 2018 Refinancing Loans in connection with a repricing of, or any amendment to the Credit Agreement in a repricing of, such loans effected on or prior to the date that is six months following October 19, 2018.

HPUSA is required to make mandatory prepayments of loans under the Credit Agreement (without payment of a premium) with (a) net cash proceeds from certain non-ordinary course asset sales (subject to reinvestment rights and other exceptions), (b) casualty proceeds and condemnation awards (subject to reinvestment rights and other exceptions), (c) net cash proceeds from issuances of debt (other than certain permitted debt), and (d) 50% of the Company's excess cash flow (subject to decrease to 25% or 0% if the Company's first lien leverage ratio is less than 2.25:1 or 1.75:1, respectively). The October 2018 Refinancing Loans are amortized in equal quarterly installments that began on December 31, 2018, in an aggregate annual amount equal to 1.00% of the original principal amount of the October 2017 Refinancing Loans (i.e. $845.8 million), as the same may be reduced from time to time pursuant to the Credit Agreement (including by prepayments made prior to the date of the October 2018 Refinancing Amendment), with any remaining balance payable on March 29, 2024, the final maturity date of the October 2018 Refinancing Loans.

The Credit Agreement contains customary representations and warranties and customary affirmative and negative covenants, including, among other things, restrictions on indebtedness, liens, investments, mergers, dispositions, prepayment of other indebtedness and dividends and other distributions.

Events of default under the Credit Agreement include: (i) the failure by any Borrower to timely make payments due under the Credit Agreement; (ii) material misrepresentations or misstatements in any representation or warranty by any Loan Party when made; (iii) failure by any Loan Party to comply with the covenants under the Credit Agreement and other related agreements; (iv) certain defaults under a specified amount of other indebtedness of the Company or its subsidiaries; (v) insolvency or bankruptcy-related events with respect to the Company or any of its material subsidiaries; (vi) certain undischarged judgments against the Company or any of its restricted subsidiaries; (vii) certain ERISA-related events reasonably expected to have a material adverse effect on the Company and its restricted subsidiaries taken as a whole; (viii) certain security interests or liens under the loan documents ceasing to be, or being asserted by the Company or its restricted subsidiaries not to be, in full force and effect; (ix) any loan document or material provision thereof ceasing to be, or any challenge or assertion by any Loan Party that such loan document or material provision is not, in full force and effect; and (x) the occurrence of a change of control. If one or more events of default occurs and continues beyond any applicable cure period, the administrative agent may, with the consent of the lenders holding a majority of the loans and commitments under the facilities, or will, at the request of such lenders, terminate the commitments of the lenders to make further loans and declare all of the obligations of the Loan Parties under the Credit Agreement to be immediately due and payable.

The interest on the Company's 2018 Term Loan Facility is variable and as of December 31, 2018, the interest rate on the 2018 Term Loan Facility was 5.56% and the effective interest rate was 5.74%.

As of December 31, 2018, the fair value of the amounts outstanding under the 2018 Term Loan Facility was approximately $779.2 million, categorized as a Level 2 instrument, as defined in Note 14.

2023 Senior Notes

On April 29, 2015, Horizon Pharma Financing Inc. ("Horizon Financing"), a wholly owned subsidiary of the Company, completed a private placement of $475.0 million aggregate principal amount of 6.625% Senior Notes due 2023 (the "2023 Senior Notes") to certain investment banks acting as initial purchasers who subsequently resold the 2023 Senior Notes to qualified institutional buyers as defined in Rule 144A under the Securities Act of 1933, as amended (the "Securities Act"), and in offshore transactions to non-U.S. persons in reliance on Regulation S under the Securities Act. The net proceeds from the offering of the 2023 Senior Notes were approximately $462.3 million, after deducting the initial purchasers' discount and offering expenses payable by Horizon Financing.

In connection with the closing of the acquisition of Hyperion Therapeutics, Inc. ("Hyperion") on May 7, 2015, Horizon Financing merged with and into HPI and on October 31, 2018, HPI merged with and into HPUSA. As a result, the 2023 Senior Notes became the general unsecured senior obligations of HPUSA, which was previously a guarantor under the 2023 Senior Notes. The obligations under the 2023 Senior Notes are fully and unconditionally guaranteed on a senior unsecured basis by the Company and all of the Company's direct and indirect subsidiaries that are guarantors from time to time under the Credit Agreement.

The 2023 Senior Notes accrue interest at an annual rate of 6.625% payable semiannually in arrears on May 1 and November 1 of each year, beginning on November 1, 2015. The 2023 Senior Notes will mature on May 1, 2023, unless earlier repurchased or redeemed.

Some or all of the 2023 Senior Notes may be redeemed at any time at specified redemption prices, plus accrued and unpaid interest to the redemption date. In addition, the 2023 Senior Notes may be redeemed in whole but not in part at a

redemption price equal to 100% of the principal amount plus accrued and unpaid interest and additional amounts, if any, to, but excluding, the redemption date, if on the next date on which any amount would be payable in respect of the 2023 Senior Notes, HPUSA or any guarantor is or would be required to pay additional amounts as a result of certain tax-related events.

If the Company undergoes a change of control, HPUSA will be required to make an offer to purchase all of the 2023 Senior Notes at a price in cash equal to 101% of the aggregate principal amount thereof plus accrued and unpaid interest to, but not including, the repurchase date. If the Company or certain of its subsidiaries engages in certain asset sales, HPUSA will be required under certain circumstances to make an offer to purchase the 2023 Senior Notes at 100% of the principal amount thereof, plus accrued and unpaid interest to the repurchase date.

The indenture governing the 2023 Senior Notes contains covenants that limit the ability of the Company and its restricted subsidiaries to, among other things, pay dividends or distributions, repurchase equity, prepay junior debt and make certain investments, incur additional debt and issue certain preferred stock, incur liens on assets, engage in certain asset sales, merge, consolidate with or merge or sell all or substantially all of their assets, enter into transactions with affiliates, designate subsidiaries as unrestricted subsidiaries, and allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to the Company. Certain of the covenants will be suspended during any period in which the notes receive investment grade ratings. The indenture governing the 2023 Senior Notes also includes customary events of default.

As of December 31, 2018, the interest rate on the 2023 Senior Notes was 6.625% and the effective interest rate was 6.68%.

As of December 31, 2018, the fair value of the 2023 Senior Notes was approximately $461.9 million, categorized as a Level 2 instrument, as defined in Note 14.

2024 Senior Notes

On October 25, 2016, HPI and HPUSA (together, in such capacity, the "2024 Issuers"), completed a private placement of $300.0 million aggregate principal amount of 8.750% Senior Notes due 2024 (the "2024 Senior Notes") to certain investment banks acting as initial purchasers who subsequently resold the 2024 Senior Notes to qualified institutional buyers as defined in Rule 144A under the Securities Act. The net proceeds from the offering of the 2024 Senior Notes were approximately $291.9 million, after deducting the initial purchasers' discount and offering expenses payable by the 2024 Issuers. On October 31, 2018, HPI merged with and into HPUSA, and as a result, HPI's obligations as co-issuer under the 2024 Senior Notes became HPUSA's general unsecured senior obligations.

The obligations under the 2024 Senior Notes are HPUSA's general unsecured senior obligations and are fully and unconditionally guaranteed on a senior unsecured basis by the Company and all of the Company's direct and indirect subsidiaries that are guarantors from time to time under the Credit Agreement.

The Company used the net proceeds from the offering of the 2024 Senior Notes as well as $375.0 million principal amount of senior secured term loans under the Company's term loan facility to fund a portion of the acquisition of Raptor, repay Raptor's outstanding debt, and pay any prepayment premiums, fees and expenses in connection with the foregoing.

The 2024 Senior Notes accrue interest at an annual rate of 8.750% payable semiannually in arrears on May 1 and November 1 of each year, beginning on May 1, 2017. The 2024 Senior Notes will mature on November 1, 2024, unless earlier repurchased or redeemed.

Except as described below, the 2024 Senior Notes may not be redeemed before November 1, 2019. Thereafter, some or all of the 2024 Senior Notes may be redeemed at any time at specified redemption prices, plus accrued and unpaid interest to the redemption date. At any time prior to November 1, 2019, some or all of the 2024 Senior Notes may be redeemed at a price equal to 100% of the aggregate principal amount thereof, plus a make-whole premium and accrued and unpaid interest to the redemption date. Also prior to November 1, 2019, up to 35% of the aggregate principal amount of the 2024 Senior Notes may be redeemed at a redemption price of 108.75% of the aggregate principal amount thereof, plus accrued and unpaid interest, with the net proceeds of certain equity offerings. In addition, the 2024 Senior Notes may be redeemed in whole but not in part at a redemption price equal to 100% of the principal amount plus accrued and unpaid interest and additional amounts, if any, to, but excluding, the redemption date, if on the next date on which any amount would be payable in respect of the 2024 Senior Notes, HPUSA or any guarantor is or would be required to pay additional amounts as a result of certain tax-related events.

If the Company undergoes a change of control, HPUSA will be required to make an offer to purchase all of the 2024 Senior Notes at a price in cash equal to 101% of the aggregate principal amount thereof plus accrued and unpaid interest to, but not including, the repurchase date. If the Company or certain of its subsidiaries engages in certain asset sales, HPUSA will be required under certain circumstances to make an offer to purchase the 2024 Senior Notes at 100% of the principal amount thereof, plus accrued and unpaid interest to the repurchase date.

The indenture governing the 2024 Senior Notes contains covenants that limit the ability of the Company and its restricted subsidiaries to, among other things, pay dividends or distributions, repurchase equity, prepay junior debt and make certain investments, incur additional debt and issue certain preferred stock, incur liens on assets, engage in certain asset sales, merge, consolidate with or merge or sell all or substantially all of their assets, enter into transactions with affiliates, designate subsidiaries as unrestricted subsidiaries, and allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to the Company. Certain of the covenants will be suspended during any period in which the notes receive investment grade ratings. The indenture also includes customary events of default.

As of December 31, 2018, the interest rate on the 2024 Senior Notes was 8.750% and the effective interest rate was 9.20%.

As of December 31, 2018, the fair value of the 2024 Senior Notes was approximately $307.5 million, categorized as a Level 2 instrument, as defined in Note 14.

Exchangeable Senior Notes

On March 13, 2015, Horizon Investment completed a private placement of $400.0 million aggregate principal amount of Exchangeable Senior Notes to certain investment banks acting as initial purchasers who subsequently resold the Exchangeable Senior Notes to qualified institutional buyers as defined in Rule 144A under the Securities Act. The net proceeds from the offering of the Exchangeable Senior Notes were approximately $387.2 million, after deducting the initial purchasers' discount and offering expenses payable by Horizon Investment.

The Exchangeable Senior Notes are fully and unconditionally guaranteed, on a senior unsecured basis, by the Company (the "Guarantee"). The Exchangeable Senior Notes and the Guarantee are Horizon Investment's and the Company's senior unsecured obligations. The Exchangeable Senior Notes accrue interest at an annual rate of 2.50% payable semiannually in arrears on March 15 and September 15 of each year, beginning on September 15, 2015. The Exchangeable Senior Notes will mature on March 15, 2022, unless earlier exchanged, repurchased or redeemed. The initial exchange rate is 34.8979 ordinary shares of the Company per $1,000 principal amount of the Exchangeable Senior Notes (equivalent to an initial exchange price of approximately $28.66 per ordinary share). The exchange rate will be subject to adjustment in some events but will not be adjusted for any accrued and unpaid interest. In addition, following certain corporate events that occur prior to the maturity date or upon a tax redemption, Horizon Investment will increase the exchange rate for a holder who elects to exchange its Exchangeable Senior Notes in connection with such a corporate event or a tax redemption in certain circumstances.

Other than as described below, the Exchangeable Senior Notes may not be redeemed by the Company.

Issuer Redemptions:

Optional Redemption for Changes in the Tax Laws of a Relevant Taxing Jurisdiction: Horizon Investment may redeem the Exchangeable Senior Notes at its option, prior to March 15, 2022, in whole but not in part, in connection with certain tax-related events.

Provisional Redemption on or After March 20, 2019: On or after March 20, 2019, Horizon Investment may redeem for cash all or a portion of the Exchangeable Senior Notes if the last reported sale price of ordinary shares of the Company has been at least 130% of the exchange price then in effect for at least twenty trading days whether or not consecutive) during any thirty consecutive trading day period ending on, and including, the trading day immediately preceding the date on which Horizon Investment provide written notice of redemption. The redemption price will be equal to 100% of the principal amount of the Exchangeable Senior Notes to be redeemed, plus accrued and unpaid interest to, but not including, the redemption date; provided that if the redemption date occurs after a regular record date and on or prior to the corresponding interest payment date, Horizon Investment will pay the full amount of accrued and unpaid interest due on such interest payment date to the record holder of the Exchangeable Senior Notes on the regular record date corresponding to such interest

payment date, and the redemption price payable to the holder who presents an Exchangeable Senior Note for redemption will be equal to 100% of the principal amount of such Exchangeable Senior Note.

Holder Exchange Rights:

Holders may exchange all or any portion of their Exchangeable Senior Notes at their option at any time prior to the close of business on the business day immediately preceding December 15, 2021 only upon satisfaction of one or more of the following conditions:

1. Exchange upon Satisfaction of Sale Price Condition – During any calendar quarter commencing after the calendar quarter ended June 30, 2015 (and only during such calendar quarter), if the last reported sale price of ordinary shares of the Company for at least twenty trading days (whether or not consecutive) during the period of thirty consecutive trading days ending on the last trading day of the immediately preceding calendar quarter is greater than or equal to 130% of the applicable exchange price on each applicable trading day.
2. Exchange upon Satisfaction of Trading Price Condition – During the five business day period after any ten consecutive trading day period in which the trading price per $1,000 principal amount of Exchangeable Senior Notes for each trading day of such period was less than 98% of the product of the last reported sale price of ordinary shares of the Company and the applicable exchange rate on such trading day.
3. Exchange upon Notice of Redemption – Prior to the close of business on the business day immediately preceding December 15, 2021, if Horizon Investment provides a notice of redemption, at any time prior to the close of business on the second scheduled trading day immediately preceding the redemption date.

As of December 31, 2018, none of the above conditions had been satisfied and no exchange of Exchangeable Senior Notes had been triggered.

On or after December 15, 2021, a holder may exchange all or any portion of its Exchangeable Senior Notes at any time prior to the close of business on the second scheduled trading day immediately preceding the maturity date regardless of the foregoing conditions.

Upon exchange, Horizon Investment will settle exchanges of the Exchangeable Senior Notes by paying or causing to be delivered, as the case may be, cash, ordinary shares or a combination of cash and ordinary shares, at its election.

The Company recorded the Exchangeable Senior Notes under the guidance in ASC Topic 470-20, *Debt with Conversion and Other Options,* and separated them into a liability component and equity component. The carrying amount of the liability component of $268.9 million was determined by measuring the fair value of a similar liability that does not have an associated equity component. The carrying amount of the equity component of $119.1 million represented by the embedded conversion option was determined by deducting the fair value of the liability component of $268.9 million from the initial proceeds of $387.2 million ascribed to the convertible debt instrument as a whole. The initial debt discount of $131.1 million is being charged to interest expense over the life of the Exchangeable Senior Notes using the effective interest rate method.

As of December 31, 2018, the interest rate on the Exchangeable Senior Notes was 2.50% and the effective interest rate was 8.88%.

As of December 31, 2018, the fair value of the Exchangeable Senior Notes was approximately $396.5 million, categorized as a Level 2 instrument, as defined in Note 14.

NOTE 16 – OTHER LONG-TERM LIABILITIES

Included in other long-term liabilities at December 31, 2018 and 2017, is $19.9 million and $26.4 million, respectively, representing the long-term portion of the contingent liability for royalties potentially payable on sales by Chiesi under agreements related to PROCYSBI and QUINSAIR.

Other long-term liabilities at December 31, 2018 and 2017, included $5.4 million and $7.8 million, respectively, related to a loss on inventory purchase commitments.

NOTE 17 – COMMITMENTS AND CONTINGENCIES

Lease Obligations

The Company has the following office space lease agreements in place for real properties:

Location	Approximate Square Footage	Lease Expiry Date
Dublin, Ireland	18,900	November 4, 2029
Lake Forest, Illinois (1)	160,000	March 31, 2031
Novato, California (2)	61,000	August 31, 2021
Brisbane, California	20,100	November 19, 2019
Chicago, Illinois	9,200	December 31, 2028
Mannheim, Germany	4,800	December 31, 2020
Other	12,400	May 31, 2020 to September 15, 2022

(1) In connection with the Lake Forest lease, the Company has provided a $2.0 million letter of credit to the landlord, through a commercial bank.

(2) In March 2017, the Company vacated an area of the office space in Novato, California and in March and April 2017, the Company entered into sublease arrangements for this space with third parties.

The Company recognizes rent expense on a monthly basis over the lease term based on a straight-line method. Rent expense was $5.6 million, $6.4 million and $5.1 million for the years ended December 31, 2018, 2017 and 2016, respectively.

As of December 31, 2018, minimum future cash payments due under lease obligations were as follows (in thousands):

2019	$	6,228
2020		6,680
2021		5,788
2022		4,565
2023		4,442
Thereafter		36,696
Total	**$**	**64,399**

Purchase Commitments

Patheon Pharmaceuticals Inc. (“Patheon”) is obligated to manufacture PROCYSBI for the Company through December 31, 2021. The Company must provide Patheon with rolling, non-binding forecasts of PROCYSBI, with a portion of the forecast being a firm written order. Cambrex Profarmaco Milano (“Cambrex”) is obligated to manufacture PROCYSBI active pharmaceutical ingredient (“API”) for the Company through November 2, 2020. The Company must provide Cambrex with rolling, non-binding forecasts, with a portion of the forecast being the minimum floor of the firm order that must be placed. At December 31, 2018, the Company had a binding purchase commitment with Patheon for PROCYSBI of $2.3 million, to be delivered through March 2019 and with Cambrex for PROCYSBI API of $1.6 million, to be delivered through December 2020.

Under an agreement with Boehringer Ingelheim Biopharmaceuticals GmbH (“Boehringer Ingelheim Biopharmaceuticals”), Boehringer Ingelheim Biopharmaceuticals is required to manufacture and supply ACTIMMUNE and IMUKIN to the Company. Following the IMUKIN sale, purchases of IMUKIN inventory are expected to be onward sold to Clinigen. The Company is required to purchase minimum quantities of finished medicine during the term of the agreement, which term extends to at least June 30, 2024. As of December 31, 2018, the minimum binding purchase commitment to Boehringer Ingelheim Biopharmaceuticals was $25.7 million (converted using a Dollar-to-Euro exchange rate of 1.1466) through July 2024. As of December 31, 2018, the Company also committed to incur an additional $1.1 million for the harmonization of the drug substance manufacturing process with Boehringer Ingelheim Biopharmaceuticals.

Under the Company’s agreement with Bio-Technology General (Israel) Ltd (“BTG Israel”), the Company has agreed to purchase certain minimum annual order quantities and is obligated to purchase at least eighty percent of its annual world-

wide bulk product requirements for KRYSTEXXA from BTG Israel. The term of the agreement runs until December 31, 2030, and will automatically renew for successive three year periods unless earlier terminated by either party upon three years' prior written notice. The agreement may be terminated earlier by either party in the event of a force majeure, liquidation, dissolution, bankruptcy or insolvency of the other party, uncured material breach by the other party or after January 1, 2024, upon three years' prior written notice. Under the agreement, if the manufacture of the bulk product is moved out of Israel, the Company may be required to obtain the approval of the Israeli Office of the Chief Scientist ("OCS") because certain KRYSTEXXA intellectual property was initially developed with a grant funded by the OCS. The Company issues eighteen-month forecasts of the volume of KRYSTEXXA that the Company expects to order. The first six months of the forecast are considered binding firm orders. At December 31, 2018, the Company had a binding purchase commitment with BTG Israel for KRYSTEXXA of $47.0 million, to be delivered through December 31, 2026. Additionally, purchase orders relating to the manufacture of KRYSTEXXA of $1.5 million were outstanding at December 31, 2018.

Jagotec AG or its affiliates are required to manufacture and supply RAYOS exclusively to the Company in bulk. The earliest the agreement can expire is December 31, 2023, and the minimum purchase commitment is in force until December 2023. At December 31, 2018, the minimum purchase commitment based on tablet pricing in effect under the agreement was $4.8 million through December 2023. Additionally, purchase orders relating to the manufacture of RAYOS of $0.7 million were outstanding at December 31, 2018. Effective January 1, 2019, the Company amended its license and supply agreements with Jagotec AG and Skyepharma AG, which are affiliates of Vectura. Under these amendments, from the earlier of the completion of certain transfer activities related to the transfer of our rights to LODOTRA in Europe, or January 1, 2020, the Company will no longer be subject to a minimum purchase commitment in respect of the supply agreement with Jagotec AG.

Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.) ("Nuvo") is obligated to manufacture and supply PENNSAID 2% to the Company. The term of the supply agreement is through December 31, 2029, but the agreement may be terminated earlier by either party for any uncured material breach by the other party of its obligations under the supply agreement or upon the bankruptcy or similar proceeding of the other party. At least ninety days prior to the first day of each calendar month during the term of the supply agreement, the Company submits a binding written purchase order to Nuvo for PENNSAID 2% in minimum batch quantities. At December 31, 2018, the Company had a binding purchase commitment with Nuvo for PENNSAID 2% of $2.6 million, to be delivered through March 2019.

Sanofi-Aventis U.S. LLC ("Sanofi-Aventis U.S.") is obligated to manufacture and supply DUEXIS to the Company in final, packaged form and the Company is obligated to purchase DUEXIS exclusively from Sanofi-Aventis U.S. for the commercial requirements of DUEXIS in North America, South America and certain countries and territories in Europe, including the European Union ("EU") member states and Scandinavia. The agreement term extends until May 2021 and automatically renews for successive two-year terms unless terminated by either party upon two years' prior written notice. At December 31, 2018, the Company had a binding purchase commitment to Sanofi-Aventis U.S. for DUEXIS of $9.2 million, to be delivered through May 2019.

Excluding the above, additional purchase orders and other commitments relating to the manufacture of RAVICTI, BUPHENYL, QUINSAIR, VIMOVO and MIGERGOT of $9.3 million were outstanding at December 31, 2018. Additionally, at December 31, 2018, the Company had a binding batch purchase commitments for teprotumumab of $5.5 million and a binding commitment related to process validation activities for teprotumumab of $1.8 million.

Royalty and Milestone Agreements

RAVICTI

Under the terms of an asset purchase agreement with Bausch Health Companies Inc. (formerly Ucyclyd Pharma, Inc.) ("Bausch"), the Company is obligated to pay to Bausch mid to high single-digit royalties on its global net sales of RAVICTI. Under the terms of a license agreement with Saul W. Brusilow, M.D. and Brusilow Enterprises, Inc. ("Brusilow"), the Company is obligated to pay low single-digit royalties to Brusilow on net sales of RAVICTI that are covered by a valid claim of a licensed patent.

PROCYSBI

Under the terms of an amended and restated license agreement with The Regents of the University of California, San Diego ("UCSD"), as amended, the Company is obligated to pay to UCSD tiered low to mid-single-digit royalties on its net sales of PROCYSBI, including a minimum annual royalty in an amount less than $0.1 million. The Company must also pay UCSD a percentage in the mid-teens of any fees it receives from its sublicensees under the agreement that are not earned royalties. The Company may also be obligated to pay UCSD aggregate developmental milestone payments of $0.3 million

and aggregate regulatory milestone payments of $1.8 million for each orphan indication, and aggregate developmental milestone payments of $0.8 million and aggregate regulatory milestone payments of $3.5 million for each non-orphan indication.

ACTIMMUNE

Under a license agreement, as amended, with Genentech Inc. ("Genentech"), who was the original developer of ACTIMMUNE, the Company is, or was, obligated to pay royalties to Genentech on its net sales of ACTIMMUNE as follows:

- For the period from November 26, 2014 through May 5, 2018, a royalty in the 20% to 30% range for the first $3.7 million in net sales achieved in any calendar year and in the 1% to 9% range for all additional net sales in any year; and
- From May 6, 2018, an annual royalty in the low single digits as a percentage of annual net sales.

Under the terms of an assignment and option agreement with Connetics Corporation (which was the predecessor parent company to InterMune Pharmaceuticals Inc. and is now part of GlaxoSmithKline), ("Connetics"), the Company is obligated to pay low single-digit royalties to Connetics on the Company's net sales of ACTIMMUNE in the United States.

BUPHENYL

Under the terms of an amended and restated collaboration agreement with Bausch, the Company is obligated to pay to Bausch mid single-digit royalties on its net sales in the United States of BUPHENYL to urea cycle disorder patients outside of the FDA approved labeled age range for RAVICTI. In December 2018, the Company received FDA approval to expand the age range for the use of RAVICTI in the chronic management of UCDs in patients from birth to two months. As a result, this BUPHENYL royalty is no longer required beyond 2018.

KRYSTEXXA

Under the terms of a license agreement with Duke and MVP, the Company is obligated to pay Duke a mid-single-digit royalty on its global net sales of KRYSTEXXA and a royalty of between 5% and 15% on any global sublicense revenue. The Company is also obligated to pay MVP a mid-single-digit royalty on its net sales of KRYSTEXXA outside of the United States and a royalty of between 5% and 15% on any sublicense revenue outside of the United States.

RAYOS and LODOTRA

During the years ended December 31, 2018, 2017 and 2016, the Company was obligated to pay Vectura a mid-single digit percentage royalty on its adjusted gross sales of RAYOS and LODOTRA and on any sub-licensing income, which includes any payments not calculated based on the adjusted gross sales of RAYOS and LODOTRA, such as license fees, and lump sum and milestone payments.

Under certain amendments to the Company's license and supply agreements with Vectura, the royalty payable by the Company to Vectura in respect of RAYOS sales in North America is amended whereby, effective January 1, 2019, the Company will pay Vectura a mid-double-digit percentage royalty on its net sales, subject to a minimum royalty of $8 million per year, with the minimum royalty requirement expiring on December 31, 2022. In addition, under the amendments, the Company will no longer record LODOTRA revenue is no longer required to pay a royalty in respect of LODOTRA.

VIMOVO

The Company is required to pay Nuvo (formerly Aralez Pharmaceuticals Inc.) a ten percent royalty on net sales of VIMOVO and other medicines sold by the Company, its affiliates or sublicensees during the royalty term that contain gastroprotective agents in a single fixed combination oral solid dosage form with nonsteroidal anti-inflammatory drugs, subject to minimum annual royalty obligations of $7.5 million. These minimum royalty obligations will continue for each year during which one of Nuvo's patents covers such medicines in the United States and there are no competing medicines in the United States. The royalty rate may be reduced to a mid-single digit royalty rate as a result of loss of market share to competing medicines. The Company's obligation to pay royalties to Nuvo will expire upon the later of (a) expiration of the last-to-expire of certain patents covering such medicines in the United States, and (b) ten years after the first commercial sale of such medicines in the United States.

The royalty obligations described above are included in accrued royalties on the Company's consolidated balance sheets.

For all of the royalty agreements entered into by the Company, a total net expense of $66.6 million was recorded during the year ended December 31, 2018, of which an expense of $68.5 million was recorded in "cost of goods sold" and a reduction of $1.9 million was recorded to "selling, general and administrative" expenses in the consolidated statements of comprehensive loss. A total royalty expense of $73.5 million was recorded during the year ended December 31, 2017, of which $72.8 million was recorded in "cost of goods sold" and $0.7 million was recorded in "selling, general and administrative" expenses in the consolidated statements of comprehensive loss. During the year ended December 31, 2016, total royalty expense of $45.4 million, was recorded in cost of goods sold in the consolidated statements of comprehensive loss.

Other Agreements

On May 8, 2017, the Company acquired River Vision for upfront cash payments totaling approximately $150.3 million, including cash acquired of $6.3 million, and potential future milestone and royalty payments contingent on the satisfaction of certain regulatory milestones and sales thresholds. Under the agreement, the Company is required to pay up to $325.0 million upon the attainment of various milestones related to FDA approval and net sales thresholds. The agreement also includes a royalty payment of three percent of the portion of annual worldwide net sales exceeding $300.0 million (if any). Under a separate agreement, the Company is also required to pay up to CHF103.0 million ($104.9 million when converted using a CHF-to-Dollar exchange rate at December 31, 2017 of 1.0185) upon the attainment of various milestones related to approval, filing and net sales thresholds. During the year ended December 31, 2017, CHF2.0 million ($2.0 million when converted using a CHF-to-Dollar exchange rate at the date of payment of 1.0169) was paid in relation to these milestones. The agreement also includes a royalty payment of between nine percent and twelve percent of the portion of annual worldwide net sales.

On December 12, 2017, the Company entered into an agreement to license HZN-003 (formerly MEDI4945), a rheumatology pipeline program with the objective of enhancing the Company's leadership position in the uncontrolled gout market, from MedImmune. Under the terms of the agreement, the Company paid MedImmune an upfront cash payment of $12.0 million. Under the license agreement, the Company is required to pay up to $153.5 million upon the attainment of various milestones linked to the initiation of clinical trials and the attainment of net sales thresholds, and royalties on net sales.

Contingencies

The Company is subject to claims and assessments from time to time in the ordinary course of business. The Company's management does not believe that any such matters, individually or in the aggregate, will have a material adverse effect on the Company's business, financial condition, results of operations or cash flows. In addition, the Company from time to time has billing disputes with vendors in which amounts invoiced are not in accordance with the terms of their contracts.

In November 2015, the Company received a subpoena from the U.S. Attorney's Office for the Southern District of New York requesting documents and information related to its patient access programs and other aspects of its marketing and commercialization activities. The Company is unable to predict how long this investigation will continue or its outcome, but it anticipates that it may continue to incur significant costs in connection with the investigation, regardless of the outcome. The Company may also become subject to similar investigations by other governmental agencies. The investigation by the U.S. Attorney's Office and any additional investigations of the Company's patient access programs and sales and marketing activities may result in damages, fines, penalties or other administrative sanctions against the Company.

Indemnification

In the normal course of business, the Company enters into contracts and agreements that contain a variety of representations and warranties and provide for general indemnifications. The Company's exposure under these agreements is unknown because it involves claims that may be made against the Company in the future, but have not yet been made. The Company may record charges in the future as a result of these indemnification obligations.

In accordance with its memorandum and articles of association, the Company has indemnification obligations to its officers and directors for certain events or occurrences, subject to certain limits, while they are serving at the Company's

request in such capacity. Additionally, the Company has entered into, and intends to continue to enter into, separate indemnification agreements with its directors and executive officers. These agreements, among other things, require the Company to indemnify its directors and executive officers for certain expenses, including attorneys' fees, judgments, fines and settlement amounts incurred by a director or executive officer in any action or proceeding arising out of their services as one of the Company's directors or executive officers, or any of the Company's subsidiaries or any other company or enterprise to which the person provides services at the Company's request. The Company also has a director and officer insurance policy that enables it to recover a portion of any amounts paid for current and future potential claims. All of the Company's officers and directors have also entered into separate indemnification agreements with HPUSA.

NOTE 18 - LEGAL PROCEEDINGS

RAVICTI

On March 17, 2014, Hyperion received notice from Par Pharmaceutical, Inc. ("Par Pharmaceutical") that it had filed an Abbreviated New Drug Application (an "ANDA") with the FDA seeking approval for a generic version of the Company's medicine RAVICTI. The ANDA contained a Paragraph IV Patent Certification alleging that two of the patents covering RAVICTI are invalid and/or will not be infringed by Par Pharmaceutical's manufacture, use or sale of the medicine for which the ANDA was submitted. Hyperion filed suit in the United States District Court for the Eastern District of Texas, Marshall Division, against Par Pharmaceutical on April 23, 2014, seeking an injunction to prevent the approval of Par Pharmaceutical's ANDA and/or to prevent Par Pharmaceutical from selling a generic version of RAVICTI. The Company subsequently took over such patent litigation and has been engaged in ANDA litigation with Par Pharmaceutical in multiple venues.

On September 4, 2015, the Company received notice from Lupin Limited of Lupin Limited's Paragraph IV Patent Certification against two of the Company's patents covering RAVICTI, advising that Lupin Limited had filed an ANDA with the FDA for a generic version of RAVICTI. On November 6, 2015, the Company also received notice of Lupin Limited's Paragraph IV Patent Certification against another of the Company's patents covering RAVICTI. On October 19, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Lupin Limited and Lupin Pharmaceuticals Inc. (collectively, "Lupin"), seeking an injunction to prevent the approval of the ANDA, and engaged in ANDA litigation with Lupin in multiple venues.

On June 27, 2018, the Company and Lupin entered into a Settlement and License Agreement ("Lupin Settlement Agreement") under which they agreed to file stipulations of dismissal with the District Courts regarding the district court litigation and a joint request for termination in the inter parte reviews (the "IPRs"). Lupin further agreed to withdraw from the appeal pending before the Federal Circuit Court of Appeals over U.S. Patent No. 9,095,559. The Lupin Settlement Agreement also provides for a full settlement and release by each party of all claims that relate to Lupin's generic version of RAVICTI or the litigation, the IPRs or the appeal. Under the Lupin Settlement Agreement, the license entry date is July 1, 2026; however, Lupin may be able to enter the market earlier in certain circumstances.

On September 17, 2018, the Company and Par Pharmaceutical entered into a Settlement and License Agreement ("Par Settlement Agreement") under which they agreed to file stipulations of dismissal with the District Courts regarding the litigation and a joint request for termination in the IPRs. The Par Settlement Agreement also provides for a full settlement and release by each party of all claims that relate to Par Pharmaceutical's generic version of RAVICTI or the litigation or the IPRs. Under the Par Settlement Agreement, the license entry date is July 1, 2025; however, Par Pharmaceutical may be able to enter the market earlier in certain circumstances.

PENNSAID 2%

On November 13, 2014, the Company received a Paragraph IV Patent Certification from Watson Laboratories, Inc., now known as Actavis Laboratories UT, Inc. ("Actavis UT"), advising that Actavis UT had filed an ANDA with the FDA for a generic version of PENNSAID 2%. On December 23, 2014, June 30, 2015, August 11, 2015 and September 17, 2015, the Company filed four separate suits against Actavis UT and Actavis plc (collectively "Actavis"), in the United States District Court for the District of New Jersey, with each of the suits seeking an injunction to prevent approval of the ANDA. The lawsuits alleged that Actavis has infringed nine of the Company's patents covering PENNSAID 2% by filing an ANDA seeking approval from the FDA to market a generic version of PENNSAID 2% prior to the expiration of certain of the Company's patents listed in the FDA's Orange Book (the "Orange Book"). These four suits were consolidated into a single suit. On October 27, 2015 and on February 5, 2016, the Company filed two additional suits against Actavis, in the United States District Court for the District of New Jersey, for patent infringement of three additional Company patents covering PENNSAID 2%.

On August 17, 2016, the District Court issued a *Markman* opinion holding certain of the asserted claims of seven of the Company's patents covering PENNSAID 2% invalid as indefinite. On March 16, 2017, the Court granted Actavis' motion for summary judgment of non-infringement of the asserted claims of three of the Company's patents covering PENNSAID 2%. In view of the *Markman* and summary judgment decisions, a bench trial was held from March 21, 2017 through March 30, 2017, regarding a claim of one of the Company's patents covering PENNSAID 2%. On May 14, 2017, the Court issued its opinion upholding the validity of claim of the patent, which Actavis had previously admitted its proposed generic diclofenac sodium topical solution product would infringe. Actavis filed its Notice of Appeal on June 16, 2017. The Company also filed its Notice of Appeal of the District Court's rulings on certain claims of eleven of the Company's patents covering PENNSAID 2%. The Company's opening brief was filed on August 14, 2017. Actavis's opening brief, challenging the District Court's judgment on U.S. Patent 9,066,913, was filed on October 10, 2017, and the Company's brief defending the judgment was filed on November 20, 2017. The parties are awaiting the decision of the Federal Circuit Court of Appeals.

On August 18, 2016, the Company filed suit in the United States District Court for the District of New Jersey against Actavis for patent infringement of four of the Company's newly issued patents covering PENNSAID 2%. All four of such patents are listed in the Orange Book. This litigation is currently stayed by agreement of the parties.

The Company received from Actavis a Paragraph IV Patent Certification notice, dated September 27, 2016, against an additional newly issued patent covering PENNSAID 2%, advising that Actavis had filed an ANDA with the FDA for a generic version of PENNSAID 2%. The subject patent is listed in the Orange Book.

On March 18, 2015, the Company received a Paragraph IV Patent Certification against seven of the Company's patents covering PENNSAID 2% from Lupin, advising that Lupin had filed an ANDA with the FDA for a generic version of PENNSAID 2%. On April 30, 2015, the Company filed suit in the United States District Court for the District of New Jersey against Lupin, seeking an injunction to prevent the approval of the ANDA, and engaged in ANDA litigation against Lupin in multiple venues. On May 30, 2018, the Company finalized settlement of the cases against Lupin and the cases were dismissed. Under the settlement agreement with Lupin, the license entry date is October 17, 2027; however, Lupin may be able to enter the market earlier in certain circumstances.

Between April 2016 and April 2017, the Company received from Apotex Inc. four notices of Paragraph IV Patent Certification against eighteen of the Company's patents covering PENNSAID 2%. All of the subject patents are listed in the Orange Book.

DUEXIS

On May 29, 2018, the Company received notice from Alkem Laboratories, Inc. ("Alkem") that it had filed an ANDA with the FDA seeking approval for a generic version of DUEXIS. The ANDA contained a Paragraph IV Patent Certification alleging that the patents covering DUEXIS are invalid and/or will not be infringed by Alkem's manufacture, use or sale of the medicine for which the ANDA was submitted. The Company filed suit in the United States District Court of Delaware against Alkem on July 9, 2018, seeking an injunction to prevent the approval of Alkem's ANDA and/or to prevent Alkem from selling a generic version of DUEXIS. The litigation is scheduled for a bench trial beginning on September 14, 2020.

On September 27, 2018, the Company received notice from Teva Pharmaceuticals USA, Inc. ("Teva") that it had filed an ANDA with the FDA seeking approval for a generic version of DUEXIS. The ANDA contained a Paragraph IV Patent Certification alleging that the patents covering DUEXIS are invalid and/or will not be infringed by Teva's manufacture, use or sale of the medicine for which the ANDA was submitted.

VIMOVO

Currently, patent litigation is pending in the United States District Court for the District of New Jersey and the Court of Appeals for the Federal Circuit against three generic companies intending to market VIMOVO prior to the expiration of certain of the Company's patents listed in the Orange Book. They are collectively known as the VIMOVO cases, and involve the following sets of defendants: (i) Dr. Reddy's Laboratories Inc. and Dr. Reddy's Laboratories Ltd. (collectively, "Dr. Reddy's"); (ii) Lupin; and (iii) Mylan Pharmaceuticals Inc., Mylan Laboratories Limited, and Mylan Inc. (collectively, "Mylan"). Patent litigation in the United States District Court for the District of New Jersey against a fourth generic company, Teva Pharmaceuticals Industries Limited (formerly known as Actavis Laboratories FL, Inc., which itself was formerly known as Watson Laboratories, Inc. – Florida) and Actavis Pharma, Inc. (collectively, "Actavis Pharma"), was dismissed on January 10, 2017, and the parties have concluded a Settlement Agreement. Under the Settlement Agreement with Actavis Pharma, the license entry date is January 1, 2025; however, Actavis Pharma may be able to enter the market earlier in certain circumstances.

The Company understands that Dr. Reddy's has entered into a settlement with AstraZeneca with respect to patent rights directed to Nexium® (esomeprazole) for the commercialization of VIMOVO. The settlement agreement, however, has no effect on the Nuvo VIMOVO patents, which are still the subject of patent litigations. As part of the Company's acquisition of the U.S. rights to VIMOVO, the Company has taken over and is responsible for the patent litigation that includes the Nuvo patents licensed to the Company under the amended and restated collaboration and license agreement for the United States with Nuvo.

The VIMOVO cases were filed on April 21, 2011, July 25, 2011, October 28, 2011, January 4, 2013, May 10, 2013, June 28, 2013, October 23, 2013, May 13, 2015 and November 24, 2015 and collectively include allegations of infringement of certain of the Company's patents covering VIMOVO.

The District Court consolidated all of the cases pending against Dr. Reddy's, Lupin, Mylan and Actavis Pharma into two separate cases for purposes of discovery. The District Court entered final judgment for one of the consolidated cases on July 21, 2017, and both sides have appealed the District Court's judgment to the Court of Appeals for the Federal Circuit. On November 19, 2018, the District Court granted Dr. Reddy's and Mylan summary judgment ruling that U.S Patent Numbers 9,220,698 and 9,393,208 are invalid, and on January 21, 2019, it entered final judgment against the '698, '208, and U.S. Patent Number 8,945,621. Proceedings on all remaining patents are currently stayed.

On August 24, 2017, Mylan filed a Petition for IPR of one of the Company's patents covering VIMOVO. The Company filed its Preliminary Patent Owner Response on December 12, 2017. On March 8, 2018, the Patent Trial and Appeals Board (the "PTAB") instituted Mylan's Petition for IPR. On March 22, 2018, the Company filed a Request for Rehearing of the decision to institute IPR, which was denied by the PTAB on May 25, 2018. On April 6, 2018, Dr. Reddy's filed a Petition for IPR of the same patent challenged by Mylan and a motion for joinder with Mylan's IPR. The Company filed an opposition to Dr. Reddy's motion for joinder on May 9, 2018. The parties are awaiting the PTAB's decision regarding Dr. Reddy's Petition.

On December 4, 2017, Mylan filed a Petition for IPR of another of the Company's patents covering VIMOVO. The PTAB instituted an IPR proceeding on Mylan's Petition on June 14, 2018.

NOTE 19 – SHAREHOLDERS' EQUITY

During the year ended December 31, 2018, the Company issued an aggregate of 4.4 million of ordinary shares in connection with stock option exercises, the vesting of restricted stock units, employee share purchase plan purchases and the vesting of performance stock units. The Company received a total of $25.6 million in net proceeds in connection with such issuances.

During the year ended December 31, 2018, the Company made payments of $14.5 million for employee withholding taxes relating to share-based awards.

In May 2017 and 2018, the Company's board of directors authorized a share repurchase program pursuant to which the Company may repurchase up to 16,000,000 of its ordinary shares. During the year ended December 31, 2017, the Company repurchased 100,000 of its ordinary shares under this repurchase program, for total consideration of $1.0 million. The timing and amount of future repurchases, if any, will depend on a variety of factors, including the price of the Company's ordinary shares, alternative investment opportunities, the Company's cash resources, restrictions under the Credit Agreement and market conditions.

NOTE 20 – SHARE-BASED AND LONG-TERM INCENTIVE PLANS

Employee Stock Purchase Plan

2014 Employee Stock Purchase Plan. On May 17, 2014, HPI's board of directors adopted the 2014 Employee Stock Purchase Plan (the "2014 ESPP"). On September 18, 2014, at a special meeting of the stockholders of HPI (the "Special Meeting"), HPI's stockholders approved the 2014 ESPP. Upon consummation of the Company's merger transaction with Vidara (the "Vidara Merger"), the Company assumed the 2014 ESPP.

As of December 31, 2018, an aggregate of 2,084,665 ordinary shares were authorized and available for future issuance under the 2014 ESPP.

Share-Based Compensation Plans

2005 Stock Plan. In October 2005, HPI adopted the 2005 Stock Plan (the "2005 Plan"). Upon the signing of the underwriting agreement related to HPI's initial public offering, on July 28, 2011, no further option grants were made under the 2005 Plan. All stock awards granted under the 2005 Plan prior to July 28, 2011 continue to be governed by the terms of the 2005 Plan. Upon consummation of the Vidara Merger, the Company assumed the 2005 Plan.

2011 Equity Incentive Plan. In July 2010, HPI's board of directors adopted the 2011 Equity Incentive Plan (the "2011 EIP"). In June 2011, HPI's stockholders approved the 2011 EIP, and it became effective upon the signing of the underwriting agreement related to HPI's initial public offering on July 28, 2011. Upon consummation of the Vidara Merger, the Company assumed the 2011 EIP, and upon the effectiveness of the Horizon Pharma Public Limited Company 2014 Equity Incentive Plan (the "2014 EIP"), no additional stock awards were or will be made under the 2011 Plan, although all outstanding stock awards granted under the 2011 Plan continue to be governed by the terms of the 2011 Plan.

2014 Equity Incentive Plan and 2014 Non-Employee Equity Plan. On May 17, 2014, HPI's board of directors adopted the 2014 EIP and the Horizon Pharma Public Limited Company 2014 Non-Employee Equity Plan (the "2014 Non-Employee Equity Plan"). At the Special Meeting, HPI's stockholders approved the 2014 EIP and 2014 Non-Employee Equity Plan. Upon consummation of the Vidara Merger, the Company assumed the 2014 EIP and 2014 Non-Employee Equity Plan, which serve as successors to the 2011 EIP.

The 2014 EIP provides for the grant of incentive and nonstatutory stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards, performance awards and other stock awards that may be settled in cash, shares or other property to the employees of the Company (or a subsidiary company). During the year ended December 31, 2017, the compensation committee of the Company's board of directors (the "Committee") approved an amendment to the 2014 EIP to reserve additional shares to be used exclusively for grants of awards to individuals who were not previously employees or non-employee directors of the Company (or following a bona fide period of non-employment with the Company) (the "2017 Inducement Pool"), as an inducement material to the individual's entry into employment with the Company within the meaning of Rule 5635(c)(4) of the Nasdaq Listing Rules, ("Rule 5635(c)(4)"). The 2014 EIP was amended by the Committee without shareholder approval pursuant to Rule 5635(c)(4). An amendment to the 2014 EIP increasing the number of ordinary shares that may be issued under the 2014 EIP by 10,800,000 ordinary shares was approved by the Committee on February 21, 2018 and by the shareholders of the Company on May 3, 2018.

The 2014 Non-Employee Equity Plan provides for the grant of nonstatutory stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards and other forms of stock awards that may be settled in cash, shares or other property to the non-employee directors and consultants of the Company (or a subsidiary company). The Company's board of directors has authority to suspend or terminate the 2014 Non-Employee Equity Plan at any time.

As of December 31, 2018, an aggregate of 7,037,630 ordinary shares were authorized and available for future grants under the 2014 EIP, of which 466,556 shares relate to the 2017 Inducement Pool. As of December 31, 2018, 116,163 ordinary shares were authorized and available for future grants under the 2014 Non-Employee Equity Plan.

Stock Options

The following table summarizes stock option activity during the year ended December 31, 2018:

	Options	Weighted Average Exercise Price	Weighted Average Contractual Term Remaining (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2017	14,275,316	$ 18.04	6.97	$ 25,005
Granted	403,973	14.41		
Exercised	(1,768,038)	9.65		
Forfeited	(676,036)	18.24		
Expired	(407,450)	21.00		
Outstanding as of December 31, 2018	**11,827,765**	**19.06**	**6.24**	**37,257**
Vested and Expected to vest as of December 31, 2018	**11,686,892**	**19.08**	**6.22**	**36,905**
Exercisable as of December 31, 2018	**10,043,374**	**$ 19.10**	**5.98**	**$ 33,033**

Stock options typically have a contractual term of ten years from grant date.

The following table summarizes the Company's outstanding stock options at December 31, 2018:

	Options Outstanding			Options Exercisable		
Exercise Price Ranges	Number of options outstanding	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (in years)	Number Exercisable	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (in years)
$2.01 - $4.00	459,812	$ 2.70	4.03	459,812	$ 2.70	4.03
$4.01 - $8.00	739,340	6.80	4.02	739,340	6.80	4.02
$8.01 - $12.00	392,531	8.97	5.44	392,531	8.97	5.44
$12.01 - $17.00	2,367,515	14.25	6.79	1,841,877	14.19	6.24
$17.01 - $22.00	2,291,328	18.11	7.24	1,475,082	18.35	6.93
$22.01 - $28.00	3,324,112	22.30	6.11	3,116,470	22.29	6.10
$28.01 - $36.00	2,253,127	29.43	6.16	2,018,262	29.39	6.13
	11,827,765	**$ 19.06**	**6.24**	**10,043,374**	**$ 19.10**	**5.98**

During the years ended December 31, 2018, 2017 and 2016, the Company granted stock options to purchase an aggregate of 403,973, 2,077,215 and 2,057,247 ordinary shares, respectively, with a weighted average grant date fair value of $6.93, $7.96 and $11.58, respectively.

The total intrinsic value of the options exercised during the years ended December 31, 2018, 2017 and 2016 was $17.0 million, $2.6 million and $6.9 million, respectively. The total fair value of stock options vested during the years ended December 31, 2018, 2017 and 2016 was $36.6 million, $41.3 million and $55.6 million, respectively.

The fair value of each stock option award is estimated on the date of grant using the Black-Scholes option pricing model. The determination of the fair value of each stock option is affected by the Company's share price on the date of grant, as well as assumptions regarding a number of highly complex and subjective variables. These variables include, but are not limited to, the Company's expected share price volatility over the expected life of the awards and actual and projected stock option exercise behavior. The weighted average fair value per share of stock option awards granted during the years ended December 31, 2018, 2017 and 2016, and assumptions used to value stock options, are as follows:

	2018	2017	2016
Dividend yield	—	—	—
Risk-free interest rate	2.3%-2.8%	1.8%-2.2%	1.3%-2.2%
Weighted average volatility	49.5%	49.1%	73.2%
Expected life (in years)	5.56	5.99	6.02
Weighted average grant date fair value per share of options granted	$ 6.93	$ 7.96	$ 11.58

Dividend yields

The Company has never paid dividends and does not anticipate paying any dividends in the near future. Additionally, the Credit Agreement (described in Note 15 above), as well as the indentures governing the 2024 Senior Notes and the 2023 Senior Notes (each as described in Note 15 above), contain covenants that restrict the Company from issuing dividends.

Risk-Free Interest Rate

The Company determined the risk-free interest rate by using a weighted average assumption equivalent to the expected term based on the U.S. Treasury constant maturity rate as of the date of grant.

Volatility

The Company used an average historical share price volatility of comparable companies to be representative of future share price volatility, as the Company did not have sufficient trading history for its ordinary shares.

Expected Term

Given the Company's limited historical exercise behavior, the expected term of options granted was determined using the "simplified" method since the Company does not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term. Under this approach, the expected term is presumed to be the average of the vesting term and the contractual life of the option.

Forfeitures

As share-based compensation expense recognized in the consolidated statements of comprehensive loss is based on awards ultimately expected to vest, it has been reduced for estimated forfeitures based on actual forfeiture experience, analysis of employee turnover and other factors. The Company adopted ASU No. 2016-09 on January 1, 2017 and has elected to retain a forfeiture rate after adoption.

Restricted Stock Units

The following table summarizes restricted stock unit activity for the year ended December 31, 2018:

	Number of Units	Weighted Average Grant-Date Fair Value Per Units
Outstanding as of December 31, 2017	5,283,850	$ 14.77
Granted	4,983,368	15.85
Vested	(2,654,259)	14.54
Forfeited	(840,141)	15.54
Outstanding as of December 31, 2018	**6,772,818**	**$ 15.56**

The grant-date fair value of restricted stock units is the closing price of the Company's shares on the date of grant.

During the years ended December 31, 2018, 2017 and 2016, the Company granted 4,983,368, 3,732,035 and 1,384,104 restricted stock units to acquire shares of the Company's ordinary shares to its employees and non-executive directors, respectively, with a weighted average grant date fair value of $15.85, $12.44 and $17.07, respectively. The restricted stock units vest annually, with a vesting period ranging from two to four years. The Company accounts for the restricted stock units as equity-settled awards in accordance with ASU No. 2017-09. The total fair value of restricted stock units vested during the years ended December 31, 2018, 2017 and 2016 was $43.6 million, $18.0 million and $16.2 million, respectively.

Performance Stock Unit Awards

The following table summarizes performance stock unit awards ("PSUs") activity for the year ended December 31, 2018:

	Number of Units	Weighted Average Grant-Date Fair Value Per Unit	Average Illiquidity Discount	Recorded Weighted Average Fair Value Per Unit
Outstanding as of December 31, 2017	7,854,880			
Granted	1,413,257	$ 16.08	2.6%	$ 15.66
Forfeited	(19,314)	16.64	0.0%	16.64
Expired (1)	(7,854,880)	14.82	14.9%	12.60
Outstanding as of December 31, 2018	**1,393,943**			

(1) During the year ended December 31, 2018, the final tranches of the Company's PSUs outstanding at December 31, 2017 expired due to failure to meet the Company's minimum total compounded annual shareholder rate of return ("TSR") requirement.

On January 5, 2018, the Company awarded PSUs to key executive participants ("2018 PSUs"). Vesting of the 2018 PSUs was contingent upon receiving shareholder approval of amendments to the 2014 EIP, which were approved on May 3, 2018. The 2018 PSUs utilize two performance metrics, a short-term component tied to business performance and a long-term component tied to relative compounded annual TSR, as follows:

- 30% of the 2018 PSUs that may vest (such portion of the PSU award, the "Relative TSR PSUs") are determined by reference to the level of the Company's relative TSR over the three-year period ending December 31, 2020, as measured against the TSR of each company included in the Nasdaq Biotechnology Index (NBI) during such three-year period. Generally, in order to earn any portion of the Relative TSR PSUs, the participant must also remain in continuous service with the Company through the earlier of January 1, 2021 or the date immediately prior to a change in control. If a change in control occurs prior to December 31, 2020, the level of the Company's relative TSR will be measured through the date of the change in control.

- 70% of the 2018 PSUs that may vest (such portion of the PSU award, the "Net Sales PSUs"), are determined by reference to the Company's net sales for its segments during 2018 (being the orphan and rheumatology segment and primary care segment), weighted with the orphan and rheumatology segment comprising the majority of the target sales (with respect to the total PSU award). During the year ended December 31, 2018, the net sales performance criteria was met at 157.4% of target. Accordingly, the first tranche of the Net Sales PSUs portion have vested and the remaining two tranches will vest in equal installments in January 2020 and January 2021, subject to the participant's continued service with the Company through the applicable vesting dates.

All PSUs outstanding at December 31, 2018, may vest in a range of between 0% and 200%, based on the performance metrics described above. The Company accounts for the 2018 PSUs as equity-settled awards in accordance with ASC 718. Because the value of the Relative TSR PSUs are dependent upon the attainment of a level of TSR, it requires the impact of the market condition to be considered when estimating the fair value of the Relative TSR PSUs. As a result, the Monte Carlo model is applied and the most significant valuation assumptions used during the year ended December 31, 2018, include:

Valuation date stock price	13.87
Expected volatility	71.3%
Risk-free rate	2.6%

Share-Based Compensation Expense

The following table summarizes share-based compensation expense included in the Company's consolidated statements of comprehensive loss for the years ended December 31, 2018, 2017 and 2016 (in thousands):

	For the Years Ended December 31,		
	2018	**2017**	**2016**
Share-based compensation expense:			
Cost of goods sold	$ 3,699	$ 2,469	$ 26
Research and development	8,880	9,263	9,413
Selling, general and administrative	102,281	109,821	104,705
Total share-based compensation expense	**$ 114,860**	**$ 121,553**	**$ 114,144**

During the years ended December 31, 2018 and 2017, the Company recognized $2.0 million of tax benefit and $2.8 million of tax detriment, respectively, related to share-based compensation resulting from the current share prices in effect at the time of the exercise of stock options and vesting of restricted stock units. In addition, during the year ended December 31, 2018, $23.3 million of deferred tax assets related to previously recognized share-based compensation expense related to PSUs was charged to income tax expense. As of December 31, 2018, the Company estimates that pre-tax unrecognized compensation expense of $107.6 million for all unvested share-based awards, including stock options, restricted stock units and PSUs, will be recognized through the first quarter of 2022. The Company expects to satisfy the exercise of stock options

and future distribution of shares for restricted stock units and PSUs by issuing new ordinary shares which have been reserved under the 2014 EIP.

Cash Incentive Program

On January 5, 2018, the Committee approved a performance cash incentive program for the Company's executive leadership team, including its executive officers (the "Cash Incentive Program"). Participants receiving awards under the Cash Incentive Program will be eligible to earn a cash bonus based upon target award levels set forth below and based upon achievement of specified Company goals. The maximum payout under the Cash Incentive Program is approximately $14.1 million. Of the total cash bonus award that may be earned under the Cash Incentive Program, 70% will be determined by reference to achieving an aggressive percentage increase in KRYSTEXXA vial sales during 2018 as compared to KRYSTEXXA vial sales during 2017. A further 30% will be determined by reference to the achievement of patient enrollment levels in the teprotumumab phase 3 clinical trial by December 31, 2018.

Both performance criteria were met on or before December 31, 2018 and the Company determined that the cash bonus award under the CIP is to be paid out at the maximum 150% target level of $14.1 million. The first installment was paid in January 2019, and the remaining installments will vest and become payable in January 2020 and 2021, subject to the participant's continued services with the Company through the applicable vesting dates, the date of any earlier change in control, or a termination due to death or disability.

The Company accounted for the Cash Incentive Program as a deferred compensation plan under ASC 710 and is recognizing the payout expense using straight-line recognition through the end of the 36-month vesting period. During the year ended December 31, 2018, the Company recorded an expense of $4.9 million to the consolidated statement of comprehensive loss related to the Cash Incentive Program.

NOTE 21 – INCOME TAXES

The Company's loss before benefit for income taxes by jurisdiction for the years ended December 31, 2018, 2017 and 2016 is as follows (in thousands):

	For the Years Ended December 31,		
	2018	2017	2016
Ireland	$ (10,944)	$ (16,956)	$ (27,955)
United States	(176,837)	(271,102)	(165,476)
Other foreign	68,635	(216,276)	(33,383)
Loss before benefit for income taxes	**$ (119,146)**	**$ (504,334)**	**$ (226,814)**

The components of the benefit for income taxes were as follows for the years ended December 31, 2018, 2017 and 2016 (in thousands):

	For the Years Ended December 31,		
	2018	2017	2016
Current provision (benefit)			
Ireland	$ (245)	$ 2,922	$ 1,187
U.S. – Federal and State	42,791	12,085	10,491
Other foreign	843	831	679
Total current provision	43,389	15,838	12,357
Deferred (benefit) provision			
Ireland	$ (14,184)	$ (6,294)	$ (2,054)
U.S. – Federal and State	(62,995)	(120,111)	(69,073)
Other foreign	(11,169)	7,818	(2,481)
Total deferred benefit	(88,348)	(118,587)	(73,608)
Total benefit for income taxes	**$ (44,959)**	**$ (102,749)**	**$ (61,251)**

Total benefit for income taxes was $45.0 million, $102.7 million and $61.3 million for the years ended December 31, 2018, 2017 and 2016, respectively. The current tax provision of $43.4 million for the year ended December 31, 2018 was primarily attributable to the U.S. federal tax liability arising on U.S. taxable income generated from an intra-company transfer of an asset other than inventory. Due to the restrictions imposed by Section 7874 of the Code, the Company could not utilize its tax attributes such as net operating losses and tax credits to reduce its U.S. federal tax liability below the minimum tax required under Section 7874, therefore the Company recorded a provision of $45.8 million on the transfer. The deferred tax benefit of $88.3 million recognized during the year ended December 31, 2018, was primarily due to a $37.4 million tax benefit recorded as a measurement period adjustment in SAB 118 to reinstate the deferred tax asset related to our U.S. interest expense carryforwards under Section 163(j) of the Internal Revenue Code to reflect the guidance issued by the U.S. Treasury Department and the U.S. Internal Revenue Service in Notice 2018-28, the mix of income and losses incurred in various tax jurisdictions of $35.3 million, $11.2 million of tax benefit recognized on intra-company inventory transfers and $4.4 million of tax credits generated during the year.

A reconciliation between the Irish statutory income tax rate to the Company's effective tax rate for 2018, 2017 and 2016 is as follows (in thousands):

	For the Years Ended December 31,		
	2018	2017	2016
Irish income tax at statutory rate (12.5%)	$ (14,893)	$ (63,042)	$ (28,352)
Foreign tax rate differential	13,221	(10,923)	(2,051)
Liquidation of foreign partnership	(42,689)	—	—
Write-off and reinstatement of U.S. deferred tax asset related to interest expense carryforwards due to the Tax Act	(37,392)	59,243	—
Notional interest deduction	(24,455)	(27,020)	(35,075)
Intra-company inventory transfers	(11,169)	(8,888)	2,154
U.S. state income taxes	(6,515)	214	8,579
U.S. federal and state tax credits	(4,405)	(3,608)	(3,613)
Change in valuation allowances	(1,115)	(1,378)	(6,117)
Impact of the Tax Act on deferred taxes	—	(134,182)	—
Non-deductible in-process research and development costs	—	51,148	—
Uncertain tax positions	2,456	4,976	2,837
Disallowed interest	3,023	2,990	2,620
Disqualified compensation expense	4,831	1,305	2,555
Change in U.S. state effective tax rate	8,103	(2,329)	(17,246)
Share-based compensation	21,383	26,811	7,125
Intra-company asset transfers	45,780	—	—
Other, net	(1,123)	1,934	5,333
Benefit for income taxes	**$ (44,959)**	**$ (102,749)**	**$ (61,251)**
Effective income tax rate	**37.7%**	**20.4%**	**27.0%**

The overall effective income tax rate for 2018 of 37.7% was a higher benefit rate than the Irish statutory rate of 12.5% primarily due to a $42.7 million U.S. federal tax benefit and $7.9 million U.S. state tax benefit was recorded with respect to the liquidation of a foreign partnership, a $37.4 million tax benefit resulting from a measurement period adjustment under SAB 118 to reinstate the deferred tax asset related to our U.S. interest expense carryforwards under Section 163(j) of the Internal Revenue Code to reflect the guidance issued by the U.S. Treasury Department and the U.S. Internal Revenue Service in Notice 2018-28, a $24.5 million tax benefit on the Company's notional interest deduction and a $11.2 million tax benefit recognized on intra-company inventory transfers. These tax benefits are partially offset by tax expense of $45.8 million on an intra-company transfer of asset other than inventory, a tax expense of $21.4 million on non-deductible share-based compensation expenses, which includes the previously recognized share-based compensation expense relating to PSUs which was charged to income tax expense during the year ended December 31, 2018, of $23.3 million, a tax expense of $13.2 million on the income earned in higher tax rate jurisdictions and a tax expense of $8.1 million resulting from the remeasurement of net U.S. deferred tax liabilities attributable to state legislation as enacted during the current year.

The overall effective income tax rate for 2017 of 20.4% was a higher benefit rate than the Irish statutory rate of 12.5% primarily due to a provisional $74.9 million net benefit recorded following the enactment of the Tax Act, which net benefit included a $134.2 million tax benefit from the revaluation of the Company's U.S. net deferred tax liability based on the revised U.S. federal tax rate of 21 percent, partially offset by the write-off of a $59.2 million deferred tax asset related to the Company's U.S. interest expense carryforwards. The higher 2017 benefit rate was also attributable to losses incurred in higher tax rate jurisdictions, the benefit realized on the notional interest deduction of $27.0 million, a tax benefit recognized on intra-company inventory transfers of $8.9 million, U.S. federal and state tax credits of $3.6 million and $2.3 million due to a decrease in the U.S. state effective tax rate. These benefits to income taxes are partially offset by non-deductible IPR&D expenses of $51.1 million recorded in connection with the acquisition of River Vision, non-deductible share-based compensation expenses of $26.8 million, including the write-off of $16.4 million of deferred tax assets related to previously recognized share-based compensation expense related to PSUs that expired unvested in December 2017, and an increase in uncertain tax positions of $5.0 million.

The overall effective income tax rate for 2016 of 27.0% was a higher benefit rate than the Irish statutory rate of 12.5% primarily due to the benefit realized on the notional interest deduction, the benefit realized from a change in U.S. state effective tax rate, and changes in valuation allowances. These benefits to income taxes were partially offset by an increase in share-based compensation not deductible for tax purposes and an increase in U.S. state income taxes.

The increase in the effective income tax rate in 2018 compared to that in 2017 was primarily due to a tax benefit of $42.7 million U.S. federal and $7.9 million U.S. state tax benefit generated on the liquidation of a foreign partnership during the year ended December 31, 2018, a tax benefit of $37.4 million recorded during the year ended December 31, 2018, as a measurement period adjustment under SAB 118, to reinstate the deferred tax asset related to our U.S. interest expense carryforwards under Section 163(j) of the Internal Revenue Code to reflect the guidance issued by the U.S. Treasury Department and the U.S. Internal Revenue Service in Notice 2018-28, and a non-deductible IPR&D expenses of $51.1 million recorded during the year ended December 31, 2017, recorded in connection with the acquisition of River Vision.

The decrease in the effective income tax rate in 2017 compared to that in 2016 was primarily due to non-deductible IPR&D expenses of $51.1 million recorded in connection with the acquisition of River Vision, an increase in non-deductible share-based compensation of $19.7 million primarily due to the write-off of $16.4 million of deferred tax assets related to previously recognized share-based compensation expense related to PSUs that expired unvested in December 2017, a $14.9 million decrease in benefit from the change in U.S. state effective tax rate, an $11.0 million movement related to intra-company inventory transfers, an $8.1 million decrease in the benefit realized on the notional interest deduction and a $4.7 million decrease in the changes in valuation allowances, partially offset by the provisional $74.9 million net impact of the Tax Act on deferred taxes.

The Company accounts for income taxes based upon an asset and liability approach. Deferred tax assets and liabilities represent the future tax consequences of the differences between the financial statement carrying amounts of assets and liabilities versus the tax basis of assets and liabilities. Under this method, deferred tax assets are recognized for future deductible temporary differences and operating loss and tax credit carryforwards. Deferred tax liabilities are recognized for future taxable temporary differences. Deferred tax assets are reduced by a valuation allowance when, in the opinion of management, it is more likely than not that some portion or all of the deferred tax assets will not be realized. The impact of tax rate changes on deferred tax assets and liabilities is recognized in the period in which the change is enacted.

The tax effects of the temporary differences, tax credits and net operating losses that give rise to significant portions of deferred tax assets and liabilities, before jurisdictional netting, are as follows (in thousands):

	As of December 31,	
	2018	2017
Deferred tax assets:		
Net operating loss carryforwards	$ 51,264	$ 65,650
Intercompany interest	52,605	—
U.S. federal and state credits	43,786	35,465
Accrued compensation	40,942	46,420
Contingent royalties	30,321	33,436
Accruals and reserves	12,381	11,089
Capital loss carryforwards	3,139	2,796
Alternative minimum tax credit	2,816	13,972
Other	1,004	2,259
Total deferred tax assets	**238,258**	**211,087**
Valuation allowance	(26,472)	(25,650)
Deferred tax assets, net of valuation allowance	**$ 211,786**	**$ 185,437**
Deferred tax liabilities:		
Intangible assets	$ 283,473	$ 315,970
Debt discount	18,795	23,372
Inventories	—	570
Total deferred tax liabilities	302,268	339,912
Net deferred income tax liability	**$ 90,482**	**$ 154,475**

On December 22, 2017, the SEC staff issued SAB 118, which provides guidance on accounting for the tax effects of the Tax Act. SAB 118 provided a measurement period that should not extend beyond one year from the date of enactment for companies to complete the accounting under ASC 740, *Income Taxes*. In accordance with SAB 118, during the year ended December 31, 2017, the Company reflected the income tax effects of those aspects of the Tax Act for which the accounting under ASC 740 was complete. To the extent that the Company's accounting for certain income tax effects of the Tax Act was incomplete but it was able to determine a reasonable estimate, the Company recorded a provisional estimate in the consolidated financial statements for the year ended December 31, 2017. As of December 31, 2017, the Company had not completed its accounting for the effects of the Tax Act. However, the Company had made reasonable estimates of the effects on its income tax provision with respect to certain items, primarily the revaluation of its existing U.S. deferred tax balances and the write-off of its U.S. deferred tax assets resulting from interest expense carryforwards under Section 163(j). The Company recognized a net income tax benefit of $74.9 million for the year ended December 31, 2017, associated with the items it could reasonably estimate. This benefit reflects the revaluation of its U.S. net deferred tax liability based on the U.S. federal tax rate of 21 percent, partially offset by the write-off of the deferred tax asset related to its U.S. interest expense carryforwards.

On April 2, 2018, the U.S. Treasury Department and the U.S. Internal Revenue Service issued Notice 2018-28 ("the Notice") which provides guidance for computing the business interest expense limitation under the Tax Act and clarifies the treatment of interest disallowed and carried forward under Section 163(j), prior to enactment of the Tax Act. In accordance with the measurement period provisions under SAB 118 and the guidance in the Notice the Company reinstated the deferred tax asset related to its U.S. interest expense carryforwards under Section 163(j) based on the revised U.S. federal tax rate of 21 percent plus applicable state tax rates. The impact of the deferred tax asset reinstatement in accordance with SAB 118 was a $37.4 million increase to the Company's benefit for income taxes and a corresponding decrease to the U.S. group net deferred tax liability position. The impact of this reinstatement has been recognized as a discrete tax adjustment during the year ended December 31, 2018 and resulted in a 31.4% increase in the Company's effective tax rate during the period. In the fourth quarter of 2018, the Company completed our analysis to determine the effect of the Tax Act and recorded immaterial adjustments as of December 31, 2018 which related to return to provision adjustments which impacted the U.S. net deferred tax liabilities.

No provision has been made for income taxes on undistributed earnings of subsidiaries because it is the Company's intention to indefinitely reinvest outside of Ireland undistributed earnings of its subsidiaries. In the event of the distribution of those earnings to Ireland in the form of dividends, a sale of the subsidiaries, or certain other transactions, the Company may be liable for income taxes in Ireland. The unremitted earnings of the Company as of December 31, 2018, were $164.4 million, and the Company estimates that it would incur no additional income tax on unremitted earnings were they to be remitted to Ireland.

As of December 31, 2018, the Company had net operating loss carryforwards of approximately $77.3 million for U.S. federal, $25.1 million for various U.S. states and $113.1 million for non-U.S. losses. Net operating loss carryforwards for U.S. federal income tax purposes that were generated prior to January 1, 2018, have a twenty-year carryforward life and the earliest layers will begin to expire in 2031. Under the Tax Act, U.S. federal net operating losses incurred in 2018 and in future years may be carried forward indefinitely, but the deductibility of such net operating losses is limited to 80% of the current year's taxable income. It is uncertain if and to what extent various U.S. states will conform to the Tax Act. U.S. state net operating losses will start to expire in 2019 for the earliest net operating loss layers to the extent there is not sufficient state taxable income to utilize those net operating loss carryovers. Net operating loss carryovers in Switzerland have a seven-year carryforward life and will start to expire in 2019 to the extent there is not sufficient taxable income to utilize those net operating loss carryovers. Irish net operating losses may be carried forward indefinitely and therefore have no expiration. Utilization of the U.S. net operating loss carryforwards may be subject to annual limitations as prescribed by federal and state statutory provisions. The imposition of the annual limitations may result in a portion of the net operating loss carryforwards expiring unused.

Utilization of certain net operating loss and tax credit carryforwards in the United States is subject to an annual limitation due to ownership change limitations provided by Sections 382 and 383 of the Internal Revenue Code. The Company is limited under the annual limitation of $7.7 million from the year 2019 until 2028 on certain net operating losses generated before an August 2, 2012 ownership change. We continue to carry forward the annual limitation related to Hyperion of $50.0 million resulting from the last ownership change in 2014 as well as the annual limitation related to Raptor of $0.2 million for the ownership change which occurred in 2009. Further, the net operating losses acquired with River Vision are subject to an annual limitation of $2.6 million. The U.S. federal net operating loss carryforward and U.S. federal tax credit carryforward limitation is cumulative such that any use of the carryforwards below the limitation in a particular tax year will result in a corresponding increase in the limitation for the subsequent tax year.

At December 31, 2018, the Company had $54.5 million and $8.0 million of U.S. federal and state income tax credits, respectively, to reduce future tax liabilities. The federal income tax credits consisted primarily of orphan drug credits, research and development credits and alternative minimum tax credits. The U.S. state income tax credits consisted primarily of California research and development credits and the Illinois Economic Development for a Growing Economy ("EDGE") tax credits. Both the U.S. federal orphan drug credits and research and development credits have a twenty-year carryforward life. The U.S. federal orphan drug credits and the U.S. federal research and development credits will both begin to expire in 2030. The U.S. federal alternative minimum tax credits and California research and development credits have indefinite lives and therefore are not subject to expiration. The EDGE credits have a five-year carryforward life following the year of generation and will begin to expire in 2019.

A reconciliation of the beginning and ending amounts of valuation allowances for the years ended December 31, 2018, 2017 and 2016 is as follows (in thousands):

Valuation allowances at December 31, 2015	$	(31,310)
Increase for 2016 activity		(14,636)
Release of valuation allowances		15,056
Additions to valuation allowances due to acquisitions		(1,642)
Valuation allowances at December 31, 2016	**$**	**(32,532)**
Increase for 2017 activity		(6,835)
Release of valuation allowances		5,313
Decreases to valuation allowances due to divestiture		8,404
Valuation allowances at December 31, 2017	**$**	**(25,650)**
Increase for 2018 activity		(3,328)
Release of valuation allowances		2,506
Valuation allowances at December 31, 2018	**$**	**(26,472)**

Deferred tax valuation allowances increased by $0.8 million during the year ended December 31, 2018, decreased by $6.9 million during the year ended December 31, 2017 and increased by $1.2 million during the year ended December 31, 2016. For the year ended December 31, 2018, the increase in valuation allowances resulted primarily from additional U.S. state net operating losses and state tax credits which are unlikely to be realized in the foreseeable future.

The Company is required to recognize the financial statement effects of a tax position when it is more likely than not, based on the technical merits, that the position will be sustained upon examination. The Company accounts for the uncertainty in income taxes by utilizing a comprehensive model for the recognition, measurement, presentation and disclosure in financial statements of any uncertain tax positions that have been taken, or are expected to be taken, on an income tax return. The changes in the Company's uncertain income tax positions for the years ended December 31, 2018, 2017 and 2016, excluding interest and penalties, consisted of the following (in thousands):

	For the Years Ended December 31,		
	2018	2017	2016
Beginning balance – uncertain tax positions	$ 23,404	$ 17,747	$ 9,812
Tax positions in the year:			
Additions	1,899	2,451	471
Acquired uncertain tax positions	—	—	5,362
Tax positions related to prior years:			
Additions	1,531	4,145	2,102
Settlements and lapses	(528)	(939)	—
Ending balance – uncertain tax positions	**$ 26,306**	**$ 23,404**	**$ 17,747**

For the year ended December 31, 2018, the increase in uncertain tax positions was attributable primarily to the additional U.S. federal orphan drug credits generated during the year and the uncertain tax position resulting from certain state nexus exposures. In the Company's consolidated balance sheet, uncertain tax positions of $10.2 million were included in other long-term liabilities, $2.4 million were included in accrued expenses and an additional $15.9 million was offset against deferred tax assets.

At December 31, 2018, penalties of $0.2 million and interest of $2.0 million are included in the balance of the uncertain tax positions and penalties of $0.2 million and interest of $1.3 million were included in the balance of uncertain tax positions at December 31, 2017. The Company classifies interest and penalties with respect to income tax liabilities as a component of income tax expense. The Company assessed that its liability for uncertain tax positions will not significantly change within the next twelve months. If these uncertain tax positions are released, the impact on the Company's tax provision would be a benefit of $28.5 million, including interest and penalties.

The Company files income tax returns in Ireland, in the United States for federal and various states, as well as in certain other jurisdictions. At December 31, 2018, all open tax years in U.S. federal and certain state jurisdictions date back to 2006 due to the taxing authorities' ability to adjust operating loss carryforwards. In Ireland, the statute of limitations expires five years from the end of the tax year or four years from the time a tax return is filed, whichever is later. Therefore the earliest year open to examination is 2014 with the lapse of statute occurring in 2019. No changes in settled tax years have occurred to date. We are currently under examination by the U.S. Internal Revenue Service for the tax year ended December 31, 2015. As of the filing of this Annual Report on Form 10-K, the Company does not currently anticipate material changes from the originally filed U.S. federal tax return for the 2015 year.

NOTE 22 – EMPLOYEE BENEFIT PLANS

The Company sponsors a defined contribution 401(k) retirement savings plan covering all of its U.S. employees, whereby an eligible employee may elect to contribute a portion of his or her salary on a pre-tax basis, subject to applicable federal limitations. The Company is not required to make any discretionary matching of employee contributions. The Company makes a matching contribution equal to 100% of each employee's elective contribution to the plan of up to 3% of the employee's eligible pay, and 50% for the next 2% of the employee's eligible pay. The full amount of this employer contribution is immediately vested in the plan. For the years ended December 31, 2018, 2017 and 2016, the Company recorded defined contribution expense of $5.2 million, $4.9 million and $2.7 million, respectively.

The Company's wholly owned Swiss subsidiary sponsors a defined benefit savings plan covering all of its employees in Switzerland. The Company's wholly owned German subsidiary sponsors a defined contribution plan for its employees in Germany. For the years ended December 31, 2018, 2017 and 2016, the Company recognized immaterial expenses under these plans.

The Company's wholly owned Irish subsidiary sponsors a defined contribution plan covering all of its employees in Ireland. For the years ended December 31, 2018, 2017 and 2016, the Company recognized expenses of $0.6 million, $0.4 million and $0.4 million, respectively, under this plan.

The Company has a non-qualified deferred compensation plan for executives. The deferred compensation plan obligations are payable in cash upon retirement, termination of employment and/or certain other times in a lump-sum distribution or in installments, as elected by the participant in accordance with the plan. As of December 31, 2018 and 2017, the deferred compensation plan liabilities totaled $8.2 million and $6.5 million, respectively, and are included in "other long-term liabilities" in the consolidated balance sheet. The Company held funds of approximately $8.2 million and $6.5 million in an irrevocable grantor's rabbi trust as of December 31, 2018 and 2017, respectively, related to this plan. Rabbi trust assets are classified as trading marketable securities and are included in "other current assets" in the consolidated balance sheets. Unrealized gains and losses on these marketable securities are included in "other income" in the consolidated statements of comprehensive loss. For the years ended December 31, 2018, 2017 and 2016, the Company recognized expenses of $0.9 million, $0.8 million and $0.6 million, respectively, under this plan.

NOTE 23 – SELECTED QUARTERLY FINANCIAL INFORMATION (UNAUDITED)

The following table provides a summary of selected financial results of operations by quarter for the years ended December 31, 2018 and 2017 (in thousands, except per share data):

2018	First	Second	Third	Fourth
Net sales	$ 223,881	$ 302,835	$ 325,311	$ 355,543
Gross profit	108,542	203,548	227,140	246,023
Operating (loss) income	(126,555)	2,609	55,086	71,252
Net (loss) income	(156,574)	(32,041)	26,870	87,558
Net (loss) income per ordinary share - basic	$ (0.95)	$ (0.19)	$ 0.16	$ 0.52
Net (loss) income per ordinary share - diluted	(0.95)	(0.19)	0.16	0.50

2017	First	Second	Third	Fourth
Net sales	$ 220,859	$ 289,507	$ 271,646	$ 274,219
Gross profit	81,971	159,596	146,380	130,950
Operating (loss) income	(105,155)	(185,428)	(25,500)	(67,345)
Net (loss) income	(90,342)	(209,297)	(63,720)	(38,225)
Net (loss) income per ordinary share - basic and diluted	$ (0.56)	$ (1.28)	$ (0.39)	$ (0.27)

Revision of Prior Period Financial Information

During the course of preparing the consolidated financial statements for the year ended December 31, 2018, the Company identified an error in the measurement of the contingent royalty liability calculation pertaining to the royalty end date for one of its medicines. See Note 1 for further details of this error and the related revisions to the Company's consolidated balance sheet as at December 31, 2017, and the consolidated statements of comprehensive (loss) income and cash flows for the years ended December 31, 2017 and 2016. The revision resulted in certain adjustments to the consolidated statements of comprehensive income (loss) for the quarters during the years ended December 31, 2018 and 2017, and the revised amounts are presented above. Additionally, the following are selected line items from the Company's unaudited consolidated financial information illustrating the effect of the revisions:

	Consolidated Statements of Comprehensive Income (Loss)					
	For the Three Months Ended September 30, 2018			For the Nine Months Ended September 30, 2018		
	As Previously Reported	Revision	As Revised	As Previously Reported	Revision	As Revised
Cost of goods sold	$ 99,011	$ (840)	$ 98,171	$ 315,185	$ (2,388)	$ 312,797
Gross profit	226,300	840	227,140	536,842	2,388	539,230
Operating income (loss)	54,246	840	55,086	(71,247)	2,388	(68,859)
Income (loss) before (benefit) expense for income taxes	24,297	840	25,137	(162,271)	2,388	(159,883)
Net income (loss)	26,030	840	26,870	(164,134)	2,388	(161,746)
Net income (loss) per ordinary share—basic	0.16	—	0.16	(0.99)	0.02	(0.97)
Net income (loss) per ordinary share—diluted	0.15	0.01	0.16	(0.99)	0.02	(0.97)
Comprehensive income (loss)	25,897	840	26,737	(164,412)	2,388	(162,024)

	Consolidated Statements of Comprehensive Loss					
	For the Three Months Ended June 30, 2018			For the Six Months Ended June 30, 2018		
	As Previously Reported	Revision	As Revised	As Previously Reported	Revision	As Revised
Cost of goods sold	$ 100,082	$ (795)	$ 99,287	$ 216,174	$ (1,548)	$ 214,626
Gross profit	202,753	795	203,548	310,542	1,548	312,090
Operating income (loss)	1,814	795	2,609	(125,494)	1,548	(123,946)
Loss before expense for income taxes	(28,874)	795	(28,079)	(186,568)	1,548	(185,020)
Net loss	(32,836)	795	(32,041)	(190,164)	1,548	(188,616)
Net loss per ordinary share—basic	(0.20)	0.01	(0.19)	(1.15)	0.01	(1.14)
Net loss per ordinary share—diluted	(0.20)	0.01	(0.19)	(1.15)	0.01	(1.14)
Comprehensive loss	(33,444)	795	(32,649)	(190,309)	1,548	(188,761)

	Consolidated Statements of Comprehensive Loss		
	For the Three Months Ended March 31, 2018		
	As Previously Reported	Revision	As Revised
Cost of goods sold	$ 116,092	$ (753)	$ 115,339
Gross profit	107,789	753	108,542
Operating loss	(127,308)	753	(126,555)
Loss before benefit for income taxes	(157,694)	753	(156,941)
Net loss	(157,327)	753	(156,574)
Net loss per ordinary share—basic	(0.96)	0.01	(0.95)
Net loss per ordinary share—diluted	(0.96)	0.01	(0.95)
Comprehensive loss	(156,864)	753	(156,111)

	Consolidated Statements of Comprehensive Loss		
	For the Three Months Ended December 31, 2017		
	As Previously Reported	Revision	As Revised
Cost of goods sold	$ 151,492	$ (8,223)	$ 143,269
Gross profit	122,727	8,223	130,950
Operating loss	(75,568)	8,223	(67,345)
Loss before benefit for income taxes	(107,059)	8,223	(98,836)
Net loss	(46,448)	8,223	(38,225)
Net loss per ordinary share—basic	(0.28)	0.05	(0.23)
Net loss per ordinary share—diluted	(0.28)	0.05	(0.23)
Comprehensive loss	(45,090)	8,223	(36,867)

	Consolidated Statements of Comprehensive Loss					
	For the Three Months Ended September 30, 2017			For the Nine Months Ended September 30, 2017		
	As Previously Reported	Revision	As Revised	As Previously Reported	Revision	As Revised
Cost of goods sold	$ 125,517	$ (251)	$ 125,266	$ 394,783	$ (718)	$ 394,065
Gross profit	146,129	251	146,380	387,229	718	387,947
Operating loss	(25,751)	251	(25,500)	(316,801)	718	(316,083)
Loss before benefit for income taxes	(56,790)	251	(56,539)	(406,216)	718	(405,498)
Net loss	(63,971)	251	(63,720)	(364,078)	718	(363,360)
Net loss per ordinary share—basic	(0.39)	—	(0.39)	(2.24)	0.01	(2.23)
Net loss per ordinary share—diluted	(0.39)	—	(0.39)	(2.24)	0.01	(2.23)
Comprehensive loss	(64,180)	251	(63,929)	(363,333)	718	(362,615)

	Consolidated Statements of Comprehensive Loss					
	For the Three Months Ended June 30, 2017			For the Six Months Ended June 30, 2017		
	As Previously Reported	Revision	As Revised	As Previously Reported	Revision	As Revised
Cost of goods sold	$ 130,150	$ (239)	$ 129,911	$ 269,266	$ (467)	$ 268,799
Gross profit	159,357	239	159,596	241,100	467	241,567
Operating loss	(185,667)	239	(185,428)	(291,050)	467	(290,583)
Loss before benefit for income taxes	(211,303)	239	(211,064)	(349,426)	467	(348,959)
Net loss	(209,536)	239	(209,297)	(300,106)	467	(299,639)
Net loss per ordinary share—basic	(1.29)	0.01	(1.28)	(1.85)	0.01	(1.84)
Net loss per ordinary share—diluted	(1.29)	0.01	(1.28)	(1.85)	0.01	(1.84)
Comprehensive loss	(208,910)	239	(208,671)	(299,152)	467	(298,685)

	Consolidated Statements of Comprehensive Loss		
	For the Three Months Ended March 31, 2017		
	As Previously Reported	Revision	As Revised
Cost of goods sold	$ 139,116	$ (228)	$ 138,888
Gross profit	81,743	228	81,971
Operating loss	(105,383)	228	(105,155)
Loss before benefit for income taxes	(138,123)	228	(137,895)
Net loss	(90,570)	228	(90,342)
Net loss per ordinary share—basic	(0.56)	—	(0.56)
Net loss per ordinary share—diluted	(0.56)	—	(0.56)
Comprehensive loss	(90,242)	228	(90,014)

SCHEDULE II – VALUATION AND QUALIFYING ACCOUNTS

For Each of the Three Fiscal Years Ended December 31, 2018, 2017 and 2016:

Valuation and Qualifying Accounts (in thousands)	Balance at beginning of period	Acquisitions	Additions charged to costs and expenses	Deductions from reserves	Balance at end of period
Year ended December 31, 2018:					
Allowance for returns	37,862	—	25,111	(23,932)	39,041
Allowance for prompt pay discounts	9,234	—	75,121	(75,242)	9,113
Year ended December 31, 2017:					
Allowance for returns	15,246	—	45,648	(23,032)	37,862
Allowance for prompt pay discounts	6,670	—	80,203	(77,639)	9,234
Year ended December 31, 2016:					
Allowance for returns	14,472	550	17,056	(16,832)	15,246
Allowance for prompt pay discounts	492	684	64,033	(58,539)	6,670

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities and Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

HORIZON PHARMA PLC

Dated: February 27, 2019

By: /s/ TIMOTHY P. WALBERT
Timothy P. Walbert

President, Chief Executive Officer and
Chairman of the Board

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Timothy P. Walbert and Paul W. Hoelscher, and each of them, his or her true and lawful attorneys-in-fact and agents, with full power of substitution and resubstitution, for him or her and in his or her name, place and stead, in any and all capacities, to sign any and all amendments (including post-effective amendments) to this report, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or either of them, or their or his or her substitutes or substitute, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

SIGNATURE	TITLE	DATE
/s/ TIMOTHY P. WALBERT Timothy P. Walbert	President, Chief Executive Officer and Chairman of the Board *(Principal Executive Officer)*	February 27, 2019
/s/ PAUL W. HOELSCHER Paul W. Hoelscher	Executive Vice President and Chief Financial Officer *(Principal Financial Officer)*	February 27, 2019
/s/ MILES W. MCHUGH Miles W. McHugh	Senior Vice President and Chief Accounting Officer *(Principal Accounting Officer)*	February 27, 2019
/s/ MICHAEL GREY Michael Grey	Director	February 27, 2019
/s/ LIAM DANIEL Liam Daniel	Director	February 27, 2019
/s/ JEFF HIMAWAN Jeff Himawan, Ph.D.	Director	February 27, 2019
/s/ RONALD PAULI Ronald Pauli	Director	February 27, 2019
/s/ GINO SANTINI Gino Santini	Director	February 27, 2019
/s/ JAMES SHANNON James Shannon M.D.	Director	February 27, 2019
/s/ H. THOMAS WATKINS H. Thomas Watkins	Director	February 27, 2019
/s/ PASCALE WITZ Pascale Witz	Director	February 27, 2019

Exhibit 4.15

THIRD SUPPLEMENTAL INDENTURE

THIRD SUPPLEMENTAL INDENTURE (this "*Third Supplemental Indenture*"), dated as of November 15, 2018, among Horizon Medicines LLC, a Delaware limited liability company (the "*Guaranteeing Entity*"), and U.S. Bank National Association, as trustee under the Indenture referred to below (the "*Trustee*").

W I T N E S S E T H

WHEREAS, Horizon Pharma, Inc., a Delaware corporation (the "*Prior Issuer*"), and Horizon Pharma USA, Inc., a Delaware corporation (the "*Company*"), have heretofore executed and delivered to the Trustee an indenture (the "*Initial Indenture*"), dated as of October 25, 2016, providing for the issuance of 8.750% Senior Notes due 2024 (the "*Notes*");

WHEREAS, on October 23, 2017, Horizon Pharma Tepro, Inc. executed and delivered to the Trustee a first supplemental indenture to the Initial Indenture (the "*First Supplemental Indenture*");

WHEREAS, on October 19, 2018, Horizon Pharma Services LLC executed and delivered to the Trustee a second supplemental indenture to the Initial Indenture (the "*Second Supplemental Indenture*" and the Initial Indenture, as supplemented by the First Supplemental Indenture and the Second Supplemental Indenture, the "*Indenture*");

WHEREAS, on October 31, 2018, the Prior Issuer merged with and into the Company, with the Company being the surviving entity of such merger and the Prior Issuer ceasing to exist;

WHEREAS, Section 4.18 and Section 10.03 of the Indenture provides that under certain circumstances the Guaranteeing Entity shall execute and deliver to the Trustee a supplemental indenture pursuant to which the Guaranteeing Entity shall unconditionally guarantee all of the Company's Obligations under the Notes and the Indenture on the terms and conditions set forth herein (the "*Note Guarantee*"); and

WHEREAS, pursuant to Section 9.01(j) of the Indenture, the Trustee and the Guaranteeing Entity are authorized to execute and deliver this Third Supplemental Indenture.

NOW, THEREFORE, in consideration of the foregoing and for other good and valuable consideration, the receipt of which is hereby acknowledged, the parties to this Third Supplemental Indenture mutually covenant and agree for the equal and ratable benefit of the Holders of the Notes as follows:

1. CAPITALIZED TERMS. Capitalized terms used herein without definition shall have the meanings assigned to them in the Indenture.

2. AGREEMENT TO GUARANTEE. The Guaranteeing Entity hereby agrees to provide an unconditional Guarantee on the terms and subject to the conditions set forth in the Note Guarantee and in the Indenture including but not limited to Article 10 thereof.

3. NO RECOURSE AGAINST OTHERS. No director, officer, employee, incorporator or stockholder of the Company or any Guarantor, as such, will have any liability for any obligations of the Company or the Guarantors under the Notes, this Indenture, the Note Guarantees or for any claim based on, in respect of, or by reason of, such obligations or their creation. Each Holder of Notes by accepting a Note waives and releases all such liability. The waiver and release are part of the consideration for issuance of the Notes. The waiver may not be effective to waive liabilities under the federal securities laws.

4. NEW YORK LAW TO GOVERN; WAIVER OF JURY TRIAL. THIS THIRD SUPPLEMENTAL INDENTURE SHALL BE GOVERNED BY, AND CONSTRUED IN ACCORDANCE WITH THE LAWS OF THE STATE OF NEW YORK. THE COMPANY AND EACH OF THE GUARANTORS CONSENTS AND IRREVOCABLY SUBMITS TO THE JURISDICTION OF ANY NEW YORK STATE OR U.S. FEDERAL COURT LOCATED IN THE BOROUGH OF MANHATTAN, CITY OF NEW YORK, COUNTY OF NEW YORK, STATE OF NEW YORK IN RELATION TO ANY LEGAL ACTION OR PROCEEDING (I) ARISING OUT OF, RELATING TO OR IN CONNECTION WITH THIS INDENTURE, AS SUPPLEMENTED, THE NOTES, THE GUARANTEES AND ANY RELATED DOCUMENTS AND/OR (II) ARISING UNDER ANY U.S. FEDERAL OR U.S. STATE SECURITIES LAWS IN RESPECT OF THE NOTES, THE GUARANTEES AND ANY SECURITIES ISSUED PURSUANT TO THE TERMS OF THE INDENTURE, AS SUPPLEMENTED. THE COMPANY AND EACH OF THE GUARANTORS WAIVES ANY OBJECTION TO PROCEEDINGS IN ANY SUCH COURTS, WHETHER ON THE GROUND OF VENUE OR ON THE GROUND THAT THE PROCEEDINGS HAVE BEEN BROUGHT IN AN INCONVENIENT FORUM. THE COMPANY AND EACH OF THE GUARANTORS, TO THE EXTENT ORGANIZED OUTSIDE OF THE UNITED STATES, SHALL APPOINT HORIZON PHARMA USA, INC. (HORIZON PHARMA USA, INC., 150 SOUTH SAUNDERS ROAD, LAKE FOREST, IL 60045), AS ITS AGENT FOR SERVICE OF PROCESS IN ANY SUCH SUIT, ACTION OR PROCEEDING AND AGREES THAT SERVICE OF PROCESS UPON SAID AUTHORIZED AGENT SHALL BE DEEMED IN EVERY RESPECT EFFECTIVE SERVICE OF PROCESS UPON IT IN ANY SUCH SUIT, ACTION OR PROCEEDING. THE COMPANY AND EACH OF THE GUARANTORS AGREES TO DELIVER, UPON THE EXECUTION AND DELIVERY OF THIS THIRD SUPPLEMENTAL INDENTURE, A WRITTEN ACCEPTANCE BY SUCH AGENT OF ITS APPOINTMENT AS SUCH AGENT. THE COMPANY AND EACH OF THE GUARANTORS, TO THE EXTENT ORGANIZED OUTSIDE OF THE UNITED STATES, FURTHER AGREES TO TAKE ANY AND ALL ACTION, INCLUDING THE FILING OF ANY AND ALL SUCH DOCUMENTS AND INSTRUMENTS, AS MAY BE REASONABLY NECESSARY TO CONTINUE SUCH DESIGNATION AND APPOINTMENT OF CT CORPORATION SYSTEM IN FULL FORCE AND EFFECT FOR SO LONG AS THE INDENTURE, AS SUPPLEMENTED, REMAINS IN FORCE. THE COMPANY, THE TRUSTEE AND EACH OF THE GUARANTORS HEREBY IRREVOCABLY WAIVES, TO THE FULLEST EXTENT PERMITTED BY APPLICABLE LAW, ANY AND ALL RIGHT TO TRIAL BY JURY IN ANY LEGAL PROCEEDING ARISING OUT OF OR RELATING TO THIS THIRD SUPPLEMENTAL INDENTURE OR THE TRANSACTIONS CONTEMPLATED HEREBY.

5. COUNTERPARTS. The parties may sign any number of copies of this Third Supplemental Indenture. Each signed copy (which may be provided via facsimile or other electronic transmission) shall be an original, but all of them together represent the same agreement.

6. EFFECT OF HEADINGS. The Section headings herein are for convenience only and shall not affect the construction hereof.

7. THE TRUSTEE. The Trustee shall not be responsible in any manner whatsoever for or in respect of the validity or sufficiency of this Third Supplemental Indenture or for or in respect of the recitals contained herein, all of which recitals are made solely by the Guaranteeing Entity.

IN WITNESS WHEREOF, the parties hereto have caused this Third Supplemental Indenture to be duly executed and attested, all as of the date first above written.

Dated: November 15, 2018

HORIZON MEDICINES LLC

By: /s/ Paul W. Hoelscher
Name: Paul W. Hoelscher
Title: Executive Vice President
and Chief Financial Officer

U.S. BANK NATIONAL ASSOCIATION,
as Trustee

By: /s/ Raymond S. Haverstock
Name: Raymond S. Haverstock
Title: Vice President

Exhibit 4.16

SEVENTH SUPPLEMENTAL INDENTURE

SEVENTH SUPPLEMENTAL INDENTURE (this "*Seventh Supplemental Indenture*"), dated as of November 15, 2018, among Horizon Medicines LLC, a Delaware limited liability company (the "*Guaranteeing Entity*") and an indirect subsidiary of Horizon Pharma USA, Inc., a Delaware corporation (the "*Company*"), and U.S. Bank National Association, as trustee under the Indenture referred to below (the "*Trustee*").

W I T N E S S E T H

WHEREAS, Horizon Pharma Financing, Inc., a Delaware corporation (the "*Escrow Issuer*") has heretofore executed and delivered to the Trustee an indenture (the "*Initial Indenture*"), dated as of April 29, 2015, providing for the issuance of 6.625% Senior Notes due 2023 (the "*Notes*");

WHEREAS, on May 7, 2015, the Escrow Issuer merged with and into Horizon Pharma, Inc., a Delaware corporation (the "*Prior Issuer*"), with the Prior Issuer being the surviving entity of such merger and the Escrow Issuer ceasing to exist (the "*2015 Merger*");

WHEREAS, in connection with the 2015 Merger, the Prior Issuer, the Escrow Issuer and the Guarantors party thereto executed and delivered to the Trustee a first supplemental indenture to the Initial Indenture (the "*First Supplemental Indenture*");

WHEREAS, on May 10, 2016, Horizon Pharma Rheumatology LLC executed and delivered to the Trustee a second supplemental indenture to the Initial Indenture (the "*Second Supplemental Indenture*");

WHEREAS, on October 25, 2016, Raptor Pharmaceutical Corp. and Raptor Pharmaceuticals Inc. executed and delivered to the Trustee a third supplemental indenture to the Initial Indenture (the "*Third Supplemental Indenture*");

WHEREAS, on October 23, 2017, Horizon Pharma Tepro, Inc. executed and delivered to the Trustee a fourth supplemental indenture to the Initial Indenture (the "*Fourth Supplemental Indenture*");

WHEREAS, on October 19, 2018, Horizon Pharma Services LLC executed and delivered to the Trustee a fifth supplemental indenture to the Initial Indenture (the "*Fifth Supplemental Indenture*";

WHEREAS, on October 31, 2018, the Prior Issuer merged with and into the Company, with the Company being the surviving entity of such merger and the Prior Issuer ceasing to exist (the "*2018 Merger*");

WHEREAS, in connection with the 2018 Merger, the Company executed and delivered to the Trustee a sixth supplemental indenture to the Initial Indenture (the "*Sixth Supplemental Indenture*" and the Initial Indenture as supplemented by the First Supplemental Indenture, the Second Supplemental Indenture, the Third Supplemental Indenture; the Fourth Supplemental Indenture, the Fifth Supplemental Indenture and the Sixth Supplemental Indenture, the "*Indenture*");

WHEREAS, Section 4.18 and Section 10.03 of the Indenture provides that under certain circumstances the Guaranteeing Entity shall execute and deliver to the Trustee a supplemental indenture pursuant to which the Guaranteeing Entity shall unconditionally guarantee all of the Company's Obligations under the Notes and the Indenture on the terms and conditions set forth herein (the "*Note Guarantee*"); and

WHEREAS, pursuant to Section 9.01(j) of the Indenture, the Trustee and the Guaranteeing Entity are authorized to execute and deliver this Seventh Supplemental Indenture.

NOW, THEREFORE, in consideration of the foregoing and for other good and valuable consideration, the receipt of which is hereby acknowledged, the parties to this Seventh Supplemental Indenture mutually covenant and agree for the equal and ratable benefit of the Holders of the Notes as follows:

1. CAPITALIZED TERMS. Capitalized terms used herein without definition shall have the meanings assigned to them in the Indenture.

2. AGREEMENT TO GUARANTEE. The Guaranteeing Entity hereby agrees to provide an unconditional Guarantee on the terms and subject to the conditions set forth in the Note Guarantee and in the Indenture including but not limited to Article 10 thereof.

3. NO RECOURSE AGAINST OTHERS. No director, officer, employee, incorporator or stockholder of the Company or any Guarantor, as such, will have any liability for any obligations of the Company or the Guarantors under the Notes, this Indenture, the Note Guarantee or for any claim based on, in respect of, or by reason of, such obligations or their creation. Each Holder of Notes by accepting a Note waives and releases all such liability. The waiver and release are part of the consideration for issuance of the Notes. The waiver may not be effective to waive liabilities under the federal securities laws.

4. NEW YORK LAW TO GOVERN; WAIVER OF JURY TRIAL. THIS SEVENTH SUPPLEMENTAL INDENTURE SHALL BE GOVERNED BY, AND CONSTRUED IN ACCORDANCE WITH THE LAWS OF THE STATE OF NEW YORK. EACH OF THE COMPANY AND THE GUARANTORS CONSENTS AND IRREVOCABLY SUBMITS TO THE JURISDICTION OF ANY NEW YORK STATE OR U.S. FEDERAL COURT LOCATED IN THE BOROUGH OF MANHATTAN, CITY OF NEW YORK, COUNTY OF NEW YORK, STATE OF NEW YORK IN RELATION TO ANY LEGAL ACTION OR PROCEEDING (I) ARISING OUT OF, RELATING TO OR IN CONNECTION WITH THIS INDENTURE, AS SUPPLEMENTED, THE NOTES, THE GUARANTEES AND ANY RELATED DOCUMENTS AND/OR (II) ARISING UNDER ANY U.S. FEDERAL OR U.S. STATE SECURITIES LAWS IN RESPECT OF THE NOTES, THE GUARANTEES AND ANY SECURITIES ISSUED PURSUANT TO THE TERMS OF THE INDENTURE, AS SUPPLEMENTED. EACH OF THE COMPANY AND THE GUARANTORS WAIVES ANY OBJECTION TO PROCEEDINGS IN ANY SUCH COURTS, WHETHER ON THE GROUND OF VENUE OR ON THE GROUND THAT THE PROCEEDINGS HAVE BEEN BROUGHT IN AN INCONVENIENT FORUM. EACH OF THE COMPANY AND THE GUARANTORS, TO THE EXTENT ORGANIZED OUTSIDE OF THE UNITED STATES, SHALL APPOINT HORIZON PHARMA USA, INC. (HORIZON PHARMA USA, INC., 150 SOUTH SAUNDERS ROAD, LAKE FOREST, IL 60045), AS ITS AGENT FOR SERVICE OF PROCESS IN ANY SUCH SUIT, ACTION OR PROCEEDING AND AGREES THAT SERVICE OF PROCESS UPON SAID AUTHORIZED AGENT SHALL BE DEEMED IN EVERY RESPECT EFFECTIVE SERVICE OF PROCESS UPON IT IN ANY SUCH SUIT, ACTION OR PROCEEDING. EACH OF THE COMPANY AND THE GUARANTORS AGREES TO DELIVER, UPON THE EXECUTION AND DELIVERY OF THIS SEVENTH SUPPLEMENTAL INDENTURE, A WRITTEN ACCEPTANCE BY SUCH AGENT OF ITS APPOINTMENT AS SUCH AGENT. EACH OF THE COMPANY AND THE GUARANTORS, TO THE EXTENT ORGANIZED OUTSIDE OF THE UNITED STATES, FURTHER AGREES TO TAKE ANY AND ALL ACTION, INCLUDING THE FILING OF ANY AND ALL SUCH DOCUMENTS AND INSTRUMENTS, AS MAY BE REASONABLY NECESSARY TO CONTINUE SUCH DESIGNATION AND APPOINTMENT OF CT CORPORATION SYSTEM IN FULL FORCE AND EFFECT FOR SO LONG AS THE INDENTURE, AS SUPPLEMENTED, REMAINS IN FORCE. THE COMPANY, THE TRUSTEE AND EACH OF THE GUARANTORS HEREBY IRREVOCABLY WAIVES, TO THE FULLEST EXTENT PERMITTED BY APPLICABLE LAW, ANY AND ALL RIGHT TO TRIAL BY JURY IN ANY LEGAL PROCEEDING ARISING OUT OF OR RELATING TO THIS SEVENTH SUPPLEMENTAL INDENTURE OR THE TRANSACTIONS CONTEMPLATED HEREBY.

5. COUNTERPARTS. The parties may sign any number of copies of this Seventh Supplemental Indenture. Each signed copy (which may be provided via facsimile or other electronic transmission) shall be an original, but all of them together represent the same agreement.

6. EFFECT OF HEADINGS. The Section headings herein are for convenience only and shall not affect the construction hereof.

7. THE TRUSTEE. The Trustee shall not be responsible in any manner whatsoever for or in respect of the validity or sufficiency of this Seventh Supplemental Indenture or for or in respect of the recitals contained herein, all of which recitals are made solely by the Guaranteeing Entity.

IN WITNESS WHEREOF, the parties hereto have caused this Seventh Supplemental Indenture to be duly executed and attested, all as of the date first above written.

Dated: November 15, 2018

HORIZON MEDICINES LLC

By: /s/ Paul W. Hoelscher
Name: Paul W. Hoelscher
Title: Executive Vice President
and Chief Financial Officer

[Signature Page to Seventh Supplemental Indenture]

U.S. BANK NATIONAL ASSOCIATION,
as Trustee

By: /s/ Raymond S. Haverstock
Name: Raymond S. Haverstock
Title: Vice President

[Signature Page to Seventh Supplemental Indenture]

Horizon Pharma Public Limited Company
Non-Employee Director Compensation Policy
Amended Effective: October 29, 2018

Each member of the Board of Directors (the ***"Board"***) of Horizon Pharma Public Limited Company (the ***"Company"***) other than (1) any member who is affiliated with any holder of more than 5% of the Company's ordinary shares or (2) any member serving as an employee of the Company or any of its subsidiaries (each such member, a ***"Director"***) will receive the following compensation for his or her Board service. The determination of whether a member of the Board meets the requirements to be eligible to receive compensation as an eligible Director under this Policy will be determined as of the date such cash compensation is otherwise payable, or the date such equity compensation would be granted, as applicable.

Annual Cash Compensation

The annual cash compensation amount set forth below is payable in equal quarterly installments, payable in arrears on the last day of each fiscal quarter in which the service occurred. If a Director joins the Board at a time other than effective as of the first day of a fiscal quarter, each annual retainer/fee set forth below will be pro-rated based on days served in the applicable fiscal year, with the pro-rated amount paid for the first fiscal quarter in which the Director provides the service, and regular full quarterly payments thereafter. All annual cash fees are vested upon payment.

1. Annual Board Service Retainer:
    a. Non-Executive Chairman of the Board/Lead Independent Director: $100,000
    b. All other Directors: $60,000
2. Annual Committee Chair Service Fee:
    a. Chairman of the Audit Committee: $30,000
    b. Chairman of the Compensation Committee: $20,000
    c. Chairman of the Nominating & Corporate Governance Committee: $15,000
    d. Chairman of the Transaction Committee: $20,000
3. Annual Committee Member (non-Chair) Service Fee:
    a. Audit Committee: $15,000
    b. Compensation Committee: $10,000
    c. Nominating & Corporate Governance Committee: $7,500
    d. Transaction Committee: $12,500

Equity Compensation

The equity compensation set forth below will be granted under the Horizon Pharma Public Limited Company 2014 Non-Employee Equity Plan, as may be amended from time to time (the ***"Plan"***).

1. Initial Grant: On the date of any Director's initial appointment or election to the Board, the Director will be automatically, and without further action by the Board, granted restricted stock units with an aggregate value equal to $400,000, prorated based on the number days between such Director's start date and the first anniversary of the date of the annual shareholder meeting of the Company that most recently preceded such start date (the "***Initial Grant***"); *provided*, that if a Director's initial election to the Board occurs at an annual shareholder meeting of the Company, such Director will receive only the Annual Grant (as defined below) for such annual shareholder meeting and not a separate Initial Grant. The restricted stock units will vest in full upon the first anniversary of the date of the annual shareholder meeting of the Company that most recently preceded such Director's start date, subject to the Director's Continuous Service (as defined in the Plan) through such vesting date. A Director who, in the one year prior to his or her initial election to serve on the Board as a non-employee director, served as an employee of the Company or one of its subsidiaries will not be eligible for an Initial Grant.

2. Annual Grant: On the date of each annual shareholder meeting of the Company, each Director will be automatically, and without further action by the Board, granted restricted stock units with an aggregate value of $400,000 (the "***Annual Grant***"). The restricted stock units will vest in full upon the first anniversary of the date of grant, subject to the Director's Continuous Service through such vesting date.

Expenses

The Company will reimburse each Director for ordinary, necessary and reasonable out-of-pocket travel expenses to cover in-person attendance at and participation in Board and/or Committee meetings; *provided*, that Directors timely submit to the Company appropriate documentation substantiating such expenses. In addition, the Company will reimburse each Director up to $15,000 annually for financial counseling services, including (1) personal financial planning, (2) estate planning and (3) preparation of tax returns and tax planning for the Directors and/or their dependent children.

Exhibit 10.69

AMENDED AND RESTATED EXECUTIVE EMPLOYMENT AGREEMENT BY AND BETWEEN HORIZON PHARMA, INC., HORIZON PHARMA USA, INC. AND GEOFF CURTIS

This Amended and Restated Executive Employment Agreement (hereinafter referred to as the "***Agreement***"), is entered into by and between Horizon Pharma, Inc., a Delaware corporation, and its wholly owned subsidiary, Horizon Pharma USA, Inc., a Delaware corporation, each having a principal place of business at 150 S. Saunders Road, Lake Forest, IL 60045, (hereinafter referred to together as the "***Company***") and Geoff Curtis (hereinafter referred as to the "***Executive***"). The terms of this Agreement shall be effective commencing August 1, 2018 (the "***Effective Date***").

RECITALS

WHEREAS, the Executive previously entered into an Executive Employment Agreement with the Company dated February 26, 2016 (the "***Prior Agreement***").

WHEREAS, the Company desires assurance of the continued association and services of the Executive in order to continue to retain the Executive's experience, skills, abilities, background and knowledge, and is willing to continue to engage the Executive's services on the terms and conditions set forth in this Agreement; and

WHEREAS, Executive desires to be in the continued employ of the Company, and is willing to accept such continued employment on the terms and conditions set forth in this Agreement, which as of the Effective Date shall replace and supersede in its entirety the terms of the Prior Agreement.

AGREEMENT

1. Employment.

1.1 Term. The Executive originally commenced employment with the Company on April 1, 2015. The Company hereby agrees to continue to employ the Executive, and the Executive hereby accepts continued employment by the Company, upon the terms and conditions set forth in this Agreement. Executive's employment shall be governed under the terms set forth in this Agreement beginning on the Effective Date and shall continue until it is terminated pursuant to Section 4 herein (hereinafter referred to as the "***Term***").

1.2 Title. From and after the Effective Date the Executive will have the title of executive vice president, corporate affairs and chief communications officer (such position held by Executive during such period is hereinafter referred to as "***EVP CCO***" and Executive shall continue to serve in such other capacity or capacities commensurate with his position as EVP CCO as the President and CEO of the Company may from time to time prescribe.

1.3 Duties. The Executive shall do and perform all services, acts or things necessary or advisable to manage and conduct the business of the Company and shall have the authority and responsibilities which are generally associated with the position of EVP CCO including being responsible for the Company's business units. The Executive shall report to the President and CEO.

1.4 Policies and Practices. The employment relationship between the parties shall be governed by this Agreement and the policies and practices established by the Company and the Board of Directors (hereinafter referred to as the "***Board***"). In the event that the terms of this Agreement differ from or are in conflict with the Company's policies or practices or the Company's Employee Handbook, this Agreement shall control.

1.5 Location. The Executive shall perform the services the Executive is required to perform pursuant to this Agreement in at the Company's U.S. Headquarters in Lake Forest Illinois. The Company may from time to time require the Executive to travel temporarily to other locations outside of Lake Forest, Illinois area in connection with the Company's business.

2. Loyalty of Executive.

2.1 Loyalty. During the Executive's employment by the Company, the Executive shall devote the Executive's business energies, interest, abilities and productive time to the proper and efficient performance of Executive's duties under this Agreement. Subject to the prior written consent of the President and CEO, the Executive is permitted to serve on the board of directors of one other company, so long as the other company does not compete with the Company.

2.2 Exclusive Employment. Except with the prior written consent of the Chief Executive Officer, Executive shall not, during the term of this Agreement, undertake or engage in any other employment, occupation or business enterprise, other than ones in which Executive is a passive investor. The Company specifically agrees that the Executive may engage in any civic and not-for-profit board membership or activities (including, but not limited to Executive role on the board of the Arthritis Foundation) so long as such activities do not materially interfere with the performance of his duties hereunder or present a conflict of interest with the Company.

2.3 Agreement not to Participate in Company's Competitors. During the Term of this Agreement, the Executive agrees not to acquire, assume or participate in, directly or indirectly, any position, investment or interest known by Executive to be adverse or antagonistic to the Company, its business or prospects, financial or otherwise or in any company, person or entity that is, directly or indirectly, in competition with the business of the Company or any of its affiliates. Notwithstanding the foregoing, Executive may invest and/or maintain investments in any public or private entity up to an amount of 2% of an entity's fully diluted shares and on a passive basis.

3. Compensation to Executive.

3.1 Base Salary. The Company shall pay the Executive a base salary at the initial annualized rate of four hundred sixty thousand dollars ($460,000.00) per year, subject to standard deductions and withholdings, or such higher rate as may be determined from time to time by the Board or the compensation committee thereof (hereinafter referred to as the "***Base Salary***") . Such Base Salary shall be paid in accordance with the Company's standard payroll practice. Payments of salary installments shall be made no less frequently than once per month. Executive's Base Salary will be reviewed annually and Executive shall be eligible to receive a salary increase (but not decrease) annually in an amount to be determined by the Board or the compensation committee thereof in its sole and exclusive discretion. Once increased, the new salary shall become the Base Salary for purposes of this Agreement and shall not be reduced without the Executive's written consent. Any material reduction in the Base Salary of the Executive, without his written consent, may be deemed Good Reason as set forth in and subject to Section 4.5.2 of this Agreement.

3.2 Discretionary Bonus. Provided the Executive meets the conditions stated in this Section 3.2, the Executive shall be eligible for an annual discretionary bonus (hereinafter referred to as the "***Bonus***") with a target amount of fifty percent (50%) of the Executive's Base Salary, subject to standard deductions and withholdings, based on the Board's determination, in good faith, and based upon the Executive's individual achievement and company performance objectives as set by the Board or the compensation committee thereof, of whether the Executive has met such performance milestones as are established for the Executive by the Board or the compensation committee thereof, in good faith, in consultation with the Executive (hereinafter referred to as the "***Performance Milestones***") . The Performance Milestones will be based on certain factors including, but not limited to, the Executive's performance and the Company's financial performance. The Executive's Bonus target will be reviewed annually and may be adjusted by the Board or the compensation committee thereof in its discretion, provided however, that the Bonus target may only be materially reduced upon Executive's written consent. The Executive must be employed on the date the Bonus is awarded to be eligible for the Bonus, subject to the termination provisions thereof. The Bonus shall be paid during the calendar year following the performance calendar year.

3.3 Prior Equity Grants. All Company equity awards previously granted to Executive shall continue in effect from and following the Effective Date in accordance with their existing terms. Executive may be eligible to receive additional grants of Company equity awards in the sole discretion and subject to the approval of the Board.

3.4 Legal Review. Upon the Executive's submission of appropriate proof and verification of reasonable and customary legal fees incurred by the Executive in obtaining legal advice associated with the review, preparation, approval, and execution of this Agreement, the Company shall pay for up to $10,000.00 of such legal fees subject to receipt of appropriate proof and verification of such legal fees no later than sixty (60) days of receipt of an invoice for legal services from the Executive and/or his attorneys.

To be eligible for reimbursement, the invoice must be submitted no later than ninety (90) days after the legal fees are incurred.

3.5 Changes to Compensation. The Executive's compensation may be changed from time to time by mutual agreement of the Executive and the Company. In the event that the Executive's Base Salary is materially decreased without his written consent, said decrease will be Good Reason for the Executive to terminate the Agreement as set forth in and subject to Section 4.5.2 of this Agreement. Without limitation, Executive shall be entitled to participate in the Company sponsored 401k and Deferred Compensation plans and other compensation/benefit plans in which Executive now participates.

3.6 Taxes. All amounts paid under this Agreement to the Executive by the Company will be paid less applicable tax withholdings and any other withholdings required by law or authorized by the Executive.

3.7 Benefits. The Executive shall, in accordance with Company policy and the terms of the applicable plan documents, be eligible to participate in benefits under any executive benefit plan or arrangement which may be in effect from time to time and made available to the Company's executives or key management employees, provided, however, that the Executive shall be entitled to at least four (4) weeks of paid vacation annually.

3.8 Expense Reimbursement. The Company shall reimburse the Executive for all reasonable and necessary out-of-pocket expenses incurred by Executive in the performance of his executive duties and responsibilities hereunder, including without limitation expenses incurred for all of Executive's travel and accommodations, subject to the Company's normal policies and procedures, including without limitation, for expense verification and documentation (it being understood by the parties hereto that the Executive's duties hereunder will differ in scope and intensity from Company's non -executive employees).

4. Termination.

4.1 Termination by the Company. The Executive's employment with the Company may be terminated only under the following conditions:

4.1.1 Termination for Death or Disability. The Executive's employment with the Company shall terminate effective upon the date of the Executive's death or "***Complete Disability***" (as defined in Section 4.5.1), provided, however, that this Section 4.1.1 shall in no way limit the Company's obligations to provide such reasonable accommodations to the Executive and/or his heirs as may be required by law.

4.1.2 Termination by the Company For Cause. The Company may terminate the Executive's employment under this Agreement for "***Cause***" (as defined in Section 4.5.3) by delivery of written notice to the Executive specifying the Cause or Causes relied upon for such termination, provided that such notice is delivered within two

(2) months following the occurrence or discovery of any event or events constituting "***Cause***". Any notice of termination given pursuant to this Section 4.1.2 shall effect termination as of the date of the notice or such date as specified in the notice. The Executive shall have the right to appear before the CEO before any termination for Cause becomes effective and binding upon the Executive.

4.1.3 Termination by the Company Without Cause. The Company may terminate the Executive's employment under this Agreement at any time and for any reason or no reason subject to the requirements set out in Section 4.4 of this Agreement. Such termination shall be effective on the date the Executive is so informed or as otherwise specified by the Company, pursuant to notice requirements set forth in Section 6 of this Agreement.

4.2 Termination By The Executive. The Executive may terminate his employment with the Company at any time and for any reason or no reason, including, but not limited, to the following conditions:

4.2.1 Good Reason. The Executive may terminate his employment under this Agreement for "***Good Reason***" (as defined below in Section 4.5.2) by delivery of written notice to the Company specifying the Good Reason(s) relied upon by the Executive for such termination in accordance with the requirements of such section.

4.2.2 Without Good Reason. The Executive may terminate the Executive's employment hereunder for other than Good Reason upon thirty (30) days written notice to the Company.

4.3 Termination by Mutual Agreement of the Parties. The Executive's employment pursuant to this Agreement may be terminated at any time upon a mutual agreement in writing of the parties. Any such termination of employment shall have the consequences specified in such mutual agreement.

4.4 Compensation to Executive Upon Termination. In connection with any termination of the Executive's employment for any reason, the Executive or the Executive's estate, as applicable, shall be entitled to any amounts payable to the Executive or the Executive's beneficiaries subject to and accordance with the terms of the Company's employee welfare benefit plans or policies (excluding any severance pay), as well as any other compensation and benefits specified in this Agreement.

4.4.1 Death or Complete Disability. If the Executive's employment shall be terminated by his death or Complete Disability as provided in Section 4.1.1, the Company shall pay to Executive, and/or Executive's heirs, all earned but unpaid Base Salary earned through the date of termination, any earned but unpaid discretionary Bonuses for any prior period at such time as bonuses would have been paid if the Executive remained employed, all accrued but unpaid business expenses, and all accrued but unused vacation time earned through the date of termination at the rate in effect at the time of termination (hereinafter collectively referred to as the "***Accrued Amounts***"), less standard deductions and withholdings. The Executive shall also be eligible to receive a

pro-rated Bonus for the year in which the date of termination occurs, as determined by the Board or the Compensation Committee of the Board based on Executive's then -current target Bonus and based on actual performance and the period of the year he was employed (hereinafter referred to as the "***Pro-rata Bonus***"), less standard deductions and withholdings, to be paid as a lump sum within thirty (30) days after the date of termination.

4.4.2 With Cause or Without Good Reason. If the Executive's employment shall be terminated by the Company for Cause, or if the Executive terminates employment hereunder without Good Reason, the Company shall pay the Executive's Base Salary earned through the date of termination, his accrued but unpaid business expenses and his accrued and unused vacation benefits earned through the date of termination at the rate in effect at the time of termination, less standard deductions and withholdings.

4.4.3 Without Cause or For Good Reason.

(i) Not in Connection With a Change in Control. If the Company terminates the Executive's employment without Cause or the Executive terminates his employment for Good Reason, and Section 4.4.3(ii) below does not apply, the Company shall pay the Accrued Amounts subject to standard deductions and withholdings, to be paid as a lump sum no later than thirty (30) days after the date of termination. In addition, subject to the limitations stated in this Agreement and upon the Executive's furnishing to the Company an executed waiver and release of claims (the form of which is attached hereto as Exhibit A) (the "***Release***") within the applicable time period set forth therein, but in no event later than forty-five days following termination of employment and permitting such Release to become effective in accordance with its terms (the "***Release Effective Date***"), and subject to Executive entering into no later than the Release Effective Date a non-competition agreement to be effective during the Severance Period (as defined below), substantially similar to Section 2.3, and continuing to abide by its terms during the Severance Period, the Executive shall be entitled to:

(a) the equivalent of the Executive's Base Salary in effect at the time of termination will continue to be paid for a period of twelve (12) months following the date of termination (hereinafter referred to as the "***Non Change in Control Severance Period***"), less standard deductions and withholdings, to be paid during the Non Change in Control Severance Period according to the Company's regular payroll practices, subject to any delay in payment required by Section 4.6 in connection with the Release Effective Date; and

(b) in the event the Executive timely elects continued coverage under COBRA, the Company will continue to pay the same portion of Executive's COBRA health insurance premium as the percentage of health insurance premiums that it paid during the Executive's employment, including any amounts that Company paid for benefits to the qualifying family members of the Executive, following the date of termination up until the earlier of either (i) the last day of the Non

Change in Control Severance Period or, (ii) the date on which the Executive begins full-time employment with another company or business entity which offers comparable health insurance coverage to the Executive (such period, the "***Non Change in Control COBRA Payment Period***"). Notwithstanding the foregoing, if the Company determines, in its sole discretion, that the Company cannot provide the COBRA premium benefits without potentially incurring financial costs or penalties under applicable law (including, without limitation, Section 2716 of the Public Health Service Act), the Company shall in lieu thereof pay Executive a taxable cash amount, which payment shall be made regardless of whether the Executive or his qualifying family members elect COBRA continuation coverage (the "***Health Care Benefit Payment***"). The Health Care Benefit Payment shall be paid in monthly or bi-weekly installments on the same schedule that the COBRA premiums would otherwise have been paid to the insurer. The Health Care Benefit Payment shall be equal to the amount that the Company otherwise would have paid for COBRA insurance premiums (which amount shall be calculated based on the premium for the first month of coverage), and shall be paid until the expiration of the Non Change in Control COBRA Payment Period.

(ii) In Connection With a Change in Control. If the Company (or its successor) terminates the Executive's employment without Cause or the Executive terminates his employment for Good Reason within the period commencing three (3) months immediately prior to a Change in Control of the Company and ending eighteen (18) months immediately following a Change in Control of the Company (as defined in Section 4.5.4 of this Agreement), the Executive shall receive the Accrued Amounts subject to standard deductions and withholdings, to be paid as a lump sum no later than thirty (30) days after the date of termination. In addition, subject to the limitations stated in this Agreement and upon the Executive's furnishing to the Company (or its successor) an executed Release within the applicable time period set forth therein, but in no event later than forty-five days following termination of employment and permitting such Release to become effective in accordance with its terms, and subject to Executive entering into no later than the Release Effective Date a non-competition agreement to be effective during the Severance Period, substantially similar to Section 2.3, and continuing to abide by its terms during the Severance Period, then in lieu of (and not additional to) the benefits provided pursuant to Section 4.4.3(i) above, the Executive shall be entitled to:

(a) the equivalent of the Executive's Base Salary in effect at the time of termination will continue to be paid for a period of eighteen (18) months following the date of termination (hereinafter referred to as the "***Change in Control Severance Period***"), less standard deductions and withholdings, to be paid during the Change in Control Severance Period according to the Company's regular payroll practices, subject to any delay in payment required by Section 4.6 in connection with the Release Effective Date;

(b) one and half (1.5) times Executive's target Bonus in effect at the time of termination, or if none, one and half (1.5) times the last target

Bonus in effect for Executive, less standard deductions and withholdings, to be paid in a lump sum within ten (10) days following the later of (i) the Release Effective Date, or (ii) the effective date of the Change in Control; and

(c) in the event the Executive timely elects continued coverage under COBRA, the Company will continue to pay the same portion of Executive's COBRA health insurance premium as the percentage of health insurance premiums that it paid during the Executive's employment, including any amounts that Company paid for benefits to the qualifying family members of the Executive, following the date of termination until the expiration of the Change in Control Severance Period. Notwithstanding the foregoing, if the Company determines, in its sole discretion, that the Company cannot provide the COBRA premium benefits without potentially incurring financial costs or penalties under applicable law (including, without limitation, Section 2716 of the Public Health Service Act), the Company shall in lieu thereof pay Executive the Health Care Benefit Payment, which payment shall be made regardless of whether the Executive or his qualifying family members elect COBRA continuation coverage. The Health Care Benefit Payment shall be paid in monthly or bi-weekly installments on the same schedule that the COBRA premiums would otherwise have been paid to the insurer. The Health Care Benefit Payment shall be equal to the amount that the Company otherwise would have paid for COBRA insurance premiums (which amount shall be calculated based on the premium for the first month of coverage), and shall be paid until the expiration of the Change in Control Severance Period.

(iii) No Duplication of Benefits. For the avoidance of doubt, in no event will Executive be entitled to benefits under Section 4.4.3(i) and Section 4.4.3(ii). If Executive commences to receive benefits under Section 4.4.3(i) due to a qualifying termination prior to a Change in Control and thereafter becomes entitled to benefits under Section 4.4.3(ii), any benefits previously provided to Executive under Section 4.4.3(i) shall offset the benefits to be provided to Executive under Section 4.4.3(ii) and shall be deemed to have been provided to Executive pursuant to Section 4.4.3(ii).

4.4.4 Equity Award Acceleration.

(i) Not in Connection With a Change in Control. In the event that the Executive's employment is terminated without Cause or for Good Reason and Section 4.4.4 (ii) below does not apply, the vesting of any equity awards granted to Executive that vest solely subject to Executive's continued services to the Company (the "***Time-Based Vesting Equity Awards***") shall be deemed vested and immediately exercisable (if applicable) by the Executive with respect to such number of shares as determined in accordance with their applicable vesting schedules as if Executive had provided an additional twelve (12) months of services as of the date of termination. Treatment of any performance based vesting equity awards granted to Executive will in all cases be governed solely by the terms of the equity award plan and/or agreement under which they were granted and will not be eligible to accelerate

vesting pursuant to the foregoing provision.

(ii) In Connection With a Change in Control. In the event that the Executive's employment is terminated without Cause or for Good Reason within the three (3) months immediately preceding or during the eighteen (18) months immediately following a Change in Control of the Company (as defined in Section 4.5.4 of this Agreement), the vesting of any Time-Based Vesting Equity Awards granted to Executive shall be fully accelerated such that on the effective date of such termination (or if later, the date of the Change in Control) one hundred percent (100%) of any Time-Based Vesting Equity Awards granted to Executive prior to such termination shall be fully vested and immediately exercisable, if applicable, by the Executive. Treatment of any performance based vesting equity awards granted to Executive will in all cases be governed solely by the terms of the equity award plan and/or agreement under which they were granted and will not be eligible to accelerate vesting pursuant to the foregoing provision.

(iii) Release and Waiver. Any equity vesting acceleration pursuant to this Section 4.4.4 shall be conditioned upon and subject to the Executive's delivery to the Company of a fully effective Release in accordance with the terms specified by Section 4.4.3 hereof and such vesting acceleration benefit shall be in addition to the benefits provided by Section 4.4.3 hereof.

4.5 Definitions. For purposes of this Agreement, the following terms shall have the following meanings:

4.5.1 Complete Disability. "***Complete Disability***" shall mean the inability of the Executive to perform the Executive's duties under this Agreement, whether with or without reasonable accommodation, because the Executive has become permanently disabled within the meaning of any policy of disability income insurance covering employees of the Company then in force. In the event the Company has no policy of disability income insurance covering employees of the Company in force when the Executive becomes disabled, the term "***Complete Disability***" shall mean the inability of the Executive to perform the Executive's duties under this Agreement, whether with or without reasonable accommodation, by reason of any incapacity, physical or mental, which the Board, based upon medical advice or an opinion provided by a licensed physician, determines to have incapacitated the Executive from satisfactorily performing all of the Executive's usual services for the Company, with or without reasonable accommodation, for a period of at least one hundred eighty (180) days during any twelve (12) month period that need not be consecutive.

4.5.2 Good Reason. "***Good Reason***" for the Executive to terminate the Executive's employment hereunder shall mean the occurrence of any of the following events without the Executive's consent:

(i) a material reduction in the Executive's duties, authority, or responsibilities relative to the duties, authority, or responsibilities in effect immediately

prior to such reduction, including by way of example, having the same title, duties, authority and responsibilities at a subsidiary level following a Change in Control;

(ii) the relocation of the Executive's primary work location to a point more than fifty (50) miles from the Executive's current work location set forth in Section 1.5 that requires a material increase in Executive's one-way driving distance;

(iii) a material reduction by the Company of the Executive's Base Salary or annual target Bonus opportunity, without the written consent of the Executive, as initially set forth herein or as the same may be increased from time to time pursuant to this Agreement; and

(iv) a material breach by the Company of Section 1.2 of this Agreement.

Provided, however that, such termination by the Executive shall only be deemed for Good Reason pursuant to the foregoing definition if (i) the Company is given written notice from the Executive within sixty (60) days following the first occurrence of the condition that he considers to constitute Good Reason describing the condition and the Company fails to satisfactorily remedy such condition within thirty (30) days following such written notice, and (ii) the Executive terminates employment within thirty (30) days following the end of the period within which the Company was entitled to remedy the condition constituting Good Reason but failed to do so.

4.5.3 Cause. "***Cause***" for the Company to terminate Executive's employment hereunder shall mean the occurrence of any of the following events, as determined reasonably and in good faith by the Board or a committee designated by the Board:

(i) the Executive's gross negligence or willful failure to substantially perform his duties and responsibilities to the Company or willful and deliberate violation of a Company policy;

(ii) the Executive's conviction of a felony or the Executive's commission of any act of fraud, embezzlement or dishonesty against the Company or involving moral turpitude that is likely to inflict or has inflicted material injury on the business of the Company, to be determined by the sole discretion of the Company;

(iii) the Executive's unauthorized use or disclosure of any proprietary information or trade secrets of the Company or any other party that the Executive owes an obligation of nondisclosure as a result of the Executive's relationship with the Company; and

(iv) the Executive's willful and deliberate breach of the obligations under this Agreement that causes material injury to the business of the Company.

4.5.4 Change in Control. For purposes of this Agreement, "***Change in Control***" means: (i) a sale of all or substantially all of the assets of the Company; (ii) a merger or consolidation in which the Company is not the surviving entity and in which the holders of the Company's outstanding voting stock immediately prior to such transaction own, immediately after such transaction, securities representing less than fifty percent (50%) of the voting power of the entity surviving such transaction or, where the surviving entity is a wholly-owned subsidiary of another entity, the surviving entity's parent; (iii) a reverse merger in which the Company is the surviving entity but the shares of Common Stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities of the surviving entity's parent, cash or otherwise, and in which the holders of the Company's outstanding voting stock immediately prior to such transaction own, immediately after such transaction, securities representing less than fifty percent (50%) of the voting power of the Company or, where the Company is a wholly-owned subsidiary of another entity, the Company's parent; or (iv) an acquisition by any person, entity or group (excluding any employee benefit plan, or related trust, sponsored or maintained by the Company or subsidiary of the Company or other entity controlled by the Company) of the beneficial ownership of securities of the Company representing at least seventy-five percent (75%) of the combined voting power entitled to vote in the election of Directors; provided, however, that nothing in this paragraph shall apply to a sale of assets, merger or other transaction effected exclusively for the purpose of changing the domicile of the Company.

4.6 Application of Internal Revenue Code Section 409A. Notwithstanding anything to the contrary set forth herein, any payments and benefits provided under this Agreement (the "***Severance Benefits***") that constitute "deferred compensation" within the meaning of Section 409A of the Internal Revenue Code of 1986, as amended (the "***Code***"), and the regulations and other guidance thereunder and any state law of similar effect (collectively "***Section 409A***"), shall not commence in connection with Executive's termination of employment unless and until Executive has also incurred a "separation from service" (as such term is defined in Treasury Regulation Section 1.409A-1(h) ("***Separation From Service***"), unless the Company reasonably determines that such amounts may be provided to Executive without causing Executive to incur the additional 20% tax under Section 409A.

It is intended that each installment of the Severance Benefits payments provided for in this Agreement is a separate "payment" for purposes of Treasury Regulation Section 1.409A-2(b)(2)(i). For the avoidance of doubt, it is intended that payments of the Severance Benefits set forth in this Agreement satisfy, to the greatest extent possible, the exemptions from the application of Section 409A provided under Treasury Regulation Sections 1.409A-1(b)(4), 1.409A-1(b)(5) and 1.409A-1(b)(9). However, if the Company (or, if applicable, the successor entity thereto) determines that the Severance Benefits constitute "deferred compensation" under Section 409A and Executive is, on the termination of service, a "specified employee" of the Company or any successor entity thereto, as such term is defined in Section 409A(a)(2)(B)(i) of the Code, then, solely to the extent necessary to avoid the incurrence of the adverse personal tax consequences

under Section 409A, the timing of the Severance Benefit payments shall be delayed until the earlier to occur of: (i) the date that is six months and one day after Executive's Separation From Service, or (ii) the date of Executive's death (such applicable date, the "***Specified Employee Initial Payment Date***"), the Company (or the successor entity thereto, as applicable) shall (A) pay to Executive a lump sum amount equal to the sum of the Severance Benefit payments that Executive would otherwise have received through the Specified Employee Initial Payment Date if the commencement of the payment of the Severance Benefits had not been so delayed pursuant to this Section and (B) commence paying the balance of the Severance Benefits in accordance with the applicable payment schedules set forth in this Agreement.

Notwithstanding anything to the contrary set forth herein, Executive shall receive the Severance Benefits described above, if and only if Executive duly executes and returns to the Company within the applicable time period set forth therein, but in no event more than forty-five days following Separation From Service, the Company's standard form of release of claims in favor of the Company (attached to this Agreement as Exhibit A) (the "***Release***") and permits the release of claims contained therein to become effective in accordance with its terms (such latest permitted date, the "***Release Deadline***"). If the severance benefits are not covered by one or more exemptions from the application of Section 409A and the Release could become effective in the calendar year following the calendar year in which Executive separates from service, the Release will not be deemed effective any earlier than the Release Deadline. Notwithstanding any other payment schedule set forth in this Agreement, none of the Severance Benefits will be paid or otherwise delivered prior to the effective date (or deemed effective date) of the Release. Except to the extent that payments may be delayed until the Specified Employee Initial Payment Date pursuant to the preceding paragraph, on the first regular payroll pay day following the effective date of the Release, the Company will pay Executive the Severance Benefits Executive would otherwise have received under the Agreement on or prior to such date but for the delay in payment related to the effectiveness of the Release, with the balance of the Severance Benefits being paid as originally scheduled.

The severance benefits are intended to qualify for an exemption from application of Section 409A or comply with its requirements to the extent necessary to avoid adverse personal tax consequences under Section 409A, and any ambiguities herein shall be interpreted accordingly.

4.7 Application of Internal Revenue Code Section 280G. If any payment or benefit Executive would receive pursuant to a Change in Control from the Company or otherwise ("***Payment***") would (i) constitute a "parachute payment" within the meaning of Section 280G of the Code, and (ii) but for this sentence, be subject to the excise tax imposed by Section 4999 of the Code (the "***Excise Tax***"), then such Payment shall be equal to the Reduced Amount. The "Reduced Amount" shall be either (x) the largest portion of the Payment that would result in no portion of the Payment being subject to the Excise Tax or (y) the largest portion, up to and including the total, of the Payment, whichever amount, after taking into account all applicable federal, state and local employment taxes, income taxes, and the Excise Tax (all computed at the highest

applicable marginal rate), results in Executive's receipt, on an after-tax basis, of the greater economic benefit notwithstanding that all or some portion of the Payment may be subject to the Excise Tax. If a reduction in payments or benefits constituting "parachute payments" is necessary so that the Payment equals the Reduced Amount, reduction shall occur in the manner that results in the greatest economic benefit for Executive. If more than one method of reduction will result in the same economic benefit, the items so reduced will be reduced pro rata.

In the event it is subsequently determined by the Internal Revenue Service that some portion of the Reduced Amount as determined pursuant to clause (x) in the preceding paragraph is subject to the Excise Tax, Executive agrees to promptly return to the Company a sufficient amount of the Payment so that no portion of the Reduced Amount is subject to the Excise Tax. For the avoidance of doubt, if the Reduced Amount is determined pursuant to clause (y) in the preceding paragraph, Executive will have no obligation to return any portion of the Payment pursuant to the preceding sentence.

Unless Executive and the Company agree on an alternative accounting firm, the accounting firm engaged by the Company for general tax compliance purposes as of the day prior to the effective date of the Change in Control shall perform the foregoing calculations. If the accounting firm so engaged by the Company is serving as accountant or auditor for the individual, entity or group effecting the Change in Control, the Company shall appoint a nationally recognized accounting firm to make the determinations required hereunder. The Company shall bear all expenses with respect to the determinations by such accounting firm required to be made hereunder.

The Company shall use commercially reasonable efforts to cause the accounting firm engaged to make the determinations hereunder to provide its calculations, together with detailed supporting documentation, to Executive and the Company within fifteen (15) calendar days after the date on which Executive's right to a Payment is triggered (if requested at that time by Executive or the Company) or such other time as requested by Executive or the Company.

4.8 Indemnification Agreements. The Company and the Executive have previously entered into indemnification agreements, copies of which are attached hereto as Exhibit B-1 and Exhibit B-2.

4.9 Confidential Information and Invention Assignment Agreement. The Executive has previously executed the Company's Confidential Information and Invention Assignment Agreement the terms of which shall continue to govern the terms of Executive's employment following the Effective Date, and a copy of which is attached as Exhibit C.

4.10 No Mitigation or Offset. The Executive shall not be required to seek or accept other employment, or otherwise to mitigate damages, as a condition to receipt of the Severance Benefits, and the Severance Benefits shall not be offset by any amounts received by the Executive from any other source, except to the extent that the Executive's rights to the benefits described in Sections 4.4.3(i)(b) or 4.4.3(ii)(c), as applicable, are

terminated by reason of the Executive obtaining full-time employment with another company or business entity which offers comparable health insurance coverage.

5. Assignment and Binding Effect.

This Agreement shall be binding upon the Executive and the Company and inure to the benefit of the Executive and the Executive's heirs, executors, personal representatives, assigns, administrators and legal representatives. Because of the unique and personal nature of the Executive's duties under this Agreement, neither this Agreement nor obligations under this Agreement shall be assignable by the Executive. This Agreement shall be binding upon and inure to the benefit of the Company and its successors, assigns and legal representatives, provided that the Agreement may only be assigned to an acquirer of all or substantially all of the Company's assets. Any such successor of the Company will be deemed substituted for the Company under the terms of this Agreement for all purposes. For this purpose, "successor" means any person, firm, corporation or other business entity which at any time, whether by purchase, merger or otherwise, directly or indirectly acquires all or substantially all of the assets or business of the Company.

6. Notice.

For the purposes of this Agreement, notices, demands, and all other forms of communication provided for in this Agreement shall be in writing and shall be deemed to have been duly given when delivered or (unless otherwise specified) mailed by registered mail, return receipt requested, postage prepaid, or by confirmed facsimile, addressed as set forth below, or to such other address as any party may have furnished to the other in writing in accordance herewith, except that notices of address shall be effective only upon receipt, as follows:

If to the Company:

Horizon Pharma, Inc.
150 S. Saunders Road,
Lake Forest, IL 60045
Attention: Timothy P. Walbert, Chairman, President & CEO
Fax: 847-572-1372

If to the Executive:

Geoff Curtis

_____

_____

Any such written notice shall be deemed given on the earlier of the date on which such notice is personally delivered or five (5) days after its deposit in the United States mail as specified above. Either party may change its address for notices by giving written notice to the other party in the manner specified in this section.

7. Choice of Law.

This Agreement shall be governed by the laws of the State of Illinois, without regard to any conflicts of law principals thereof that would call for the application of the laws of any other jurisdiction. The parties consent to the exclusive jurisdiction and venue of the federal court in the Northern District of Illinois, and state courts located in the state of Illinois, county of Cook. Nothing in this Section 7 limits the rights of the parties to seek appeal of a decision of an Illinois court outside of Illinois that has proper jurisdiction over the decision of a court sitting in Illinois.

8. Integration.

This Agreement, including Exhibit A, Exhibit B-1, Exhibit B-2 and Exhibit C contains the complete, final and exclusive agreement of the parties relating to the terms and conditions of the Executive's employment and the termination of Executive's employment, and supersedes all prior and contemporaneous oral and written employment agreements or arrangements between the parties, including but not limited to the Prior Agreement.

9. Amendment.

This Agreement cannot be amended or modified except by a written agreement signed by the Executive and the Company.

10. Waiver.

No term, covenant or condition of this Agreement or any breach thereof shall be deemed waived, except with the written consent of the party against whom the wavier is claimed, and any waiver or any such term, covenant, condition or breach shall not be deemed to be a waiver of any preceding or succeeding breach of the same or any other term, covenant, condition or breach.

11. Severability.

The finding by a court of competent jurisdiction of the unenforceability, invalidity or illegality of any provision of this Agreement shall not render any other provision of this Agreement unenforceable, invalid or illegal. Such court shall have the authority to modify or replace the invalid or unenforceable term or provision with a valid and enforceable term or provision, which most accurately represents the parties' intention with respect to the invalid, unenforceable, or illegal term or provision.

12. Interpretation; Construction.

The headings set forth in this Agreement are for convenience of reference only and shall not be used in interpreting this Agreement. This Agreement has been drafted and negotiated by legal counsel representing the Company and the Executive. The parties acknowledge that each party and its counsel has reviewed and revised, or had an opportunity to review and revise, this Agreement, and any rule of construction to the

effect that any ambiguities are to be resolved against the drafting party shall not be employed in the interpretation of this Agreement.

13. Execution by Facsimile Signatures and in Counterparts.

The parties agree that facsimile signatures shall have the same force and effect as original signatures. This Agreement may be executed in one or more counterparts, each of which shall be deemed an original but all of which together shall constitute one and the same instrument.

14. Survival.

The provisions of this Agreement, and of all other agreements referenced herein, shall survive the termination of this Agreement, and of the Executive's employment by the Company for any reason, to the extent necessary to enable the parties to enforce their respective rights hereunder.

[Remainder of Page Intentionally Left Blank]

IN WITNESS WHEREFORE, the parties have signed this Agreement on the date first written above.

COMPANY:

HORIZON PHARMA, INC.
HORIZON PHARMA USA, INC.

By:

Title: Chairman, President & CEO

Print Name: Timothy P. Wa1bert

/s/ Timothy P. Walbert
Signature

As authorized agent of the Company

11/5/18
Date

EXECUTIVE:

/s/ Geoff Curtis
Geoff Curtis, individually

11/5/18
Date

Exhibit 21.1

Subsidiaries of Horizon Pharma Public Limited Company:

NAME:	JURISDICTION OF INCORPORATION:
Andromeda Biotech Limited	Israel
Horizon European Products, LLC	Delaware
Horizon Medicines LLC	Delaware
Horizon Orphan LLC	Delaware
Horizon Pharma Aon Limited	Ireland
Horizon Pharma Capital Limited	Ireland
Horizon Pharma Dó Limited	Ireland
Horizon Pharma Finance Limited	Ireland
Horizon Pharma Finance S.à.r.l	Luxembourg
Horizon Pharma GmbH	Germany
Horizon Pharma Holdings Limited	Ireland
Horizon Pharma Investment Limited	Bermuda
Horizon Pharma Ireland Limited	Ireland
Horizon Pharma Israel Holding Corp. Ltd	Israel
Horizon Pharma Rheumatology LLC	Delaware
Horizon Pharma Switzerland GmbH	Switzerland
Horizon Pharma Tepro, Inc	Delaware
Horizon Pharma Treasury Limited	Ireland
Horizon Pharma Trí Limited	Ireland
Horizon Pharma USA, Inc.	Delaware
Horizon Pharmaceutical LLC	Delaware
Horizon Therapeutics, LLC	Delaware
Horizon Pharma Services LLC	Delaware
Hyperion Therapeutics Ireland Holding Limited	Ireland
Hyperion Therapeutics Ireland Operating Limited	Ireland
HZNP Canada Limited	Canada
HZNP Bermuda LLC	Bermuda
HZNP Limited	Ireland
HZNP Medicines LLC	Bermuda
HZNP Holdings LLC	Bermuda
HZNP USA LLC	Delaware
Misneach Europe LLC	Delaware

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-8 (No. 333-198865, 333-203933, 333-211118, 333-220316, 333-222516, and 333-224866) of Horizon Pharma plc of our report dated February 27, 2019 relating to the financial statements, financial statement schedule and the effectiveness of internal control over financial reporting, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP
Chicago, Illinois
February, 27, 2019

Exhibit 31.1

Certification of Principal Executive Officer

I, Timothy P. Walbert, certify that:

1. I have reviewed this annual report on Form 10-K of Horizon Pharma PLC (the "registrant");

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

    a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

    b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

    c. Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

    d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

    a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

    b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 27, 2019

/s/ Timothy P. Walbert
Timothy P. Walbert
Chairman, President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

Certification of Principal Financial Officer

I, Paul W. Hoelscher, certify that:

1. I have reviewed this annual report on Form 10-K of Horizon Pharma PLC (the "registrant");

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

    a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

    b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

    c. Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

    d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

    a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

    b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 27, 2019

/s/ Paul W. Hoelscher
Paul W. Hoelscher
Executive Vice President, Chief Financial Officer
(Principal Financial Officer)

Exhibit 32.1

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and 18 U.S.C. Section 1350, I, Timothy P. Walbert, President, Chief Executive Officer and Chairman of the Board of Horizon Pharma PLC (the "Company"), certify to the best of my knowledge that:

1. the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2018 (the "Report"), to which this Certification is attached as Exhibit 32.1, fully complies with the requirements of Section 13(a) or 15(d) of the Exchange Act; and
2. the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 27, 2019

/s/ Timothy P. Walbert
Timothy P. Walbert
Chairman, President and Chief Executive Officer
(Principal Executive Officer)

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of the Company under the Securities Act of 1933, as amended, or the Exchange Act (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.

Exhibit 32.2

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and 18 U.S.C. Section 1350, I, Paul W. Hoelscher, Executive Vice President and Chief Financial Officer of Horizon Pharma PLC (the "Company"), certify to the best of my knowledge that:

1. the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2018 (the "Report"), to which this Certification is attached as Exhibit 32.2, fully complies with the requirements of Section 13(a) or 15(d) of the Exchange Act; and
2. the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 27, 2019

/s/ Paul W. Hoelscher
Paul W. Hoelscher
Executive Vice President, Chief Financial Officer
(Principal Financial Officer)

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of the Company under the Securities Act of 1933, as amended, or the Exchange Act (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2019

or

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to

Commission File Number 001-35238

HORIZON THERAPEUTICS PUBLIC LIMITED COMPANY

(Exact name of Registrant as specified in its charter)

Ireland	**Not Applicable**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
Connaught House, 1st Floor **1 Burlington Road, Dublin 4, D04 C5Y6, Ireland**	**Not Applicable**
(Address of principal executive offices)	**(Zip Code)**

011 353 1 772 2100
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	Trading Symbol	Name of Each Exchange on Which Registered
Ordinary shares, nominal value $0.0001 per share	**HZNP**	**The Nasdaq Global Select Market**

Securities registered pursuant to Section 12(g) of the Act:

None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐.

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒.

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	☒	Accelerated filer	☐
Non-accelerated filer	☐	Smaller reporting company	☐
Emerging growth company	☐		

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined by Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

The aggregate market value of the registrant's voting ordinary shares held by non-affiliates of the registrant, based upon the $24.06 per share closing sale price of the registrant's ordinary shares on June 28, 2019 (the last business day of the registrant's most recently completed second quarter), was approximately $4.5 billion. Solely for purposes of this calculation, the registrant's directors and executive officers and holders of 10% or more of the registrant's outstanding ordinary shares have been assumed to be affiliates and an aggregate of 949,834 ordinary shares held by such persons on June 28, 2019 are not included in this calculation.

As of February 19, 2020, the registrant had outstanding 189,941,651 ordinary shares.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement for the registrant's 2020 Annual General Meeting of Shareholders are incorporated by reference into Part III of this Annual Report on Form 10-K.

HORIZON THERAPEUTICS PLC
FORM 10-K — ANNUAL REPORT
For the Fiscal Year Ended December 31, 2019

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PART I

Special Note Regarding Forward-Looking Statements

This Annual Report on Form 10-K contains "forward-looking statements" — that is, statements related to future, not past, events — as defined in Section 21E of the Securities Exchange Act of 1934, as amended, that reflect our current expectations regarding our future growth, results of operations, business strategy and plans, financial condition, cash flows, performance, development plans and timelines, business prospects, and opportunities, as well as assumptions made by, and information currently available to, our management. Forward-looking statements include any statement that does not directly relate to a current or historical fact. Forward-looking statements generally can be identified by words such as "believe," "may," "could," "will," "estimate," "continue," "anticipate," "intend," "seek," "plan," "expect," "should," "would", or similar expressions. These statements are based on current expectations and assumptions that are subject to risks and uncertainties inherent in our business, which could cause our actual results to differ materially from those indicated in the forward-looking statements. Factors that could cause actual results to differ materially from those indicated in the forward-looking statements include, without limitation: our ability to successfully execute our sales and marketing strategy, including continuing to successfully recruit and retain sales and marketing personnel and to successfully build the market for our medicines; our ability to build a sustainable pipeline of new medicine candidates; whether we will be able to realize the expected benefits of strategic transactions, including whether and when such transactions will be accretive to our net income; the rate and degree of market acceptance of, and our ability and our distribution and marketing partners' ability to obtain coverage and adequate reimbursement and pricing for, our medicines from government and third-party payers and risks relating to the success of our patient assistance programs; our ability to maintain regulatory approvals for our medicines; our ability to conduct clinical development and obtain regulatory approvals for our medicine candidates, including potential delays in initiating and completing studies and filing for and obtaining regulatory approvals and whether data from clinical studies will support regulatory approval; our need for and ability to obtain additional financing; the accuracy of our estimates regarding future financial results; our ability to successfully execute our strategy to develop or acquire additional medicines or companies, including disruption from any future acquisition or whether any acquired development programs will be successful; our ability to manage our anticipated future growth; the ability of our medicines to compete with generic medicines, especially those representing the active pharmaceutical ingredients in our medicines as well as new medicines that may be developed by our competitors; our ability and our distribution and marketing partners' ability to comply with regulatory requirements regarding the sales, marketing and manufacturing of our medicines and medicine candidates; the performance of our third-party distribution partners, licensees and manufacturers over which we have limited control; our ability to obtain and maintain intellectual property protection for our medicines; our ability to defend our intellectual property rights with respect to our medicines; our ability to operate our business without infringing the intellectual property rights of others; the loss of key commercial or management personnel; regulatory developments in the United States and other countries, including potential changes in healthcare laws and regulations; and other risks detailed below in Part I — Item 1A. "Risk Factors".

Although we believe that the expectations reflected in our forward-looking statements are reasonable, we cannot guarantee future results, events, levels of activity, performance or achievement. We undertake no obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, unless required by law.

Item 1. Business

Unless otherwise indicated or the context otherwise requires, references to the "Company", "we", "us" and "our" refer to Horizon Therapeutics plc (formerly known as Horizon Pharma plc) and its consolidated subsidiaries.

Overview

We are focused on researching, developing and commercializing medicines that address critical needs for people impacted by rare and rheumatic diseases. Our pipeline is purposeful: we apply scientific expertise and courage to bring clinically meaningful therapies to patients. We believe science and compassion must work together to transform lives.

Our Strategy

Horizon today is a leading biopharma company focused on rare diseases, delivering innovative therapies to patients and generating value for our shareholders. We are strongly focused on executing our strategy to maximize the benefit and value of our key growth drivers and expand our pipeline for sustainable growth.

We have taken a different approach from typical biopharma companies. Instead of starting with a pipeline and raising capital to finance development opportunities, after our initial public offering in 2011, we developed a successful commercial business. Our initial portfolio of two medicines generated cash flows and significant growth, establishing a strong foundation for our future.

Beginning in 2014, we deployed the cash flows in building out our portfolio of rare disease medicines, including the acquisition of our key growth driver KRYSTEXXA®, and now have seven rare disease medicines. One of those medicines is TEPEZZA™ (teprotumumab-trbw), our other key growth driver, which we acquired in 2017 as part of our acquisition of River Vision Development Corp., or River Vision.

TEPEZZA represents the evolution of our strategy to its third – and current phase – expanding our pipeline and maximizing the value of our medicines, in particular our growth drivers KRYSTEXXA and TEPEZZA and expanding our pipeline for sustainable growth. To support our pipeline strategy, we expanded our research and development organization, adding an experienced leadership team and augmenting the organization's capabilities. It was our new leadership team that drove the successful Phase 3 clinical program and U.S. Food and Drug Administration, or FDA, approval of TEPEZZA in early 2020.

Today, in addition to reinvesting in our key growth drivers, our priority is to expand our pipeline, concentrating on developing a deeper presence in our four core therapeutic areas of rheumatology, nephrology, ophthalmology and endocrinology.

We have significantly transformed Horizon since our beginnings as a public company in 2011, then with two medicines and total net sales of approximately $7.0 million. In a span of only eight years, we have evolved to a biopharma company with eleven on-market medicines, seven of them for the treatment of rare diseases, total net sales in 2019 of $1.3 billion, and a growing pipeline of development programs.

Prior to 2020, our two reportable segments were (i) the orphan and rheumatology segment and (ii) the inflammation segment (previously the primary care segment). The orphan and rheumatology segment is our strategic growth segment. Effective in the first quarter of 2020, we (i) reorganized our commercial operations and moved responsibility for RAYOS® to the inflammation segment and (ii) renamed the orphan and rheumatology segment the orphan segment. With the approval of TEPEZZA on January 21, 2020, net sales generated by this medicine will be reported as part of the renamed orphan segment.

Our Company

We are a public limited company formed under the laws of Ireland. We operate through a number of U.S. and other international subsidiaries with principal business purposes to perform research and development or manufacturing operations, serve as distributors of our medicines, hold intellectual property assets or provide us with services and financial support.

Our principal executive offices are located at Connaught House, 1st Floor, 1 Burlington Road, Dublin 4, D04 C5Y6, Ireland and our telephone number is 011 353 1 772 2100. Our website address is www.horizontherapeutics.com. Information found on, or accessible through, our website is not a part of, and is not incorporated into, this Annual Report on Form 10-K.

Acquisitions and Divestitures

Since January 1, 2017, we completed the following acquisitions and divestitures:

- On June 28, 2019, we sold our rights to MIGERGOT to Cosette Pharmaceuticals, Inc., for an upfront payment and potential additional contingent consideration payments, or the MIGEROT transaction.
- Effective January 1, 2019, we amended our license and supply agreements with Jagotec AG and Skyepharma AG, which are affiliates of Vectura Group plc, or Vectura. Under these amendments, we agreed to transfer all economic benefits of LODOTRA® in Europe to Vectura.
- On December 28, 2018, we sold our rights to RAVICTI® and AMMONAPS® (known as BUPHENYL® in the United States) outside of North America and Japan to Medical Need Europe AB, part of the Immedica Group, or Immedica. We have retained rights to RAVICTI and BUPHENYL in North America and Japan.
- On June 30, 2017, we completed our acquisition of certain rights to interferon gamma-1b from Boehringer Ingelheim International GmbH, or Boehringer Ingelheim International, in all territories outside of the United States, Canada and Japan. Interferon gamma-1b is known as IMUKIN® outside of the United States, Canada and Japan. On July 24, 2018, we sold the rights to IMUKIN in all territories outside of the United States, Canada and Japan to Clinigen Group plc, or Clinigen, for an upfront payment and a potential additional contingent consideration payment that was subsequently received in September 2019, or the IMUKIN sale.
- On June 23, 2017, we sold our European subsidiary that owned the marketing rights to PROCYSBI® (cysteamine bitartrate) delayed-release capsules and QUINSAIR™ (levofloxacin inhalation solution) in Europe, the Middle East and Africa, or EMEA, regions, to Chiesi Farmaceutici S.p.A., or Chiesi.
- On May 8, 2017, we completed our acquisition of River Vision, which added the late development-stage rare disease biologic medicine TEPEZZA to our research and development pipeline. In January 2020, the FDA approved TEPEZZA for the treatment of thyroid eye disease, or TED.

The consolidated financial statements presented herein include the results of operations of the acquired businesses from the applicable dates of acquisition. See Note 4 of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K, for further details of our acquisitions and divestitures.

Our Medicines

We believe our medicines address unmet therapeutic needs in orphan diseases, arthritis, pain and inflammation, and inflammatory diseases and provide significant advantages over existing therapies.

In January 2020, the FDA approved TEPEZZA for the treatment of TED, a serious, progressive and vision-threatening rare autoimmune condition.

As of December 31, 2019, our marketed medicine portfolio consisted of the following:

Medicine	Indication	2019 Net Sales (in millions)	Marketing Rights
ORPHAN AND RHEUMATOLOGY SEGMENT:			
KRYSTEXXA	Chronic refractory gout ("uncontrolled gout")	$ 342.4	Worldwide
RAVICTI	Urea cycle disorders	$ 228.8	North America and Japan (1)
PROCYSBI	Nephropathic cystinosis	$ 161.9	United States and certain other countries (2)
ACTIMMUNE®	Chronic granulomatous disease and severe, malignant osteopetrosis	$ 107.3	United States, Canada and Japan (3)
RAYOS	Rheumatoid arthritis, polymyalgia rheumatic, systemic lupus erythematosus and multiple other indications	$ 78.6	North America (4)
BUPHENYL	Urea cycle disorders	$ 9.8	North America and Japan (5)
QUINSAIR	Treatment of chronic pulmonary infections due to *Pseudomonas aeruginosa* in cystic fibrosis patients	$ 0.8	Canada and certain other countries (6)
INFLAMMATION SEGMENT(7)**:**			
PENNSAID 2%®	Pain of osteoarthritis of the knee(s)	$ 200.8	United States
DUEXIS®	Signs and symptoms of osteoarthritis and rheumatoid arthritis	$ 115.8	Worldwide (8)
VIMOVO®	Signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis	$ 52.1	United States

(1) On December 28, 2018, we sold our rights to RAVICTI outside of North America and Japan to Immedica. RAVICTI is also available in Canada through an exclusive distribution agreement with Innomar Strategies Inc., or Innomar.

(2) We market PROCYSBI in the United States and Canada. Innomar is our exclusive distributor for PROCYSBI in Canada. We also have marketing rights to PROCYSBI in Asia. PROCYSBI is also available in Latin America through a managed access program through our partner Uno Healthcare Inc.

(3) ACTIMMUNE is known as IMUKIN outside the United States, Canada and Japan. On July 24, 2018, we sold the rights to IMUKIN in all territories outside of the United States, Canada and Japan to Clinigen.

(4) Outside the United States, RAYOS is sold and marketed as LODOTRA. Effective January 1, 2019, we amended our license and supply agreements with Jagotec AG and Skyepharma AG, which are affiliates of Vectura Group plc, or Vectura. Under these amendments, we agreed to transfer all economic benefits of LODOTRA in Europe to Vectura.

(5) BUPHENYL is known as AMMONAPS outside of North America and Japan. On December 28, 2018, we sold our rights to AMMONAPS outside of North America and Japan to Immedica. The amount shown in the table above includes net sales for AMMONAPS of $5.6 million for 2018. Orphan Pacific, Inc. holds an exclusive distribution agreement for the distribution of BUPHENYL in Japan.

(6) We market QUINSAIR in Canada and Latin America. Innomar is our exclusive distributor for QUINSAIR in Canada. We also have marketing rights for QUINSAIR in the United States and Asia. We have not received regulatory approval to market QUINSAIR in the United States.

(7) On June 28, 2019, we sold our rights to MIGERGOT. We recorded net sales for MIGERGOT of $1.8 million during 2019 prior to selling our rights.

(8) DUEXIS rights in Mexico and Chile have been licensed to Grünenthal GmbH, or Grünenthal.

Information on our total revenues by product in each of the years ended December 31, 2019, 2018 and 2017, is included in the section titled "Management's Discussion and Analysis of Financial Condition and Results of Operations" in this Annual Report on Form 10-K.

ORPHAN AND RHEUMATOLOGY

During 2019, our orphan and rheumatology segment included the marketed medicines, KRYSTEXXA, RAVICTI, PROCYSBI, ACTIMMUNE, RAYOS, BUPHENYL and QUINSAIR. In January 2020, the FDA approved TEPEZZA for the treatment of TED.

KRYSTEXXA

A PEGylated uric acid specific enzyme (uricase), KRYSTEXXA is the first and only FDA approved medicine for the treatment of uncontrolled gout. Uncontrolled gout occurs in patients who have failed to normalize serum uric acid, or sUA, and whose signs and symptoms are inadequately controlled with conventional therapies, such as xanthine oxidase inhibitors, or XOIs, at the maximum medically appropriate dose, or for whom these drugs are contraindicated.

KRYSTEXXA has a unique mechanism of action that can rapidly reverse disease progression. Unlike conventional XOI therapies, which address the over-production or under-excretion of uric acid, KRYSTEXXA converts uric acid into allantoin, a water-soluble molecule, which the body can easily eliminate through the urine. Renal excretion of allantoin is ten times more efficient than uric acid excretion. Additionally, many chronic kidney disease, or CKD, patients have gout, and the disease tends to be more prevalent as CKD advances. While conventional XOI gout therapies can place additional burden on the kidneys and have dosing limitations, KRYSTEXXA has been proven effective and safe for uncontrolled gout patients with CKD without the need to adjust dosing.

Gout is one of the most common forms of inflammatory arthritis and can be assessed by a simple blood test for the amounts of uric acid in the blood (sUA levels). Typically in gout, when uric acid levels are greater than 6.8 milligrams per deciliter, urate will crystallize and deposit. These hard deposits are known as tophi and may occur anywhere in the body, including joints, as well as organs, such as the kidney and heart. When under-treated medically, tophi often lead to bone erosions and loss of functional ability. Gout flares, a common characteristic of uncontrolled gout, are intensely painful. They may or may not be accompanied by tophi. A systemic disease, uncontrolled gout frequently causes crippling disabilities and significant joint damage. Of the 9.5 million gout sufferers in the United States, we estimate that greater than 100,000 patients have uncontrolled gout.

KRYSTEXXA was approved by the FDA in 2010 following the results of two replicate clinical trials six months in duration involving 85 patients treated with KRYSTEXXA. The mean baseline sUA levels for patients in the trial were greater than 10 mg/dL, and 71 percent of patients had visible tophi. The primary endpoint for the trials was the ability to maintain a low sUA for 80 percent of the samples taken at months three and six. As a result of the every-other-week dosing of KRYSTEXXA at 8 mg, 42 percent of KRYSTEXXA patients achieved complete response versus 0 percent for the placebo group; and 45 percent of KRYSTEXXA patients achieved complete resolution of tophi versus 8 percent for the placebo group over six months.

We are focused on optimizing and maximizing the potential of KRYSTEXXA by expanding our commercialization efforts, as well as investing in education, patient and physician outreach, activities related to label expansion and investigation programs that demonstrate KRYSTEXXA as an effective treatment for uncontrolled gout. We believe that KRYSTEXXA represents a significant opportunity and potential growth driver for our company.

We doubled our KRYSTEXXA commercial team in 2018, we increased our promotional efforts to further penetrate rheumatology and initiate marketing to nephrology and we are growing our customer base from both new and existing prescribers. In 2019, we added a separate group of sales representatives to call exclusively on nephrologists. We believe KRYSTEXXA offers a solution to a clinical need experienced by many nephrologists in dealing with uncontrolled gout patients with CKD.

As the only FDA-approved medication for the treatment of uncontrolled gout, KRYSTEXXA faces limited direct competition. We believe that the complexity of manufacturing KRYSTEXXA provides a barrier to potential biosimilar competition. However, a number of competitors have medicines in Phase 1 or Phase 2 trials, including Selecta Biosciences, Inc., which has presented Phase 2 clinical data and is conducting a six-month trial comparing their candidate that uses an immunomodulator to KRYSTEXXA alone.

RAVICTI

RAVICTI is formed by the catalyzed esterification of glycerol with 4-phenylbutyric acid and the subsequent purification of the glycerol phenylbutyrate formed. The purified glycerol phenylbutyrate drug substance is filled into glass bottles for use as an oral dosage liquid.

RAVICTI is indicated for use as a nitrogen-binding agent for chronic management of adult and pediatric patients (beginning at birth) with urea cycle disorders, or UCDs, that cannot be managed by dietary protein restriction and/or amino acid supplementation alone. UCDs are rare, life-threatening genetic disorders. RAVICTI must be used with dietary protein restriction and, in some cases, dietary supplements (for example, essential amino acids, arginine, citrulline or protein-free calorie supplements).

UCDs are inherited metabolic diseases caused by a deficiency of one of the enzymes or transporters that constitute the urea cycle. The urea cycle involves a series of biochemical steps in which ammonia, a potent neurotoxin, is converted to urea, which is excreted in the urine. UCD patients may experience episodes during which the ammonia levels in their blood become excessively high, called hyperammonemic crises, which may result in irreversible brain damage, coma or death. We estimate that there are approximately 2,600 patients with UCDs living in the United States, including approximately 1,000 diagnosed patients.

UCD symptoms may first occur at any age depending on the severity of the disorder, with more severe defects presenting earlier in life. However, a prompt diagnosis and careful management of the disease can lead to good clinical outcomes.

RAVICTI competes with older-generation nitrogen scavenger medicines. In the United States, RAVICTI competes with generic forms of sodium phenylbutyrate, including BUPHENYL. RAVICTI has advantages over older-generation medicines leading to better patient adherence and compliance rates, such as its better tolerability for patients. It is ingested by mouth and therefore requires little preparation and it has little taste and lower sodium content than its competitors. A few competitors have medicine candidates in early-stage development, including a gene-therapy candidate by Ultragenyx Pharmaceutical Inc., a generic taste-masked formulation option of BUPHENYL by ACER Therapeutics Inc., and an enzyme replacement for a specific UCD subtype (ARG) by Aeglea Bio Therapeutics Inc. If successful, these medicine candidates could compete with RAVICTI.

Our strategy for RAVICTI is to drive growth through increased awareness and diagnosis of UCDs; to drive conversion to RAVICTI from older-generation nitrogen scavengers, such as generic forms of sodium phenylbutyrate based on the medicine's differentiated benefits; to position RAVICTI as the first line of therapy; and increase compliance rates.

On December 28, 2018, we sold our rights to RAVICTI outside of North America and Japan to Immedica. We previously distributed RAVICTI through a commercial partner in Europe and other non-U.S. markets. We have retained rights to RAVICTI in North America and Japan.

PROCYSBI

PROCYSBI is indicated for nephropathic cystinosis, or NC, a rare and life-threatening metabolic disorder. PROCYSBI capsules contain cysteamine bitartrate in the form of innovative microspheronized beads that are individually coated to create delayed and extended-release properties, allowing patients to maintain consistent therapeutic systemic drug levels over a twelve-hour dosing period. The enteric-coated beads are pH sensitive and bypass the stomach for dissolution and absorption in the more alkaline environment of the proximal small intestine. Randomized controlled clinical trials and extended treatment with PROCYSBI therapy demonstrated consistent cystine depletion as monitored by levels of the biomarker (and surrogate marker), white blood cell cystine.

In February 2020, the FDA approved PROCYSBI Delayed-Release Oral Granules in Packets for adults and children one year of age and older living with nephropathic cystinosis. The PROCYSBI Delayed-Release Oral Granules in Packets product is the same as the currently available PROCYSBI capsules product except in respect of the packaging format. This new dosage form provides another administration option for patients, in addition to the PROCYSBI capsules. The PROCYSBI Delayed-Release Oral Granules in Packets are expected to be commercially available in the first half of 2020.

PROCYSBI is differentiated by its ability to control cystine concentration continuously over twelve hours. Older therapies require administration of medicine every six hours. By taking PROCYSBI, patients have to dose only twice a day, providing them greater control over their medication schedule and lifestyle. Additionally, because PROCYSBI can be administered through a feeding tube or mixed with approved foods and beverages, the patient can choose a more flexible dosing regimen. PROCYSBI also has fewer known side effects, such as less severe body odor, than older-generation therapies.

We estimate that there are approximately 500 patients diagnosed with cystinosis living in the United States. NC comprises 95 percent of known cases of cystinosis. In these patients, elevated cystine can lead to cellular dysfunction and death; without treatment, the disease is usually fatal by the end of the first decade of life. Cystinosis is progressive, eventually causing irreversible tissue damage and multi-organ failure, including kidney failure, blindness, muscle wasting and premature death. NC is usually diagnosed in infancy after children display symptoms to physicians, including markedly increased urination, thirst, dehydration, gastrointestinal distress, failure to thrive, rickets, photophobia and kidney symptoms specific to Fanconi syndrome. Management of cystinosis requires lifelong therapy.

In addition to patients who have already been identified, we believe that a number of patients with atypical phenotypic presentation and end-stage renal disease have their condition as a result of undiagnosed late-onset NC and would benefit from treatment with PROCYSBI.

Other than PROCYSBI, we are aware of two pharmaceutical products currently approved to treat cystinosis, Cystagon® and Cystaran®. Cystagon, an immediate-release cysteamine bitartrate capsule, is an older-generation systemic cystine-depleting therapy for cystinosis in the United States marketed by Mylan N.V., and by Orphan Europe SARL in markets outside of the United States. Cystagon is PROCYSBI's primary competitor. Cystaran, a cysteamine ophthalmic solution, is approved in the United States for treatment of corneal crystal accumulation in patients with cystinosis and is marketed by Leadiant Biosciences, Inc. Additionally, we are also aware that AVROBIO, Inc., has an early-stage gene therapy candidate in development for the treatment of cystinosis. We believe that PROCYSBI will continue to be well received in the market and continue to expect Cystagon to be the primary competitor for PROCYSBI for the foreseeable future.

Our strategy for PROCYSBI is to drive conversion of patients from older-generation immediate-release capsules of cysteamine bitartrate; to increase the uptake of the medicine by diagnosed but untreated patients; to identify previously undiagnosed patients who are suitable for treatment; to position PROCYSBI as a first line of therapy; and to increase compliance rates.

ACTIMMUNE

ACTIMMUNE is indicated for chronic granulomatous disease, or CGD, and severe, malignant osteopetrosis, or SMO. It is a biologically manufactured protein called interferon gamma-1b that is similar to a protein the human body makes naturally. Interferon gamma helps prevent infection in CGD patients and enhances osteoclast function in SMO patients. ACTIMMUNE is the only medicine approved by the FDA to reduce the frequency and severity of serious infections associated with CGD and for delaying disease progression in patients with SMO. ACTIMMUNE is believed to work by modifying the cellular function of various cells, including those in the immune system and those that help form bones.

CGD is a genetic disorder of the immune system. It is described as a primary immunodeficiency disorder, which means it is not caused by another disease or disorder. In people who have CGD, a type of white blood cell called a phagocyte is defective. These defective phagocytes cannot generate superoxide, leading to an inability to kill harmful microorganisms such as bacteria and fungi. As a result, the immune system is weakened. People with CGD are more likely to have certain problems, such as recurrent severe bacterial and fungal infections and chronic inflammatory conditions. These patients are prone to developing masses called granulomas, which can occur repeatedly in organs throughout the body and cause a variety of problems. We estimate that there are approximately 1,600 patients with CGD in the United States.

SMO is a form of osteopetrosis and is sometimes referred to as marble bone disease or malignant infantile osteopetrosis because it occurs in very young children. While exact numbers are not known, it has been estimated that one out of 250,000 children is born with SMO.

ACTIMMUNE currently faces limited competition. There are additional or alternative approaches used to treat patients with CGD and SMO, including the increasing trend towards the use of bone marrow transplants in patients with CGD, however, there are currently no medicines on the market that compete directly with ACTIMMUNE.

Our strategy with respect to ACTIMMUNE, our medicine for the treatment of CGD, includes increasing awareness and diagnosis of CGD and increasing compliance rates.

RAYOS

RAYOS is indicated for the treatment of multiple conditions: rheumatoid arthritis, or RA; ankylosing spondylitis, or AS; polymyalgia rheumatica, or PMR; primary systemic amyloidosis; asthma; chronic obstructive pulmonary disease; systemic lupus erythematosus, or SLE; and a number of other conditions. We focus our promotion of RAYOS on rheumatology indications, including RA and PMR.

RAYOS is composed of an active core containing prednisone that is encapsulated by an inactive porous shell, and acts as a barrier between the medicine's active core and the patient's gastrointestinal, or GI, fluids. RAYOS was developed using Vectura's proprietary GeoClock™ and GeoMatrix™ technologies, for which we hold an exclusive worldwide license for the delivery of glucocorticoid, a class of corticosteroid. The delivery system enables a delayed release, synchronizing the prednisone delivery time with the patient's elevated cytokine levels, thereby taking effect at a physiologically optimal point to inhibit cytokine production, and thus significantly reducing the signs and symptoms of RA and PMR.

RA is a chronic disease that causes pain, stiffness and swelling, primarily in the joints; PMR is an inflammatory disorder that causes significant muscle pain and stiffness; SLE is a chronic autoimmune disease that primarily affects women and causes inflammation and pain in the joints and muscles as well as overall fatigue.

RAYOS competes with a number of medicines in the market to treat RA, including corticosteroids, such as prednisone; traditional disease-modifying anti-rheumatic drugs, or DMARDs, such as methotrexate; and biologic agents, such as Humira and Enbrel. The majority of RA patients are treated with DMARDs, which are typically used as initial therapy in patients with RA. Biologic agents are typically added to DMARDs as combination therapy. It is common for an RA patient to take a combination of a DMARD, an oral corticosteroid, a non-steroidal anti-inflammatory drug, or NSAID, and/or a biologic agent.

Outside the United States, RAYOS is sold and marketed as LODOTRA. Effective January 1, 2019, we amended our license and supply agreements with Jagotec AG and Skyepharma AG, which are affiliates of Vectura. Under these amendments, we agreed to transfer all economic benefits of LODOTRA in Europe to Vectura during an initial transition period, with full rights transferring to Vectura when certain transfer activities have been completed. These transfer activities are ongoing. We ceased recording LODOTRA revenue from January 1, 2019. See "Manufacturing, Commercial, Supply and License Agreements" below for further details of the amendments.

BUPHENYL

BUPHENYL tablets and BUPHENYL powder are made from granules that contain sodium phenylbutyrate as the active (chemically synthesized) ingredient and microcrystalline cellulose as a diluent.

BUPHENYL tablets for oral administration and BUPHENYL powder for oral, nasogastric, or gastrostomy tube administration are indicated as adjunctive therapy in the chronic management of patients with UCDs involving deficiencies of carbamoyl phosphate synthetase, ornithine transcarbamylase or argininosuccinic acid synthetase.

BUPHENYL is indicated in all patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first twenty-eight days of life). It is also indicated in patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy. It is important that the diagnosis be made early and treatment initiated immediately to improve chances of survival. BUPHENYL must be combined with dietary protein restriction and, in some cases, essential amino acid supplementation. We distribute BUPHENYL in the United States.

On December 28, 2018, we sold our rights to AMMONAPS outside of North America and Japan to Immedica. We previously distributed AMMONAPS through a commercial partner in Europe and other non-U.S. markets. We have retained rights to BUPHENYL in North America and Japan.

QUINSAIR

QUINSAIR is a formulation of the antibiotic drug levofloxacin, suitable for inhalation via a nebulizer and indicated for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adult patients with cystic fibrosis, or CF. CF is a rare, life-threatening genetic disease affecting approximately 70,000 people worldwide, and results in buildup of abnormally thick secretions that can cause chronic lung infections and progressive lung damage in many patients that eventually leads to death.

QUINSAIR's route of delivery allows higher concentrations of drug in the lung sputum than can be achieved via systemic (for example, oral) administration. QUINSAIR, as approved in Canada and Latin America, is administered twice daily in twenty-eight-day cycles, using a hand-held nebulizer with a disposable handset known as the Zirela® device, manufactured by our partner PARI Pharma GmbH, or PARI, and configured specifically for use with QUINSAIR. QUINSAIR is not approved in the United States.

Chronic pulmonary infections due to *Pseudomonas aeruginosa* are currently treated primarily with inhaled antibiotics, including tobramycin, an aminoglycoside-class antibiotic sold by Novartis Pharmaceuticals Corporation as TOBI® or in dry-powder-inhalation format as TOBI Podhaler® and sold by others in generic form, aztreonam, a monobacter-class antibiotic which is marketed in an inhaled formulation by Gilead Sciences, Inc. under the tradename Cayston®, and colistimethate sodium, a polymixin-class antibiotic which is approved and marketed in inhaled formulations in Europe. Tobramycin, aztreonam and colistimethane are primarily effective against gram-negative bacteria such as *Pseudomonas aeruginosa*. However, the prevalence of multi-drug-resistant *Pseudomonas aeruginosa* is growing. Thus, we believe there is an unmet need that might be addressed with a new class of inhaled antibiotic such as the fluoruquinolone class that levofloxacin represents.

TEPEZZA

TEPEZZA is a fully human monoclonal antibody (mAb) and a targeted inhibitor of the insulin-like growth factor-1 receptor, or IGF-1R, that is the first and only FDA-approved medicine for the treatment of TED. TED is a serious, progressive and vision-threatening rare autoimmune condition. While TED often occurs in people living with hyperthyroidism or Graves' disease, it is a distinct disease that is caused by autoantibodies activating an IGF-1R-mediated signaling complex on cells within the retro-orbital space. This leads to a cascade of negative effects, which may cause long-term, irreversible eye damage. As TED progresses, it causes serious damage – including proptosis (eye bulging), strabismus (misalignment of the eyes) and diplopia (double vision) – and in some cases can lead to blindness. Historically, patients have had to live with TED until the inflammation subsides, after which they are often left with permanent and vision-impairing consequences and may require multiple surgeries that do not completely return the patient to their pre-disease state.

TEPEZZA was approved by the FDA in January 2020 following the positive results from the Phase 2 clinical trial, as well as the Phase 3 confirmatory clinical trial, OPTIC. The OPTIC trial found that significantly more patients treated with TEPEZZA (82.9%) had a meaningful improvement in proptosis (≥ 2 mm) as compared with placebo patients (9.5%) ($p < 0.001$) without deterioration in the fellow eye at Week 24. Additional secondary endpoints were also met, including a change from baseline of at least one grade in diplopia (double vision) in 67.9% of patients receiving TEPEZZA compared to 28.6% of patients receiving placebo ($p=0.001$) at Week 24. In a related analysis of the Phase 2 and Phase 3 clinical trials, there were more patients with complete resolution of diplopia among those treated with TEPEZZA (53%) compared with those treated with placebo (25%). The majority of adverse events experienced with TEPEZZA treatment were graded as mild to moderate and were manageable in the trials, with few discontinuations or therapy interruptions.

Our commercialization strategy for TEPEZZA is focused on four pillars: establishing the market structure and simplifying the diagnosis and treatment of TED for patients; educating the multiple stakeholders about TED and TEPEZZA; supporting the commercialization of TEPEZZA with our comprehensive approach and patient-centric model; and facilitating access to TEPEZZA by establishing an infusion site-of-care referral process for treating physicians who may not have infusion capabilities.

As the only FDA-approved medication for the treatment of TED, TEPEZZA has no direct approved competition. We believe that the results of the TEPEZZA Phase 3 and Phase 2 clinical trials present a significantly high hurdle for potential competitors, given that candidate medicines would be expected to demonstrate similar or greater efficacy in the treatment of TED. In addition, the complexity of manufacturing TEPEZZA could pose a barrier to potential biosimilar competition. Although TEPEZZA does not face direct competition, other therapies, such as corticosteroids, have been used on an off-label basis to alleviate some of the symptoms of TED. While these therapies have not proved effective in treating the underlying disease, and carry with them significant side effects, their off-label use could reduce or delay treatment with TEPEZZA in the addressable patient population. Immunovant Inc. is also conducting clinical studies of a medicine candidate for the treatment of active TED, also referred to as Graves' ophthalmopathy.

INFLAMMATION

During 2019, our inflammation segment included PENNSAID 2% w/w, or PENNSAID 2%, DUEXIS and VIMOVO.

PENNSAID 2%

PENNSAID 2% is indicated for the treatment of pain of osteoarthritis, or OA, of the knee(s). OA is a type of arthritis that is caused by the breakdown and eventual loss of the cartilage of one or more joints.

An analgesic that is easy-to-apply topically directly to the knee, PENNSAID 2% contains diclofenac sodium, a commonly prescribed NSAID to treat OA pain, and dimethyl sulfoxide, or DMSO, a penetrating agent that helps ensure that diclofenac sodium is absorbed through the skin to the site of inflammation and pain. Topical NSAIDs such as PENNSAID 2% are generally viewed as safer alternatives to oral NSAID treatment because they reduce systemic exposure to a fraction of that of an oral NSAID. PENNSAID 2% is the only topical NSAID offered with the convenience of a metered-dose pump, which ensures that the patient receives the correct amount of PENNSAID 2% solution with each use. PENNSAID 2% competes primarily with the generic version of Voltaren Gel, a market leader in the topical NSAID category.

DUEXIS

DUEXIS is indicated for the relief of signs and symptoms of RA and OA and to decrease the risk of developing upper-GI ulcers in patients who are taking ibuprofen for these indications. RA is a chronic disease that causes pain, stiffness and swelling, primarily in the joints.

DUEXIS provides a fixed-dose combination in tablet form of ibuprofen, the most widely prescribed NSAID, and famotidine, a well-established GI agent used to treat dyspepsia, gastroesophageal reflux disease and active ulcers.

Fixed-dose combination therapy provides significant advantages over multiple-pill regimens: fixed-dose combinations can reduce the number of pills taken; ensure that the correct dosage of each component is taken at the correct time, improving compliance; and is often associated with better treatment outcomes.

In general, DUEXIS faces competition from the separate use of NSAIDs for pain relief and GI medications to address the risk of NSAID-induced ulcers. However, the prescribing information for DUEXIS states that DUEXIS should not be substituted with the single-ingredient products of ibuprofen and famotidine. DUEXIS competes with other NSAIDs, including Celebrex®, manufactured by Pfizer Inc., and celecoxib, a generic form of the medicine supplied by other pharmaceutical companies. DUEXIS also competes with TIVORBEX™ (indomethacin) capsules, VIVLODEX® (meloxicam) capsules and ZORVOLEX ® (diclofenac) capsules marketed by Iroko Pharmaceuticals, LLC.

VIMOVO

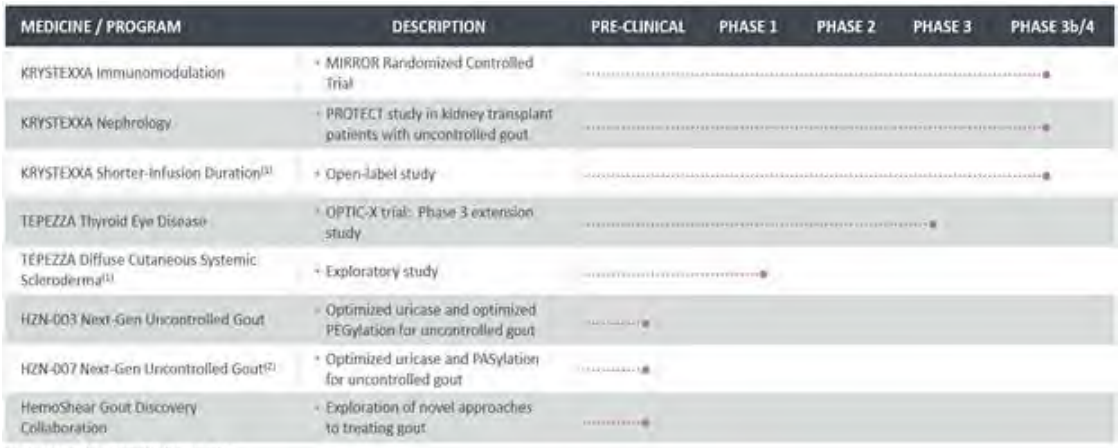
VIMOVO is indicated for the relief of signs and symptoms of OA, RA and AS and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers. It is a proprietary, fixed-dose, delayed-release tablet that combines enteric-coated naproxen, an NSAID, surrounded by a layer of immediate-release esomeprazole magnesium. Naproxen has proven anti-inflammatory and analgesic properties, and esomeprazole magnesium reduces the stomach acid secretions that can cause upper-GI ulcers. Both naproxen and esomeprazole magnesium have well-documented and excellent long-term safety profiles, and both medicines have been used by millions of patients worldwide. VIMOVO has been shown to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID associated gastric ulcers.

Patent litigation is currently pending in the United States District Court for the District of New Jersey and the Court of Appeals for the Federal Circuit against Dr. Reddy's Laboratories Inc. and Dr. Reddy's Laboratories Ltd., or collectively Dr. Reddy's, who intends to market a generic version of VIMOVO before the expiration of certain of our patents listed in the Orange Book. The cases arise from Paragraph IV Patent Certification notice letters from Dr. Reddy's advising that it had filed an ANDA with the FDA seeking approval to market generic versions of VIMOVO before the expiration of the patents-in-suit. On July 30, 2019, the Federal Circuit Court of Appeals denied our request for a rehearing of the Court's invalidity ruling against the 6,926,907 and 8,557,285 patents for VIMOVO coordinated-release tablets. As a result, the District Court entered judgment in September 2019 invalidating the '907 and '285 patents, which ended any restriction against the FDA from granting final approval to Dr. Reddy's generic version of VIMOVO. On February 18, 2020, the FDA granted final approval for Dr. Reddy's generic version of VIMOVO. We anticipate that Dr. Reddy's will immediately launch its product at-risk notwithstanding the ongoing patent litigation. Patent litigation is currently pending in the United States District Court for the District of New Jersey against Ajanta Pharma LTD, or Ajanta, intending to market a generic version of VIMOVO before the expiration of certain of our patents listed in the Orange Book. If we are unsuccessful in any of the VIMOVO cases, we will likely face generic competition with respect to VIMOVO and sales of VIMOVO will be substantially harmed.

In addition, similar to DUEXIS, VIMOVO faces competition from the separate use of NSAIDs for pain relief and GI medications to address the risk of NSAID-induced ulcers. However, the prescribing information for VIMOVO states that VIMOVO should not be substituted with the single-ingredient products of naproxen and esomeprazole magnesium. VIMOVO also competes with other NSAIDs, including Celebrex, TIVORBEX, VIVLODEX and ZORVOLEX.

Research and Development

Our research and development programs currently include pre-clinical and clinical development of new medicine candidates and activities related to label expansions for existing medicines. We devote significant resources to research and development activities associated with our medicines and medicine candidates. The graphic below summarizes our significant research and development activities in order of the program stage, from post-market to pre-clinical:



(1) Planned study expected to begin in 2020.
(2) Being developed under a collaboration agreement with XL Protein GmbH.
MIRROR: Trial evaluating use of KRYSTEXXA in combination with immunomodulator methotrexate to increase the patient response rate.
PROTECT: Clinical study evaluating the effect of KRYSTEXXA on sUA levels in kidney transplant patients with uncontrolled gout.
OPTIC-X: Open-label extension study of the Phase 3 trial evaluating TEPEZZA for the treatment of TED.

KRYSTEXXA MIRROR Randomized Clinical Trial

KRYSTEXXA is a recombinant protein of uricase, an enzyme not found in humans, and PEGylation. As with many biologic medicines, some people treated with KRYSTEXXA develop antidrug antibodies as part of an immune response to the medicine and lose response to therapy.

We are evaluating ways to maximize KRYSTEXXA benefit to patients by improving its response rate. In the KRYSTEXXA pivotal trials, 42 percent of patients achieved a complete response, defined as the proportion of sUA responders (sUA < 6 mg/dL) at Months 3 and 6. While this is an impressive result relative to the response rate of biologic medicines used for other types of inflammatory arthritis, we are investigating ways to increase the number of patients who can achieve a complete response by co-administering KRYSTEXXA with methotrexate, an immunomodulator medicine commonly used by rheumatologists. There is well-documented evidence that the addition of immunomodulators to biological therapies can decrease rates of immunogenicity, as the immunomodulators work to reduce the formation of anti-drug antibodies to the medicine, allowing it to maintain appropriate blood levels over a longer period of time. MIRROR, our randomized, placebo-controlled clinical trial, was initiated in June 2019, and is expected to enroll 135 patients. The trial is designed to support the potential for registration and modification of our KRYSTEXXA FDA label.

The MIRROR randomized trial was preceded by a smaller open-label study, which also evaluated the use of the immunomodulator methotrexate with KRYSTEXXA to increase the response rate and was completed in 2019. Of the 14 patients in the study, 79 percent, or 11 patients, achieved a complete response, defined as the proportion of sUA responders (sUA < 6 mg/dL) at Month 6. The 79 percent response rate is clinically importantly higher than the 42 percent response rate in the KRYSTEXXA Phase 3 clinical program, which evaluated KRYSTEXXA alone. No new safety concerns associated with the combination were identified.

KRYSTEXXA PROTECT Study in Kidney Transplant Patients with Uncontrolled Gout

PROTECT is an open-label clinical study evaluating the effect of KRYSTEXXA on sUA levels in adults with uncontrolled gout who have undergone a kidney transplant. The objective of the study is to demonstrate that KRYSTEXXA provides effective disease control in a severe uncontrolled gout population. Kidney transplant patients have more than a tenfold increase in the prevalence of gout when compared to the general population, and literature suggests that persistently high sUA levels can be associated with organ rejection. Managing uncontrolled gout is one of the most common and significant unmet needs of kidney transplant patients. The PROTECT study is expected to enroll 20 adults.

KRYSTEXXA Shorter-Infusion Duration Study

We expect to begin an initial proof of concept study in mid-2020 to evaluate the impact of administering KRYSTEXXA over a significantly shorter infusion duration. Currently, KRYSTEXXA is infused over a two-hour long interval. A shorter infusion duration could meaningfully improve the experience and convenience for patients, physicians and sites of care.

TEPEZZA OPTIC-X

TEPEZZA is a fully human monoclonal antibody inhibitor of IGF-1R approved early in 2020 for the treatment of TED after an accelerated Priority Review by the FDA. TEPEZZA is the first and only approved treatment for this serious, progressive and vision-threatening rare autoimmune condition in which the muscles and fatty tissue behind the eye become inflamed and expand. This can lead to proptosis (eye bulging) and diplopia (double vision) and seriously impact activities of daily living and patients' quality of life. In rare instances, it can result in compression of the optic nerve that can lead to blindness.

In 2019, we completed OPTIC, the TEPEZZA Phase 3 confirmatory clinical trial. Patients included in the study had a clinical diagnosis of TED. The results were statistically significant and clinically meaningful: 82.9 percent of TEPEZZA patients achieved the primary endpoint, defined as a reduction of proptosis of at least 2mm ($p<0.001$), compared to 9.5 percent of placebo patients. All secondary endpoints were met, and the manageable safety profile was consistent across the Phase 3 and Phase 2 trials. The trial results for both the TEPEZZA Phase 3 and Phase 2 clinical trial results were published in *The New England Journal of Medicine*, a significant achievement.

OPTIC-X is an extension study of OPTIC and is currently ongoing. Patients who participated in the OPTIC trial had the option to participate in the extension study and receive an additional eight infusions of TEPEZZA. The results of OPTIC-X are expected to provide additional data on whether non-responders from the initial twenty-four weeks of treatment during OPTIC would benefit from longer treatment and if patients who lose response off drug after the initial twenty-four weeks of treatment would benefit from retreatment.

TEPEZZA Diffuse Cutaneous Scleroderma

We expect to initiate an exploratory TEPEZZA study in 2020 in diffuse cutaneous scleroderma, a rare fibrotic disease with no approved treatment options, as part of our approach to evaluate additional indications for TEPEZZA. Diffuse cutaneous scleroderma is a subtype of scleroderma in which excess collagen production causes skin thickening and hardening, or fibrosis, over large areas of the skin and internal organs. There can be significant associated organ damage, including to the gastrointestinal tract, kidneys, lungs and heart. Literature suggests that the mechanism of action of TEPEZZA, which is to block the IGF-1R, could have an impact on fibrotic processes, such as those that are relevant to diffuse cutaneous scleroderma. The objective of the exploratory study is to evaluate biomarkers and safety, tolerability of TEPEZZA in patients with diffuse cutaneous scleroderma and to inform potential subsequent larger and longer duration clinical trials.

HZN-003: Potential Next-Generation Biologic for Uncontrolled Gout Using Optimized Uricase and Optimized PEGylation Technology

A potential biologic for uncontrolled gout, HZN-003 is a pre-clinical, genetically engineered uricase with optimized PEGylation technology that has the potential to improve the half-life and reduce immunogenicity of this molecule. In addition, it has the potential for subcutaneous dosing. We licensed HZN-003 from MedImmune LLC, the global biologics research and development arm of the AstraZeneca Group, in late 2017. HZN-003 is a rheumatology pipeline program with the objective of enhancing our leadership position in the uncontrolled gout market.

HZN-007: PASylated Uricase for Uncontrolled Gout Using Optimized Uricase and PASylation Technology

HZN-007 is a PASylated uricase, resulting from a collaboration program to identify uncontrolled gout biologic candidates. HZN-007 is a pre-clinical medicine candidate, using PASylation technology as a biological alternative to synthetic PEGylation. PASylation is a new approach for extending the half-life of pharmaceutically active proteins and reducing immunogenicity. In addition, it has the potential for subcutaneous dosing.

HemoShear Gout Discovery Collaboration

We have a collaboration agreement with HemoShear Therapeutics, LLC, a biotechnology company, to discover and develop novel therapeutics for gout. The collaboration provides us an opportunity to address unmet treatment needs for people with gout by evaluating new targets for the control of sUA levels as well as new targets to address the inflammation associated with acute flares of gout.

With the objective to enhance our leadership position in uncontrolled gout, HZN-003, HZN-007 and the HemoShear programs are all exploring innovative approaches to improve the treatment of this painful, debilitating systemic disease.

Distribution

We use central third-party logistics and FDA-compliant warehouses for storage and distribution of our medicines into the supply chain. Our third-party logistics providers specialize in integrated operations that include warehousing and transportation services that can be scaled and customized to our needs based on market conditions and the demands and delivery service requirements for our medicines and materials. Their services eliminate the need to build dedicated internal infrastructures that would be difficult to scale without significant capital investment. Our third-party logistics providers warehouse all medicines in controlled FDA-registered facilities. Incoming orders are prepared and shipped through an order entry system to ensure just in time delivery of the medicines.

Sales and Marketing

As of December 31, 2019, our sales force was composed of approximately 480 sales representatives consisting of approximately 75 orphan disease sales representatives (including approximately 50 TEPEZZA sales representatives), 170 rheumatology sales specialists and 235 inflammation sales representatives.

Our orphan and rheumatology sales representatives focus on marketing our orphan and rheumatology medicines to a limited number of healthcare practitioners who specialize in fields such as pediatric immunology, allergy, infectious diseases, metabolic disorders, rheumatology, nephrology, ophthalmology and endocrinology with the approval of TEPEZZA, to help them understand the potential benefits of our medicines. We have entered into, and may continue to enter into, agreements with third parties for commercialization of our medicines outside the United States.

We offer discount card and other programs such as our HorizonCares program to patients under which the patient receives a discount on his or her prescription. In certain circumstances when a patient's prescription is rejected by a managed care vendor, we will pay for the full cost of the prescription. Patients are able to fill prescriptions for our inflammation medicines through pharmacies participating in our HorizonCares patient assistance program, as well as other pharmacies. In addition, we have business arrangements with pharmacy benefit managers, or PBMs, and other payers to secure formulary status and reimbursement of our inflammation medicines. The business arrangements with the PBMs generally require us to pay administrative fees and rebates to the PBMs and other payers for qualifying prescriptions.

We have a comprehensive compliance program in place to address adherence with various laws and regulations relating to our sales, marketing, and manufacturing of our medicines, as well as certain third-party relationships, including pharmacies. Specifically with respect to pharmacies, the compliance program utilizes a variety of methods and tools to monitor and audit pharmacies, including those that participate in our patient assistance programs, to confirm their activities, adjudication and practices are consistent with our compliance policies and guidance.

Manufacturing, Commercial, Supply and License Agreements

We have agreements with third parties for active pharmaceutical ingredients, or APIs, and manufacturing of our medicines, formulation and development services, fill, finish and packaging services, transportation, and distribution and logistics services for certain medicines. In most cases, we retain certain levels of safety stock or maintain alternate supply relationships that we can utilize without undue disruption of our manufacturing processes if a third party fails to perform its contractual obligations.

KRYSTEXXA

KRYSTEXXA is produced by fermentation of a genetically engineered Escherichia coli bacterium containing the DNA which encodes for uricase. The complementary DNA coding for the uricase is based on mammalian sequences. Uricase is purified and is then PEGylated with a PEGylation agent to produce the bulk medicine, pegloticase. PEGylation and purification of the active drug substance is achieved by conventional column chromatography. The resulting highly purified sterile solution is filled in a single-use vial for intravenous infusion following dilution. In support of its manufacturing process, we store multiple vials of the Escherichia coli bacterium master cell bank and working cell bank at multiple locations in order to ensure adequate backup should any cell bank be lost in a catastrophic event.

NOF Supply Agreement

In August 2015, Crealta Holdings LLC, or Crealta, and NOF Corporation, or NOF, in Japan, entered into an exclusive supply agreement for the PEGylation agent used in the manufacture of KRYSTEXXA. We assumed this agreement as part of our acquisition of Crealta in January 2016, or the Crealta acquisition. Under the terms of this agreement, we are required to issue NOF forecasts of our requirements for the PEGylation agent, a portion of which are binding. The agreement expires in August 2020 and we expect to extend the agreement beyond this date. Either we or NOF may also terminate the agreement upon a material breach, if not cured within a specified period of time, or in the event of the other party's insolvency. While there are no minimum purchase obligations under the agreement, we are required to use NOF as our exclusive supplier for the PEGylation agent, subject to certain exceptions if NOF is unable to supply the PEGylation agent.

Bio-Technology General (Israel) Supply Agreement

In March 2007, Savient Pharmaceuticals, Inc. (as predecessor in interest to Crealta), or Savient, entered into a commercial supply agreement with Bio-Technology General (Israel) Ltd, or BTG Israel, which was subsequently amended, for the production of the bulk KRYSTEXXA medicine, or bulk product. We assumed this agreement as part of the Crealta acquisition and further amended the agreement in September 2016. Under this agreement, we have agreed to purchase certain minimum annual order quantities and are obligated to purchase at least 80 percent of our annual world-wide bulk product requirements from BTG Israel. The term of the agreement runs until December 31, 2030, and will automatically renew for successive three-year periods unless earlier terminated by either party upon three years' prior written notice. The agreement may be terminated earlier by either party in the event of a force majeure, liquidation, dissolution, bankruptcy or insolvency of the other party, uncured material breach by the other party or after January 1, 2024, upon three years' prior written notice. Under this agreement, if the manufacture of the bulk product is moved out of Israel, we may be required to obtain the approval of the Israeli Office of the Chief Scientist, or OCS, because certain KRYSTEXXA intellectual property was initially developed with a grant funded by the OCS and we may be required to pay the OCS additional amounts as a repayment for the OCS grant funding. We issue eighteen-month forecasts of the volume of KRYSTEXXA that we expect to order. The first six months of the forecasts are considered binding firm orders.

Exelead PharmaSource Supply Agreement

In October 2008, Savient and Exelead, Inc. (formerly known as Sigma Tau PharmaSource, Inc. (as successor in interest to Enzon Pharmaceuticals, Inc.)), or Exelead, entered into a commercial supply agreement, which was subsequently amended, for the packaging and supply of the final drug product KRYSTEXXA. This agreement remains in effect until terminated, and either we or Exelead may terminate the agreement with three years notice, given thirty days prior to the agreement anniversary date. Either we or Exelead may also terminate the agreement upon a material default, if not cured within a specified period of time, or in the event of the other party's insolvency or bankruptcy.

Duke University and Mountain View Pharmaceutical License Agreement

In August 1998, Savient entered into an exclusive, worldwide license agreement with Duke University, or Duke, and Mountain View Pharmaceuticals Inc., or MVP, which was subsequently amended, and which we acquired as part of the Crealta acquisition. Duke developed the recombinant uricase enzyme used in KRYSTEXXA and MVP developed the PEGylation technology used in the manufacture of KRYSTEXXA. Duke and MVP may terminate the agreement if we commit fraud or for our willful misconduct or illegal conduct; upon our material breach of the agreement, if not cured within a specified period of time; upon written notice if we have committed two or more material breaches under the agreement; or in the event of our bankruptcy or insolvency. Under the terms of the agreement, we are obligated to pay Duke a mid-single digit percentage royalty on our global net sales of KRYSTEXXA and a royalty of between 5 percent and 15 percent on any global sublicense revenue. We are also obligated to pay MVP a mid-single digit percentage royalty on our net sales of KRYSTEXXA outside of the United States and royalty of between 5 percent and 15 percent on any sublicense revenue outside of the United States.

RAVICTI

We have clinical and commercial supplies of glycerol phenylbutyrate API manufactured for us by two alternate suppliers, Helsinn Advanced Synthesis SA (Switzerland) and Patheon Austria GmbH & Co KG (formerly DSM Fine Chemicals Austria) on a purchase-order basis. We have manufacturing agreements to manufacture finished RAVICTI drug product with Lyne Laboratories, Inc., Halo Pharmaceuticals, Inc. and PCI Pharma Services.

Bausch Health Asset Purchase Agreement

As a result of our acquisition of Hyperion Therapeutics, Inc., or Hyperion, in May 2015, or the Hyperion acquisition, we became subject to an asset purchase agreement with Bausch Health Companies, Inc. (formerly Ucyclyd Pharma, Inc.), or Bausch, pursuant to which we are obligated to pay to Bausch mid single-digit royalties on our global net sales of RAVICTI. The asset purchase agreement cannot be terminated for convenience by either party. We have a license to certain Bausch manufacturing technology, however Bausch is permitted to terminate the license if we fail to comply with any payment obligations relating to the license and do not cure such failure within a defined time period.

Brusilow License Agreement

As a result of the Hyperion acquisition, we became subject to a license agreement, as amended, with Saul W. Brusilow, M.D. and Brusilow Enterprises, Inc., or Brusilow, pursuant to which we license patented technology related to RAVICTI from Brusilow. Under such agreement, we are obligated to pay low-single digit royalties to Brusilow on net sales of RAVICTI that are, or were, covered by a valid claim of a licensed patent. The license agreement may be terminated for any uncured breach as well as bankruptcy. We may also terminate the agreement at any time by giving Brusilow prior written notice, in which case all rights granted to us would revert to Brusilow.

PROCYSBI

PROCYSBI drug product is comprised of enteric-coated beads of cysteamine bitartrate encapsulated in gelatin capsules or packaged directly into packets. PROCYSBI drug product and API, cysteamine bitartrate, are manufactured and packaged on a contract basis by third parties.

Patheon Manufacturing Services Agreement

As a result of our acquisition of Raptor Pharmaceutical Corp, in October 2016, or the Raptor acquisition, we assumed a manufacturing services agreement, as amended, with Patheon Pharmaceuticals Inc., or Patheon, for the manufacture and supply of PROCYSBI. Pursuant to the agreement, we must provide a rolling, non-binding forecast of PROCYSBI, with a portion of the forecast being a firm written order. The agreement has a term that runs until December 31, 2021 and which automatically renews for successive two-year terms if not terminated at least eighteen months in advance.

Cambrex Profarmaco Milano Supply Agreement

As a result of the Raptor acquisition, we assumed an API supply agreement, as amended, with Cambrex Profarmaco Milano, or Cambrex. Pursuant to the agreement, we must provide rolling, non-binding forecasts, with a portion of the forecast being the minimum floor of the firm order that must be placed. The Cambrex supply agreement has an initial term that runs until November 30, 2020, and which automatically renews for successive two-year terms if not terminated at least one year in advance.

UCSD License Agreement

In May 2017, we entered into an amended and restated license agreement with The Regents of the University of California, San Diego, or UCSD, which was amended in September 2018. We must pay UCSD a royalty in the mid-single digits on net sales of PROCYSBI in countries where PROCYSBI is covered by a patent right, and a royalty in the low-single digits on net sales of PROCYSBI in countries where PROCYSBI is not covered by a patent right. Each such royalty is subject to reduction for sales of PROCYSBI in countries in the event a generic substitute for PROCYSBI is sold in such countries. We must pay UCSD a minimum annual royalty in an amount less than $0.1 million. Royalties terminate upon the later of (a) the expiration date of the longest-lived patent rights on a country-by-country basis; and (b) twenty years after first commercial sale of PROCYSBI. We must also pay UCSD a percentage in the mid-teens of any fees we receive from our sublicensees under the agreement that are not earned royalties. We may also be obligated to pay UCSD aggregate developmental milestone payments of $0.3 million and aggregate regulatory milestone payments of $1.8 million for each orphan indication and aggregate developmental milestone payments of $0.8 million and aggregate regulatory milestone payments of $3.5 million for each non-orphan indication. We are also subject to certain diligence obligations relating to performing activities for specified indications, including maintaining existing regulatory approvals for PROCYSBI and commercializing PROCYSBI in countries where regulatory approvals have been obtained and using commercially reasonable efforts to develop, obtain regulatory approval, and commercialize certain other licensed medicines in the United States and other countries. Under the terms of our agreement with Chiesi, royalties due to UCSD on sales of PROCYSBI in EMEA will be paid by Chiesi to us, which we will forward to UCSD unless we instruct Chiesi to make such payments directly to UCSD.

ACTIMMUNE

ACTIMMUNE is a recombinant protein that is produced by fermentation of a genetically engineered Escherichia coli bacterium containing the DNA which encodes for the human protein. Purification of the active drug substance is achieved by conventional column chromatography. The resulting active drug substance is then formulated as a highly purified sterile solution and filled in a single-use vial for subcutaneous injection, which is the ACTIMMUNE finished drug product. In support of its manufacturing process, we and Boehringer Ingelheim RCV GmbH & Co KG, or Boehringer Ingelheim, store multiple vials of the Escherichia coli bacterium master cell bank and working cell bank in order to ensure adequate backup should any cell bank be lost in a catastrophic event.

Boehringer Ingelheim Supply Agreement

In June 2017, we entered into an exclusive global supply agreement with Boehringer Ingelheim Biopharmaceuticals GmbH, or Boehringer Ingelheim Biopharmaceuticals, pursuant to which Boehringer Ingelheim Biopharmaceuticals is required to manufacture and supply ACTIMMUNE and IMUKIN active drug substance and commercial quantities of the ACTIMMUNE and IMUKIN finished drug product. Boehringer Ingelheim Biopharmaceuticals is our sole source supplier for ACTIMMUNE active drug substance and finished drug product. Pursuant to the agreement, we are required to purchase minimum quantities of finished drug product during the term of the agreement. Boehringer Ingelheim Biopharmaceuticals manufactures our commercial requirements of ACTIMMUNE based on our forecasts and the annual contractual minimum purchase quantity. The supply agreement continues for an indefinite period but can be terminated by either party upon three years notice (but, in such case, cannot be terminated sooner than June 30, 2024), for an uncured material breach by the other party, upon the other party's bankruptcy or insolvency, or upon certain changes of control of the other party. We can terminate the supply agreement in the event we are prevented by regulatory authorities from distributing the product on the market for all indications.

License Agreements

Under a license agreement, as amended, with Genentech Inc., or Genentech, who was the original developer of ACTIMMUNE, we are obligated to pay a low single-digit royalty to Genentech on our annual net sales of ACTIMMUNE.

Either Genentech or we may terminate the agreement if the other party becomes bankrupt or defaults, however, in the case of a default, the defaulting party has thirty days to cure the default before the license agreement may be terminated.

Under the terms of an assignment and option agreement with Connetics Corporation (which was the predecessor parent company to InterMune Pharmaceuticals Inc. and is now part of GlaxoSmithKline), or Connetics, we are obligated to pay low single-digit royalties to Connetics on our net sales of ACTIMMUNE in the United States.

RAYOS and LODOTRA

We purchase the API for RAYOS from Tianjin Tianyao Pharmaceuticals Co., Ltd. in China and from Sanofi Chimie SA in France. We have contracted with Jagotec AG, which is an affiliate of Vectura, for the production of RAYOS tablets and we entered into an agreement with Patheon for the packaging and assembling of RAYOS.

Effective January 1, 2019, we amended our license and supply agreements with Jagotec AG and Skyepharma AG, which is also an affiliate of Vectura. Under these amendments, we agreed to transfer all economic benefits of LODOTRA in Europe to Vectura during an initial transition period, with full rights transferring to Vectura when certain transfer activities have been completed. These transfer activities are ongoing. In exchange for transferring the LODOTRA economic benefits and rights, the royalty payable by us to Vectura in respect of RAYOS sales in North America was amended whereby, effective January 1, 2019, we were obligated to pay Vectura a mid-teens percentage royalty on our net sales, subject to a minimum royalty of $8.0 million per year, with the minimum royalty requirement expiring on December 31, 2022. Under the amendments, we ceased recording LODOTRA revenue and we are no longer required to pay a royalty in respect of LODOTRA. In addition, under the amendments, from January 1, 2020, we are no longer subject to a minimum purchase commitment in respect of the supply agreement with Jagotec AG.

BUPHENYL

When Hyperion purchased BUPHENYL, Hyperion assumed all of Bausch's rights and obligations under its manufacturing agreements for the medicine. We assumed these agreements when we acquired Hyperion. We purchase API for BUPHENYL from CU Chemie Uetikon GmbH and final manufacturing, testing and packaging of the medicine is provided by Patheon UK Limited.

QUINSAIR

QUINSAIR drug product, its API, levofloxacin hemihydrate, and the Zirela nebulizer device are all manufactured on a contract basis by third parties. The API is exclusively supplied by TEVA API Inc. QUINSAIR drug product is manufactured by Catalent Pharma Solutions, LLC. Nebulizers are supplied by PARI in Starnberg, Germany.

TEPEZZA

TEPEZZA is produced by culture of a genetically engineered mammalian cell line containing the DNA which encodes for teprotumumab-trbw, a fully human IgG1 monoclonal antibody. Cell culture broth is harvested and purified through filtration processes and chromatography processes prior to being formulated, frozen and shipped to the site of drug product manufacture.

AGC Biologics Supply Agreement

In February 2018, we entered into a commercial supply agreement with AGC Biologics A/S (formerly known as CMC Biologics A/S), or AGC, which was amended in May 2019 and December 2019, for the supply of TEPEZZA drug substance. Pursuant to the agreement, we have agreed to purchase certain minimum annual order quantities of TEPEZZA drug substance. In addition, we must provide AGC with rolling forecasts of TEPEZZA drug substance requirements, with a portion of the forecast being a firm and binding order. The agreement has a term that runs indefinitely. Either party may terminate the agreement by giving notice at least three years in advance, but notice may not be given before February 14, 2022. Either party may also terminate the agreement for the other party's failure to pay any undisputed sum payable under the agreement within a specified period of time, for a material breach by the other party if not cured within a specified period of time, upon the other party's insolvency, or in the event that any material permit or regulatory license is permanently revoked preventing the performance of specified services by the other party.

Catalent Indiana Supply Agreement

In December 2018, we entered into a commercial supply agreement with Catalent Indiana, LLC, or Catalent, for the supply of TEPEZZA drug product. Pursuant to the agreement, we must provide Catalent with rolling forecasts of TEPEZZA drug product requirements, with a portion of the forecast being a firm and binding order. The agreement has a term that runs until December 18, 2023, and automatically renews for two successive two-year terms unless terminated by either party at least two years in advance. The agreement may be terminated earlier by either party for a material breach by the other party, if not cured within a specified period of time, or upon the other party's insolvency.

Roche License Agreement

As a result of our acquisition of River Vision, we have a license of intellectual property rights to TEPEZZA under a license agreement with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., or Roche, effective as of June 15, 2011, as amended. Pursuant to the agreement, we are obligated to pay tiered royalties between 9 and 12 percent on annual worldwide net sales. The royalty terminates upon the later of (a) the expiration date of the longest-lived patent rights on a country-by-country basis; and (b) ten years after first commercial sale of TEPEZZA. We have paid development and regulatory milestones totaling CHF5.0 million relating to the United States and will pay an additional milestone payment of CHF5.0 million during the first quarter of 2020. We may be obligated to pay Roche additional development and regulatory milestones for activities outside the United States or for additional indications. We may also be obligated to pay Roche aggregate sales milestone payments totaling up to mid-double-digit million Swiss francs. We are also obligated to use commercially reasonable efforts to develop and commercialize TEPEZZA. Either party may terminate the agreement upon the other party's breach of the agreement, if not cured within a specified period of time, or in the event of the other party's bankruptcy or insolvency. Roche may also terminate the agreement if we challenge the validity of Roche's patents. Upon providing written notice to Roche, we may also terminate the agreement within six-months of such notice before the first commercial sale of TEPEZZA or within nine months of such notice after the first commercial sale of TEPEZZA.

Lundquist Institute License Agreement

As a result of our acquisition of River Vision, we have a license of patent rights to TEPEZZA under a license agreement with Lundquist Institute (formerly known as Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center), or Lundquist, dated December 5, 2012. Pursuant to the agreement, we are obligated to pay Lundquist a royalty payment of less than 1 percent of TEPEZZA net sales. The royalty terminates upon the expiration date of the longest-lived patent rights. We may terminate the agreement upon sixty days' prior written notice to Lundquist. Either party may terminate the agreement upon the other party's material breach of the agreement if not cured within a specified period of time. Lundquist may also terminate the agreement in the event of our bankruptcy or insolvency.

Boehringer Ingelheim Biopharmaceuticals License Agreement

As a result of our acquisition of River Vision, we have a license of certain manufacturing technology for TEPEZZA under a license agreement with Boehringer Ingelheim Biopharmaceuticals, effective as of December 21, 2016. Pursuant to the agreement, we may be obligated to pay Boehringer Ingelheim Biopharmaceuticals milestone payments totaling low-single-digit million euros upon the achievement of certain TEPEZZA sales milestones. Either party may terminate the agreement upon the other party's material breach of the agreement if not cured within a specified period of time. Boehringer Ingelheim Biopharmaceuticals may also terminate the agreement if we challenge the validity of certain of its patent rights.

In addition to the above supply and license agreements, under the agreement for the acquisition of River Vision, we are required to pay up to $325.0 million upon the attainment of various milestones, composed of $100.0 million related to FDA approval and $225.0 million related to net sales thresholds for TEPEZZA. The agreement also includes a royalty payment of 3 percent of the portion of annual worldwide net sales exceeding $300.0 million (if any). We will make a milestone payment of $100.0 million related to FDA approval during the first quarter of 2020.

PENNSAID 2%

In October 2014, in connection with the acquisition of the U.S. rights to PENNSAID 2% from Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.), or Nuvo, we entered into an exclusive supply agreement with Nuvo, which was amended in February 2016, January 2017 and February 2018, under which Nuvo is obligated to manufacture and supply PENNSAID 2% to us. The term of our supply agreement is through December 31, 2029, but the agreement may be terminated earlier by either party for any uncured material breach by the other party of its obligations under the supply agreement or upon the bankruptcy or similar proceeding of the other party.

A key excipient used in PENNSAID 2% as a penetration enhancer is DMSO. We and Nuvo rely on a sole proprietary form of DMSO for which we maintain a substantial safety stock. However, should this supply become inadequate, damaged, destroyed or unusable, we and Nuvo may not be able to qualify a second source.

DUEXIS

We purchase DUEXIS in final, packaged form exclusively from Sanofi-Aventis U.S. LLC, or Sanofi, for our commercial requirements in North America. The first API in DUEXIS is ibuprofen in a direct compression blend called DC85 and is supplied to Sanofi by BASF Corporation, or BASF, in Bishop, Texas. The second API in DUEXIS is famotidine, which is available from a number of international suppliers. Famotidine is currently sourced from two manufacturers. We currently receive both APIs in powder form and each is blended with a number of U.S. Pharmacopeia inactive ingredients.

BASF

In July 2010, we entered into a contract with BASF for the purchase of DC85, which was subsequently amended effective as of January 2016. Pursuant to the agreement, which expired in December 2018, we were obligated to source a significant majority of our commercial demand for DC85 from BASF. During 2018, BASF notified customers that were being supplied by the Bishop manufacturing facility, including us, that it would not be renewing supply agreements due to a technical issue at the facility that has prevented it from supplying these customers. During 2019, BASF has supplied us with a limited amount of DC85 and informed us of their intention to return to full supply. While we consider our DUEXIS inventory on hand to be sufficient to meet current and future commercial requirements, we cannot guarantee that BASF's manufacturing facility will return to full operations or we will be able to enter into a new supply agreement with BASF for DC85.

Manufacturing and Supply Agreement with Sanofi

In May 2011, we entered into a manufacturing and supply agreement with Sanofi, which was amended in September 2013 and May 2018. Pursuant to the agreement, Sanofi is obligated to manufacture and supply DUEXIS to us in final, packaged form, and we are obligated to purchase DUEXIS exclusively from Sanofi for our commercial requirements in North America and certain countries and territories in Europe, including the EU member states and Scandinavia, and South America. Sanofi must acquire the components necessary to manufacture DUEXIS, including the APIs, and is obligated to acquire all DC85 under the terms of our agreements with suppliers. In order to allow Sanofi to perform its obligations under the agreement, we granted Sanofi a non-exclusive license to our related intellectual property. The agreement term extends until September 2021, and automatically extends for successive two-year terms unless terminated by either party upon two years' prior written notice. Either party may terminate the agreement upon thirty days' prior written notice to the other party in the event of breach by the other party that is not cured within thirty days of notice (which notice period may be longer in certain, limited situations) or in the event we lose regulatory approval to market DUEXIS in all countries worldwide, and either party may terminate the agreement without cause upon two years' prior written notice to the other party at any time after the third anniversary of the first commercial sale of DUEXIS in any country worldwide.

VIMOVO

We purchase VIMOVO in final, packaged form from Patheon for our commercial requirements in North America. The first API in VIMOVO is naproxen which is supplied to Patheon by Divis Laboratories Limited in India. The second API in VIMOVO is esomeprazole magnesium trihydrate, which we source from Minakem Holding SAS in France.

Under a license agreement with Nuvo (formerly Aralez Pharmaceuticals Inc.), we are required to pay Nuvo a 10 percent royalty based on net sales of VIMOVO sold by us, our affiliates or sublicensees during the royalty term, subject to a minimum annual royalty obligation of $7.5 million, which minimum royalty obligations will continue for each year during which one of Nuvo's patents covers VIMOVO in the United States and there are no competing medicines in the United States. The royalty rate may be reduced to a mid-single digit royalty rate as a result of loss of market share to competing medicines.

Intellectual Property

Our objective is to aggressively patent the technology, inventions and improvements that we consider important to the development of our business. We have a portfolio of patents and applications based on clinical and pharmacokinetic/pharmacodynamic modeling discoveries, and our novel formulations. We intend to continue filing patent applications seeking intellectual property protection as we generate anticipated formulation refinements, new methods of manufacturing and clinical trial results.

We will only be able to protect our technologies and medicines from unauthorized use by third parties to the extent that valid and enforceable patents or trade secrets cover them. As such, our commercial success will depend in part on receiving and maintaining patent protection and trade secret protection of our technologies and medicines as well as successfully defending these patents against third-party challenges.

The patent positions of life sciences companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in such companies' patents has emerged to date in the United States. The patent situation outside the United States is even more uncertain. Changes in either the patent laws or in interpretations of patent laws in the United States or other countries may diminish the value of our intellectual property. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in our patents or in third-party patents. For example:

- we or our licensors might not have been the first to make the inventions covered by each of our pending patent applications and issued patents;
- we or our licensors might not have been the first to file patent applications for these inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies;
- it is possible that none of our pending patent applications or the pending patent applications of our licensors will result in issued patents;
- our issued patents and the issued patents of our licensors may not provide a basis for commercially viable drugs, or may not provide us with any competitive advantages, or may be challenged and invalidated by third parties;
- we may not be successful in any patent litigation to enforce our patent rights, including our pending patent litigation regarding PENNSAID 2%, DUEXIS and/or VIMOVO;
- we may not develop additional proprietary technologies or medicine candidates that are patentable; or
- the patents of others may have an adverse effect on our business.

KRYSTEXXA

We have licenses to U.S. and foreign patents and applications covering KRYSTEXXA. If not otherwise invalidated, those patents expire between 2021 and 2030. We continue to prosecute and pursue patent protection to obtain additional patent coverage on KRYSTEXXA and its uses.

In the United States, KRYSTEXXA has received twelve years of biologic exclusivity, expiring in 2022.

RAVICTI

We have ownership of U.S. and foreign patents and patent applications covering RAVICTI. If not otherwise invalidated, those patents expire between 2030 and 2036. We license our rights to patents and patent applications outside of North America and Japan to Immedica. We continue to prosecute and pursue patent protection to obtain additional patent coverage on RAVICTI and its uses.

In the United States, RAVICTI received two separate orphan drug exclusivities for two patient populations. The first of those orphan drug exclusivities expired on February 1, 2020, and the second will expire on April 28, 2024. Under our settlement and license agreement with Par Pharmaceutical, Inc., Par Pharmaceutical, Inc. may enter the market on July 1, 2025, or earlier in certain circumstances. We also have a settlement and license agreement with Lupin Limited and Lupin Pharmaceuticals, Inc., or collectively Lupin, pursuant to which Lupin may enter the market on July 1, 2026, or earlier under certain circumstances.

PROCYSBI

We have U.S. and foreign patents and patent applications covering PROCYSBI, as well as licenses from UCSD to U.S. and foreign patents and patent applications covering PROCYSBI. If not otherwise invalidated, those patents expire between 2027 and 2034. We continue to prosecute and pursue patent protection to obtain additional patent coverage on PROCYSBI and its uses.

PROCYSBI received marketing authorization in September 2013 from the European Commission, or the EC, for marketing in the EU as an orphan medicinal product for the management of proven NC.

PROCYSBI received seven years of market exclusivity, through 2020, for patients six years and older as an orphan drug in the United States, and ten years of market exclusivity, through 2023, as an orphan drug in Europe. PROCYSBI received seven years of market exclusivity, through 2022, for patients two years of age to less than six years of age, and seven years of market exclusivity, through 2024, for patients one year of age to less than two years of age, as an orphan drug in the United States. During December 2017, the FDA awarded pediatric exclusivity to PROCYSBI in the United States, which adds an additional six-month exclusivity period to the end of each orphan exclusivity period and patent term covering PROCYSBI.

ACTIMMUNE

We have licenses to U.S. patents covering ACTIMMUNE. If not otherwise invalidated, those patents expire in 2022. We continue to prosecute and pursue patent protection to obtain additional patent coverage on ACTIMMUNE and its uses.

RAYOS/LODOTRA

We have an exclusive license to U.S. and foreign patents and patent applications from Vectura covering RAYOS/LODOTRA. If not otherwise invalidated, those in-licensed patents expire between 2020 and 2028. We continue to prosecute and pursue additional patent coverage on RAYOS/LODOTRA and its uses. Under our settlement agreement with Teva Pharmaceuticals Industries Limited (formerly known as Actavis Laboratories FL, Inc., which itself was formerly known as Watson Laboratories, Inc. – Florida), or Teva, Teva may enter the market on December 23, 2022, or earlier under certain circumstances. Effective January 1, 2019, we amended our license and supply agreements with Jagotec AG and Skyepharma AG, which is also an affiliate of Vectura. Under these amendments, we agreed to transfer all economic benefits of LODOTRA in Europe to Vectura during an initial transition period, with full rights transferring to Vectura when certain transfer activities have been completed. These transfer activities are ongoing.

QUINSAIR

We have U.S. and foreign patents and patent applications covering QUINSAIR, as well as licenses from PARI and Tripex Pharmaceuticals, LLC to U.S. and foreign patents and patent applications covering QUINSAIR. If not otherwise invalidated, those patents expire between 2020 and 2032. We continue to prosecute and pursue patent protection to obtain additional patent coverage on QUINSAIR and its uses.

QUINSAIR received ten years of market exclusivity in the EU, beginning with its March 2015 marketing authorization and expiring in March 2025.

PENNSAID 2%

We have ownership of U.S. patents and patent applications covering PENNSAID 2% from Nuvo. We also co-own other U.S. patent applications with Mallinckrodt LLC. If not otherwise invalidated, those patents expire between 2027 and 2030. Under our settlement agreements with Amneal Pharmaceuticals, LLC., Teligent, Inc., Perrigo Company plc, Taro Pharmaceuticals Industries Ltd., and Lupin, such parties may enter the market on October 17, 2027, or earlier under certain circumstances.

DUEXIS

We have multiple patents and patent applications related to DUEXIS. Unless otherwise invalidated, those patents expire in 2026. Under a settlement agreement with Par Pharmaceutical, Inc. and Par Pharmaceutical Companies, Inc., or collectively Par, Par may enter the market on January 1, 2023, or earlier under certain circumstances.

VIMOVO

We have licenses to U.S. patents and patent applications and trademarks covering VIMOVO from Nuvo and AstraZeneca AB. We co-own other U.S. patents and patent applications with Nuvo. If not otherwise invalidated, those in-licensed patents expire between 2022 and 2031. We continue to prosecute and pursue patent protection in the United States to obtain additional patent coverage on VIMOVO and its uses.

For a description of our legal proceedings related to intellectual property matters, see Note 16 of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K.

Third-Party Coverage and Reimbursement

In both U.S. and foreign markets, our ability to commercialize our medicines successfully depends in significant part on the availability of coverage and adequate reimbursement to healthcare providers from third-party payers, including, in the United States, government payers such as the Medicare and Medicaid programs, managed care organizations and private health insurers. Third-party payers are increasingly challenging the prices charged for medicines and examining their cost effectiveness, in addition to their safety and efficacy. This is especially true in markets where over-the-counter and generic options exist. Even if coverage is made available by a third-party payer, the reimbursement rates paid for covered medicines might not be adequate. For example, third-party payers may use tiered coverage and may adversely affect demand for our medicines by not covering our medicines or by placing them in a more expensive formulary tier relative to competitive medicines (where patients have to pay relatively more out of pocket than for medicines in a lower tier). We cannot be certain that our medicines will be covered by third-party payers or that such coverage, where available, will be adequate, or that our medicines will successfully be placed on the list of drugs covered by particular health plan formularies. Many states have also created preferred drug lists for use in their Medicaid programs and include drugs on those lists only when the manufacturers agree to pay a supplemental rebate. The industry competition to be included on such formularies and preferred drug lists often leads to downward pricing pressures on pharmaceutical companies. Also, third-party payers may refuse to include a particular branded drug on their formularies or otherwise restrict patient assistance to a branded drug when a less costly generic equivalent or other therapeutic alternative is available. In addition, because each third-party payer individually approves coverage and reimbursement levels, obtaining coverage and adequate reimbursement is a time-consuming and costly process. We may be required to provide scientific and clinical support for the use of any medicine to each third-party payer separately with no assurance that approval would be obtained, and we may need to conduct pharmacoeconomic studies to demonstrate the cost effectiveness of our medicines for formulary coverage and reimbursement. Even with studies, our medicines may be considered less safe, less effective or less cost-effective than competitive medicines, and third-party payers may not provide coverage and adequate reimbursement for our medicines or our medicine candidates. These pricing and reimbursement pressures may create negative perceptions to any medicine price increases, or limit the amount we may be able to increase our medicine prices, which may adversely affect our medicine sales and results of operations. Where coverage and reimbursement are not adequate, physicians may limit how much or under what circumstances they will prescribe or administer such medicines, and patients may decline to purchase them. This, in turn, could affect our ability to successfully commercialize our medicines and impact our profitability, results of operations, financial condition, and future success.

The U.S. market has seen a trend in which retail pharmacies have become increasingly involved in determining which prescriptions will be filled with the requested medicine or a substitute medicine, based on a number of factors, including potentially perceived medicine costs and benefits, as well as payer medicine substitution policies. Many states have in place requirements for prescribers to indicate “dispense as written” on their prescriptions if they do not want pharmacies to make medicine substitutions; these requirements are varied and not consistent across states. We may need to increasingly spend time and resources to ensure the prescriptions written for our medicines are filled as written, where appropriate.

Coverage policies, third-party reimbursement rates and medicine pricing regulation have been subject to significant change, and may change further at any time, particularly given recent political focus on the pharmaceutical industry. Even if favorable coverage and adequate reimbursement status is attained for one or more medicines, less favorable coverage policies and reimbursement rates may be implemented in the future.

Government Regulation

The FDA and comparable regulatory agencies in state and local jurisdictions and in foreign countries impose extensive requirements upon the clinical development, pre-market approval, manufacture, labeling, marketing, promotion, pricing, import, export, storage and distribution of medicines. These agencies and other regulatory agencies regulate research and development activities and the testing, approval, manufacture, quality control, safety, effectiveness, labeling, storage, recordkeeping, advertising and promotion of drugs and biologics. Failure to comply with applicable FDA or foreign regulatory agency requirements may result in warning letters, fines, civil or criminal penalties, additional reporting obligations and/or agency oversight, suspension or delays in clinical development, recall or seizure of medicines, partial or total suspension of production or withdrawal of a medicine from the market.

In the United States, the FDA regulates drug products under the Federal Food, Drug, and Cosmetic Act and its implementing regulations and biologics additionally under the Public Health Service Act. The process required by the FDA before medicine candidates may be marketed in the United States generally involves the following:

- submission to the FDA of an investigational new drug, or IND, which must become effective before human clinical trials may begin and must be updated annually;
- completion of extensive pre-clinical laboratory tests and pre-clinical animal studies, all performed in accordance with the FDA's Good Laboratory Practice, or GLP, regulations;
- performance of adequate and well-controlled human clinical trials to establish the safety and efficacy of the medicine candidate for each proposed indication;
- submission to the FDA of a new drug application, or NDA, or BLA as appropriate, after completion of all pivotal clinical trials to demonstrate the safety, purity and potency of the medicine candidate for the indication for use;
- a determination by the FDA within sixty days of its receipt of an NDA or BLA to file the application for review;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facilities to assess compliance with the FDA's current good manufacturing practices, or cGMPs, regulations for pharmaceuticals; and
- FDA review and approval of an NDA or BLA prior to any commercial marketing or sale of the medicine in the United States.

The development and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our medicine candidates will be granted on a timely basis, if at all.

The results of pre-clinical tests (which include laboratory evaluation as well as GLP studies to evaluate toxicity in animals) for a particular medicine candidate, together with related manufacturing information and analytical data, are submitted as part of an IND to the FDA. The IND automatically becomes effective thirty days after receipt by the FDA, unless the FDA, within the thirty-day time period, raises concerns or questions about the conduct of the proposed clinical trial, including concerns that human research subjects will be exposed to unreasonable health risks. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. IND submissions may not result in FDA authorization to commence a clinical trial. A separate submission to an existing IND must also be made for each successive clinical trial conducted during medicine development. Further, an independent institutional review board, or IRB, for each medical center proposing to conduct the clinical trial must review and approve the plan for any clinical trial before it commences at that center and it must monitor the study until completed. The FDA, the IRB or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk. Clinical testing also must satisfy extensive good clinical practice regulations and regulations for informed consent and privacy of individually identifiable information. Similar requirements to the U.S. IND are required in the European Economic Area, or the EEA, and other jurisdictions in which we may conduct clinical trials.

Clinical Trials. For purposes of NDA or BLA submission and approval, clinical trials are typically conducted in the following sequential phases, which may overlap:

- *Phase 1*. Studies are initially conducted in a limited population to test the medicine candidate for safety, dose tolerance, absorption, distribution, metabolism, and excretion, typically in healthy humans, but in some cases in patients.
- *Phase 2*. Studies are generally conducted in a limited patient population to identify possible adverse effects and safety risks, explore the initial efficacy of the medicine for specific targeted indications and to determine dose range or pharmacodynamics. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more expensive Phase 3 clinical trials.

- *Phase 3*. These are commonly referred to as pivotal studies. When Phase 2 evaluations demonstrate that a dose range of the medicine is effective and has an acceptable safety profile, Phase 3 clinical trials are undertaken in large patient populations to further evaluate dosage, provide substantial evidence of clinical efficacy and further test for safety in an expanded and diverse patient population at multiple, geographically dispersed clinical trial centers.
- *Phase 4*. The FDA may approve an NDA or BLA for a medicine candidate, but require that the sponsor conduct additional clinical trials to further assess the medicine after approval under a post-marketing commitment or post- marketing requirement. In addition, a sponsor may decide to conduct additional clinical trials after the FDA has approved a medicine. Post-approval trials are typically referred to as Phase 4 clinical trials.

The results of drug development, pre-clinical studies and clinical trials are submitted to the FDA as part of an NDA or BLA, as appropriate. Applications also must contain extensive chemistry, manufacturing and control information. Applications must be accompanied by a significant user fee. Once the submission has been accepted for filing, the FDA's goal is to review applications within twelve months of submission or, if the application relates to an unmet medical need in a serious or life-threatening indication, eight months from submission. The review process is often significantly extended by FDA requests for additional information or clarification. The FDA will typically conduct a pre-approval inspection of the manufacturer to ensure that the medicine can be reliably produced in compliance with cGMPs and will typically inspect certain clinical trial sites for compliance with good clinical practice, or GCP. The FDA may refer the application to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it typically follows such recommendations. The FDA may deny approval of an application by issuing a Complete Response Letter if the applicable regulatory criteria are not satisfied. A Complete Response Letter may require additional clinical data and/or trial(s), and/or other significant, expensive and time- consuming requirements related to clinical trials, pre-clinical studies or manufacturing. Data from clinical trials are not always conclusive and the FDA may interpret data differently than we or our collaborators interpret data. Approval may occur with boxed warnings on medicine labeling or Risk Evaluation and Mitigation Strategies, or REMS, which limit the labeling, distribution or promotion of a medicine. Once issued, the FDA may withdraw medicine approval if ongoing regulatory requirements are not met or if safety problems occur after the medicine reaches the market. In addition, the FDA may require testing, including Phase 4 clinical trials, and surveillance programs to monitor the safety effects of approved medicines which have been commercialized and the FDA has the power to prevent or limit further marketing of a medicine based on the results of these post-marketing programs or other information.

Clinical Trials in the EU. Clinical trials of medicinal products in the EU must be conducted in accordance with EU and national regulations and the international council for harmonization, or ICH, guidelines on GCP. Additional GCP guidelines from the EC, focusing in particular on traceability, apply to clinical trials of advanced therapy medicinal products. The sponsor must take out a clinical trial insurance policy, and in most EU countries, the sponsor is liable to provide "no fault" compensation to any study subject injured in the clinical trial.

Prior to commencing a clinical trial, the sponsor must obtain a clinical trial authorization from the competent authority, and a positive opinion from an independent ethics committee. The application for a clinical trial authorization must include, among other things, a copy of the trial protocol and an investigational medicinal product dossier containing information about the manufacture and quality of the medicinal product under investigation. Currently, clinical trial authorization applications must be submitted to the competent authority in each EU Member State in which the trial will be conducted. Under the new Regulation on Clinical Trials, which is expected to take effect in 2020, there will be a centralized application procedure where one national authority takes the lead in reviewing the application and the other national authorities have only a limited involvement. Any substantial changes to the trial protocol or other information submitted with the clinical trial applications must be notified to or approved by the relevant competent authorities and ethics committees. Medicines used in clinical trials must be manufactured in accordance with cGMP. Other national and EU-wide regulatory requirements also apply.

During the development of a medicinal product, the European Medicines Agency, or EMA, and national medicines regulators within the EU provide the opportunity for dialogue and guidance on the development program. At the EMA level, this is usually done in the form of scientific advice, which is given by the Scientific Advice Working Party of the Committee for Medicinal Products for Human Use. A fee is incurred with each scientific advice procedure. Advice from the EMA is typically provided based on questions concerning, for example, quality (chemistry, manufacturing and controls testing), nonclinical testing and clinical studies, and pharmacovigilance plans and risk-management programs.

Orphan Medicines. Under the Orphan Drug Act, the FDA may designate a medicine as an "orphan drug" if it is intended to treat a rare disease or condition, meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a medicine available in the United States for treatment of the disease or condition will be recovered from sales of the medicine. A company must request orphan drug designation before submitting an NDA for the drug and rare disease or condition. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan drug designation does not shorten the Prescription Drug User Fee Act, or PDUFA, goal dates for the regulatory review and approval process, although it does convey certain advantages such as tax benefits and exemption from the PDUFA application fee.

If a medicine with orphan designation receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the medicine generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor's marketing application for the same drug for the same indication for seven years, except in certain limited circumstances. Orphan exclusivity does not block the approval of a different drug for the same rare disease or condition, nor does it block the approval of the same drug for different indications. If a drug designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity. Orphan exclusivity will not bar approval of another medicine under certain circumstances, including if a subsequent medicine with the same drug for the same indication is shown to be clinically superior to the approved medicine on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand.

In the EU, Regulation (EC) No 141/2000 and Regulation (EC) No. 847/2000 provide that a medicine can be designated as an orphan medicinal product by the EC if its sponsor can establish: that the medicine is intended for the diagnosis, prevention or treatment of (1) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the EU when the application is made, or (2) a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that the marketing of the medicinal product in the EU would generate sufficient return to justify the necessary investment. For either of these conditions, the applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the EU or, if such method exists, the medicinal product will be of significant benefit to those affected by that condition. Once authorized, orphan medicinal products are entitled to ten years of market exclusivity in all EU Member States (extendable to twelve years for medicines that have complied with an agreed pediatric investigation plan pursuant to Regulation 1901/2006) and in addition a range of other benefits during the development and regulatory review process including scientific assistance for study protocols, authorization through the centralized marketing authorization procedure covering all member countries and a reduction or elimination of registration and marketing authorization fees. However, marketing authorization may be granted to a similar medicinal product with the same orphan indication during the regulatory exclusivity period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if this medicine is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if, at the end of the fifth year, it can be demonstrated on the basis of available evidence that the criteria for its designation as an orphan medicine are no longer satisfied, for example if the original orphan medicinal product has become sufficiently profitable not to justify maintenance of market exclusivity.

Other Regulatory Requirements. Medicines manufactured or distributed pursuant to FDA approvals are subject to continuing regulation by the FDA, including recordkeeping, annual medicine quality review, payment of program fees and reporting requirements. Adverse event experience with the medicine must be reported to the FDA in a timely fashion and pharmacovigilance programs to proactively look for these adverse events are mandated by the FDA. Our medicines may be subject to REMS requirements that affect labeling, distribution or post market reporting. Drug manufacturers and their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMPs, which impose certain procedural and documentation requirements upon us and our third-party manufacturers. Following such inspections, the FDA may issue notices on Form 483 and untitled letters or warning letters that could cause us or our third-party manufacturers to modify certain activities. A Form 483 notice, if issued at the conclusion of an FDA inspection, can list conditions the FDA investigators believe may have violated cGMP or other FDA regulations or guidelines. In addition to Form 483 notices and untitled letters, failure to comply with the statutory and regulatory requirements can subject a manufacturer to possible legal or regulatory action, such as suspension of manufacturing, seizure of medicine, injunctive action, additional reporting requirements and/or oversight by the agency, import alert or possible civil penalties. The FDA may also require us to recall a drug from distribution or withdraw approval for that medicine.

The FDA closely regulates the post-approval marketing and promotion of pharmaceuticals, including standards and regulations for direct-to-consumer advertising, dissemination of off-label information, industry-sponsored scientific and educational activities and promotional activities involving the Internet, including certain social media activities. Medicines may be marketed only for the approved indications and in accordance with the provisions of the approved label. Further, if there are any modifications to the medicine, including changes in indications, labeling, or manufacturing processes or facilities, we may be required to submit and obtain FDA approval of a new or supplemental application, which may require us to develop additional data or conduct additional pre-clinical studies and clinical trials. Failure to comply with these requirements can result in adverse publicity, untitled letters, corrective advertising and potential administrative, civil and criminal penalties, as well as damages, fines, withdrawal of regulatory approval, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs, additional reporting requirements and/or oversight by the agency, and imprisonment, any of which could adversely affect our ability to sell our medicines or operate our business and also adversely affect our financial results.

Physicians may, in their independent medical judgment, prescribe legally available pharmaceuticals for uses that are not described in the medicine's labeling and that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, impose stringent restrictions on manufacturers' communications regarding off-label use. Additionally, a significant number of pharmaceutical companies have been the target of inquiries and investigations by various U.S. federal and state regulatory, investigative, prosecutorial and administrative entities in connection with the promotion of medicines for off-label uses and other sales practices. These investigations have alleged violations of various U.S. federal and state laws and regulations, including claims asserting antitrust violations, violations of the Food, Drug and Cosmetic Act, false claims laws, the Prescription Drug Marketing Act, or PDMA, anti-kickback laws, and other alleged violations in connection with the promotion of medicines for unapproved uses, pricing and Medicare and/or Medicaid reimbursement. If our promotional activities, including any promotional activities that a contracted sales force may perform on our behalf, fail to comply with these regulations or guidelines, we may be subject to warnings from, or enforcement action by, these authorities. In addition, our failure to follow FDA rules and guidelines relating to promotion and advertising may cause the FDA to issue warning letters or untitled letters, suspend or withdraw an approved medicine from the market, require corrective advertising or a recall or institute fines or civil fines, additional reporting requirements and/or oversight or could result in disgorgement of money, operating restrictions, injunctions or criminal prosecution, any of which could harm our business. In addition, the distribution of prescription medicines is subject to the PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription medicine samples and impose requirements to ensure accountability in distribution, including a drug pedigree which tracks the distribution of prescription drugs. Further, under the Drug Quality and Security Act, drug manufacturers are subject to a number of requirements, including, medicine identification, tracing and verification, among others, that are designed to detect and remove counterfeit, stolen, contaminated or otherwise potentially harmful drugs from the U.S. drug supply chain.

Outside the United States, the ability of our partners and us to market a medicine is contingent upon obtaining marketing authorization from the appropriate regulatory authorities. The requirements governing marketing authorization, pricing and reimbursement vary widely from country to country and region to region.

The EU and the EEA consist, at the time of writing, of the twenty-seven Member States of the EU (for details on the impact the United Kingdom leaving the EU will have, see the section entitled 'The Impact of Brexit' below), plus Norway, Iceland and Liechtenstein which are Member States of the EEA. These Member States have all acceded to the single market rules governing the supervision of medicinal products. Under the prevailing rules, medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. There are three procedures for an MA to be obtained:

- the Centralized MA, which is issued by the EC through the Centralized Procedure, based on the scientific opinion of the Committee for Medicinal Products for Human Use of the EMA, and which is valid throughout the entire territory of the EU/EEA. The Centralized Procedure is mandatory for certain types of products, such as (i) biotechnology medicinal products such as genetic engineering, (ii) orphan medicinal products, (iii) medicinal products containing a new active substance indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune and viral diseases and (iv) advanced-therapy medicines, such as gene therapy, somatic cell therapy or tissue-engineered medicines. The Centralized Procedure is optional for products containing a new active substance not yet authorized in the EU/EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU.
- Decentralized Procedure MAs are available for products not falling within the mandatory scope of the Centralized Procedure. An identical dossier is submitted to the competent authorities of each of the Member States in which the MA is sought, one of which is selected by the applicant as the Reference Member State, or RMS, to lead the evaluation of the regulatory submission. The competent authority of the RMS prepares a draft assessment report, a draft summary of the product characteristics, or SmPC, and a draft of the labeling and package leaflet as distilled from the preliminary evaluation, which are sent to the other Member States (referred to as the Concerned Member States) for their approval. If the Concerned Member States raise no objections, based on a potential serious risk to public health, to the assessment, SmPC, labeling, or packaging proposed by the RMS, the RMS records the agreement, closes the procedure and informs the applicant accordingly. Each Member State concerned by the procedure is required to adopt a national decision to grant a national MA in conformity with the approved assessment report, SmPC and the labeling and package leaflet as approved. Where a product has already been authorized for marketing in a Member State of the EEA, the granted national MA can be used for mutual recognition in other Member States through the Mutual Recognition Procedure, or MRP, resulting in progressive national approval of the product in the EU/EEA.
- National MAs, which are issued by a single competent authority of the Member States of the EEA and only covers their respective territory, are also available for products not falling within the mandatory scope of the Centralized Procedure. Once a product has been authorized for marketing in a Member State of the EEA through the National Procedure, this National MA can also be recognized in other Member States through the MRP.

Under the procedures described above, before granting the MA, the EMA or the competent authority(ies) of the Member State(s) of the EEA prepare an assessment of the risk-benefit balance of the product against the scientific criteria concerning its quality, safety and efficacy.

Under Regulation (EC) No 726/2004/EC and Directive 2001/83/EC (each as amended), the EU has adopted a harmonized approach to data and market protection or exclusivity (known as the 8 + 2 + 1 formula). The data exclusivity period begins to run on the date when the first MA is granted in the EU. It confers on the MA holder of the reference medicinal product eight years of data protection and ten years of market protection. A reference medicinal product is defined to mean a medicinal product authorized based on a full dossier consisting of pharmaceutical and pre-clinical testing results and clinical trial data, such as a medicinal product containing a new active substance. The ten-year market protection can be extended cumulatively to a maximum period of eleven years if during the first eight years of those ten years of protection period, the MA holder obtains an authorization for one or more new therapeutic indications that are deemed to bring a significant clinical benefit compared to existing therapies.

The protection period means that an applicant for a generic medicinal product is not permitted to rely on pre-clinical pharmacological, toxicological, and clinical data contained in the file of the reference medicinal product of the originator until the first eight years of data protection have expired. Thereafter, a generic product application may be submitted and generic companies may rely on the pre-clinical and clinical data relating to the reference medicinal product to support approval of the generic product. However, a generic cannot market until ten years have elapsed from the initial authorization of the reference medicinal product or eleven years if the protection period is extended, based on the formula of 8+2+1.

In addition to the above, where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication. Finally, where a change of classification of a medicinal product has been authorized on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorization for a change of classification of the same substance for one year after the initial change was authorized.

The 8 + 2 + 1 exclusivity scheme applies to products that have been authorized in the EU by either the EMA through the Centralized Procedure or the competent authorities of the Member States of the EEA nationally, including through the Decentralized and Mutual Recognition procedures.

For a medicinal product which has received orphan designation under Regulation 141/2000, it will, as set out in further detail in the section entitled 'Orphan Medicines' above, benefit from a period of ten years of orphan market exclusivity which essentially constitutes a period of market monopoly. During this period of orphan market exclusivity, no EU regulatory authority is permitted to accept or approve an application for marketing authorization for a similar medicinal product or an extension application for the same therapeutic indication. This period can be extended cumulatively to a total of twelve years if the marketing authorization holder or applicant complies with the requirements for an agreed pediatric investigation plan pursuant to Regulation 1901/2006.

The holder of a Centralized MA or National MA is subject to various obligations under the applicable EU laws, such as pharmacovigilance obligations, requiring it to, among other things, report and maintain detailed records of adverse reactions, and to submit periodic safety update reports, or PSURs, to the competent authorities. All new marketing authorization applications must include a risk management plan, or RMP, describing the risk management system that the company will put in place and documenting measures to prevent or minimize the risks associated with the product. The regulatory authorities may also impose specific obligations as a condition of the marketing authorization. Such risk-minimization measures or post-authorization obligations may include additional safety monitoring, more frequent submission of PSURs, or the conduct of additional clinical trials or post-authorization safety studies. RMPs and PSURs are routinely available to third parties requesting access, subject to limited redactions. All advertising and promotional activities for the product must be consistent with the approved summary of product characteristics, and therefore all off-label promotion is prohibited. Direct-to-consumer advertising of prescription medicines is also prohibited in the EU. The holder must also ensure that the manufacturing and batch release of its product is in compliance with the applicable requirements. The MA holder is further obligated to ensure that the advertising and promotion of its products complies with applicable EU laws and industry code of practice as implemented in the domestic laws of the Member States of the EU/EEA. The advertising and promotional rules are enforced nationally by the EU/EEA Member States.

The Impact of Brexit. The withdrawal of the United Kingdom from the EU (commonly referred to as "Brexit") took effect on January 31, 2020. Since a significant portion of the regulatory framework in the United Kingdom applicable to our business and our products is derived from EU directives and regulations, Brexit could materially impact the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our products in the United Kingdom and/or the EU.

Healthcare Fraud and Abuse Laws. As a pharmaceutical company, certain federal and state healthcare laws and regulations pertaining to fraud and abuse and patients' rights are and will be applicable to our business. We may be subject to various federal and state laws targeting fraud and abuse in the healthcare industry. For example, in the United States, there are federal and state anti-kickback laws that prohibit the payment or receipt of kickbacks, bribes or other remuneration intended to induce the purchase or recommendation of healthcare products and services or reward past purchases or recommendations. Violations of these laws can lead to civil and criminal penalties, including fines, imprisonment, additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement, and exclusion from participation in federal healthcare programs. These laws are applicable to manufacturers of products regulated by the FDA, such as us, and pharmacies, hospitals, physicians and other potential purchasers of such products.

The federal Anti-Kickback Statute prohibits persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, to induce either the referral of an individual, or the furnishing, recommending, or arranging for a good or service, for which payment may be made under a federal healthcare program, such as the Medicare and Medicaid programs. The term "remuneration" is defined as any remuneration, direct or indirect, overt or covert, in cash or in kind, and has been broadly interpreted to include anything of value, including for example, gifts, discounts, the furnishing of supplies or equipment, credit arrangements, payments of cash, waivers of payment, ownership interests and providing anything at less than its fair market value. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute may have been violated, and enforcement will depend on the relevant facts and circumstances. The Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the ACA, among other things, amended the intent requirement of the federal Anti-Kickback Statute to state that a person or entity need not have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the ACA provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act (discussed below) or the civil monetary penalties statute, which imposes penalties against any person who is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent, or to have offered improper inducements to federal health care program beneficiaries to select a particular provider or supplier. The federal Anti-Kickback Statute is broad, and despite a series of narrow safe harbors, prohibits many arrangements and practices that are lawful in businesses outside of the healthcare industry. Many states have also adopted laws similar to the federal Anti-Kickback Statute, some of which apply to the referral of patients for healthcare items or services reimbursed by any source, not only the Medicare and Medicaid programs, and do not contain identical safe harbors. In addition, where such activities involve foreign government officials, they may also potentially be subject to the Foreign Corrupt Practices Act. Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities, including our activities with physician customers, pharmacies, and patients, as well as our activities pursuant to partnerships with other companies and pursuant to contracts with contract research organizations, could be subject to challenge under one or more of such laws.

The federal False Claims Act prohibits any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. A claim includes "any request or demand" for money or property presented to the U.S. government. In addition, the ACA specified that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act. The federal False Claims Act has been the basis for numerous enforcement actions and settlements by pharmaceutical and other healthcare companies in connection with various alleged financial relationships with customers. In addition, a number of pharmaceutical manufacturers have reached substantial financial settlements in connection with allegedly causing false claims to be submitted because of the companies' marketing of products for unapproved, and thus non-reimbursable, uses. Certain marketing practices, including off-label promotion, may also violate false claims laws, as might violations of the federal physician self-referral laws, such as the Stark laws, which prohibit a physician from making a referral to certain designated health services with which the physician or the physician's family member has a financial interest and prohibit submission of a claim for reimbursement pursuant to the prohibited referral. The "qui tam" provisions of the False Claims Act allow a private individual to bring civil actions on behalf of the federal government alleging that the defendant has submitted a false claim to the federal government, and to share in any monetary recovery. In addition, various states have enacted similar fraud and abuse statutes or regulations, including, without limitation, false claims laws analogous to the False Claims Act, and laws analogous to the federal Anti-Kickback Statute, that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payer, and there are also federal criminal false claims laws.

Separately, there are a number of other fraud and abuse laws that pharmaceutical manufacturers must be mindful of, particularly after a medicine candidate has been approved for marketing in the United States. For example, a federal criminal law enacted as part of, the Health Insurance Portability and Accountability Act of 1996, or HIPAA, prohibits knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payers. The false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. There are also federal civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payers that are false or fraudulent, as well as federal and state consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

Privacy and Security Laws. We may be subject to, or our marketing activities may be limited by, HIPAA, as amended by the Health Information Technology and Clinical Health Act (HITECH) and their respective implementing regulations, which established uniform standards for certain "covered entities" (healthcare providers, health plans and healthcare clearinghouses) governing the conduct of certain electronic healthcare transactions and protecting the security and privacy of protected health information. Among other things, HIPAA's privacy and security standards are directly applicable to "business associates" — independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. In addition to possible civil and criminal penalties for violations, state attorneys general are authorized to file civil actions for damages or injunctions in federal courts to enforce HIPAA and seek attorney's fees and costs associated with pursuing federal civil actions. Accordingly, state attorneys general (along with private plaintiffs) have brought civil actions seeking injunctions and damages resulting from alleged violations of HIPAA's privacy and security rules. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

In the EU/EEA, the General Data Protection Regulation (2016/679), or GDPR, went into effect in 2018 and replaced Directive 95/46/EC (the EU Privacy Directive). The GDPR applies to identified or identifiable personal data processed by automated means (for example, a computer database of customers) and data contained in, or intended to be part of, non-automated filing systems (traditional paper files) as well as transfer of such data to a country outside of the EU/EEA. Under the GDPR, fines of up to €20.0 million or up to 4% of the annual global turnover of the infringer, whichever is greater, could be imposed for significant non-compliance. The GDPR includes more stringent operational requirements for processors and controllers of personal data and creates additional rights for data subjects. Additionally, Brexit took effect in January 2020, which is also expected to lead to further legislative and regulatory changes. While the Data Protection Act of 2018, that "implements" and complements the GDPR has achieved Royal Assent on May 23, 2018 and is now effective in the United Kingdom, it is still unclear whether transfer of data from the EEA to the United Kingdom will remain lawful under GDPR. We may incur liabilities, expenses, costs, and other operational losses under GDPR and applicable EU Member States and the United Kingdom privacy laws in connection with any measures we take to comply with them.

Additionally, the California Consumer Privacy Act, or CCPA, became effective on January 1, 2020. The CCPA has been dubbed the first "GDPR-like" law in the United States since it creates new individual privacy rights for consumers (as that word is broadly defined in the law) and places increased privacy and security obligations on entities handling personal data of consumers or households (including health information). The CCPA requires covered companies to provide new disclosures to California consumers, provide such consumers new ways to opt-out of certain sales of personal information, and allows for a new cause of action for data breaches. It is unclear how the CCPA will be interpreted, but as currently written, it will likely impact our business activities and exemplifies the vulnerability of our business to not only cyber threats but also the evolving regulatory environment related to personal data and protected health information.

"Sunshine" and Marketing Disclosure Laws. There are an increasing number of federal and state "sunshine" laws that require pharmaceutical manufacturers to make reports to states on pricing and marketing information. Several states have enacted legislation requiring pharmaceutical companies to, among other things, establish marketing compliance programs, file periodic reports with the state, and make periodic public disclosures on sales and marketing activities, and prohibiting certain other sales and marketing practices. In addition, a similar federal requirement requires manufacturers, including pharmaceutical manufacturers, to track and report to the federal government the following: certain payments and other transfers of value made to physicians, teaching hospitals and, in 2021, other healthcare professionals including physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives; and ownership or investment interests held by physicians and their immediate family members. The federal government began disclosing the reported information on a publicly available website in 2014. Certain states, such as Massachusetts, also make the reported information publicly available. In addition, there are state and local laws that require pharmaceutical representatives to be licensed and comply with codes of conduct, transparency reporting, and other obligations. These laws may adversely affect our sales, marketing, and other activities with respect to our medicines in the United States by imposing administrative and compliance burdens on us. If we fail to track and report as required by these laws or otherwise comply with these laws, we could be subject to the penalty provisions of the pertinent state and federal authorities. In the EU/EEA, declaration of transfers of value to healthcare professionals is subject to the requirements under the voluntary industry code of practice. France however has a statutory regime similar to the U.S. Sunshine Act.

Government Price Reporting. For those marketed medicines which are covered in the United States by the Medicaid programs, we have various obligations, including government price reporting and rebate requirements, which generally require medicines be offered at substantial rebates/discounts to Medicaid and certain purchasers (including "covered entities" purchasing under the 340B Drug Discount Program). We are also required to discount such medicines to authorized users of the Federal Supply Schedule of the General Services Administration, under which additional laws and requirements apply. These programs require submission of pricing data and calculation of discounts and rebates pursuant to complex statutory formulas, as well as the entry into government procurement contracts governed by the Federal Acquisition Regulations, and the guidance governing such calculations is not always clear. Compliance with such requirements can require significant investment in personnel, systems and resources, but failure to properly calculate our prices, or offer required discounts or rebates could subject us to substantial penalties. One component of the rebate and discount calculations under the Medicaid and 340B programs, respectively, is the "additional rebate", a complex calculation which is based, in part, on the extent that a branded drug's price increases over time more than the rate of inflation (based on the Consumer Price Index for All Urban Consumers). This comparison is based on the baseline pricing data for the first full quarter of sales associated with a branded drug's NDA, and baseline data cannot generally be reset, even on transfer of the NDA to another manufacturer. This "additional rebate" calculation can, in some cases where price increase have been relatively high versus the first quarter of sales of the NDA, result in Medicaid rebates up to 100 percent of a drug's "average manufacturer price" and 340B prices of one penny. Governments influence the price of medicinal products in the EU through their pricing and reimbursement rules and control of national healthcare systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular product candidate to currently available therapies. Other EU Member States allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on healthcare costs in general, particularly prescription medicines, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products.

In General. Because of the breadth of these laws and the narrowness of available statutory and regulatory exemptions, it is possible that some of our business activities in the United States could be subject to challenge under one or more of such laws. Moreover, state governmental agencies may propose or enact laws and regulations that extend or contradict federal requirements. If we or our operations are found to be in violation of any of the state or federal laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including significant civil and criminal penalties, damages, fines, imprisonment, exclusion from participation in U.S. federal or state healthcare programs, additional reporting requirements and/or oversight and the curtailment or restructuring of our operations. To the extent that any medicine we make is sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals. Any penalties, damages, fines, curtailment or restructuring of our operations could materially adversely affect our ability to operate our business and our financial results. Although compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. Moreover, achieving and sustaining compliance with applicable federal, state and foreign privacy, security, sunshine, government price reporting, and fraud laws may prove costly.

Impact of Healthcare Reform and Recent Public Scrutiny of Drug Pricing on Coverage, Reimbursement, and Pricing. In the United States and other potentially significant markets for our medicines, federal and state lawmakers and regulatory authorities as well as third-party payers are increasingly attempting to regulate the price of medical products and services, particularly for new and innovative medicines and therapies, which has resulted in delays of coverage decisions, barriers for product access including higher patient copays and in certain cases, leads to lower average net selling prices. Further, there is increased scrutiny of prescription drug pricing practices by federal and state lawmakers and enforcement authorities. In addition, there is an emphasis on managed healthcare in the United States and on country-specific and regional pricing and reimbursement controls in the EU, both of which will put additional pressure on medicine pricing, reimbursement and usage, which may adversely affect our future medicine sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical reimbursement policies and pricing in general.

The U.S. and some foreign jurisdictions are considering or have enacted a number of additional legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our medicines profitably. Among policy makers and payers in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs (including a number of proposals pertaining to prescription drugs, specifically), improving quality and/or expanding access. In the United States, some of the additional proposals to reduce the cost of prescription drug prices considered at the federal level include directing Medicare to negotiate directly with manufacturers for the costliest drugs; various Medicare Part D and Medicaid reforms; price reporting transparency; importation rulemaking; an international pricing index proposal to require additional discounts to Medicare, as well as a proposal requiring manufacturers to pay a rebate to the federal government if the price of a Medicare Part B or Part D drug increases more than the rate of inflation. Also at the federal level, the Trump administration's budget proposal for fiscal year 2020 contained further drug price control measures that could be enacted during the 2020 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid and to eliminate cost sharing for generic drugs for low-income patients. For example, in May 2019, CMS issued a final regulation that would require Part D plans to include drug pricing information and lower cost therapeutic alternatives as well as allow "step therapy" in Medicare Advantage for Part B drugs. While these final measures will require additional rulemaking and action by Congress to pass legislation to become effective, these provisions reinforce the administration's focus on controlling drug prices. At the state level, in Massachusetts, the MassHealth program has requested permission from the federal government to use commercial tools, such as a closed formulary, to negotiate more favorable rebate agreements from drug manufacturers. There also has been particular and increasing legislative and enforcement interest in the United States with respect to drug pricing practices in recent years, particularly with respect to drugs that have been subject to relatively large price increases over relatively short time periods. There have been several recent state and federal lawmaker inquiries, proposed legislation and enacted legislation as was the case in California designed to, among other things, bring more transparency to drug pricing, by requiring drug companies to notify insurers and government regulators of price increases and provide an explanation of the reasons for the increase. There have also been actions to review the relationship between pricing and manufacturer patient assistance programs, and reform government program reimbursement methodologies for drugs. In the United States, the pharmaceutical industry has already been significantly affected by major legislative initiatives, including, for example, the ACA. The ACA, among other things, imposes a significant annual fee on companies that manufacture or import branded prescription drug products. It also contains substantial provisions intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, and impose additional health policy reforms, any or all of which may affect our business. Since its enactment, there have been judicial and Congressional challenges to numerous provisions of the ACA. These challenges include Executive Orders directing federal agencies with authorities and responsibilities under the ACA, to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices as well as legislation passed by the House of Representatives and Senate, but not yet signed into law, to repeal certain aspects of the ACA. On October 12, 2017, U.S. President Donald Trump signed another Executive Order directing certain federal agencies (including HHS) to propose regulations or guidelines, such regulations that HHS finalized by HHS in 2019 to permit small businesses to form association health plans, expand the availability of short-term, limited duration insurance, and expand the use of health reimbursement arrangements, which may circumvent some of the requirements for health insurance mandated by the ACA. In addition, citing legal guidance from the U.S. Department of Justice and the U.S. Department of Health and Human Services, the Trump administration has concluded that cost-sharing reduction, or CSR, payments to insurance companies required under the ACA have not received necessary appropriations from Congress and announced that it will discontinue these payments immediately until such appropriations are made. The loss of the CSR payments is expected to increase premiums on certain policies issued by qualified health plans under the ACA. Finally, while Congress has not passed comprehensive ACA repeal or replace legislation, the federal income tax legislation signed into law on December 22, 2017 includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate". We continue to evaluate the effect that the ACA and additional actions by Congress to possibly repeal and replace it has on our business.

Other legislative changes have also been proposed and adopted since the ACA was enacted. For example, the Budget Control Act of 2011 resulted in aggregate reductions in Medicare payments to providers of up to 2 percent per fiscal year, starting in 2013, and the American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Such laws, and others that may affect our business that have been recently enacted or may in the future be enacted, may result in additional reductions in Medicare and other healthcare funding. In the future, there will likely continue to be additional proposals relating to the reform of the U.S. healthcare system, some of which could further limit coverage and reimbursement of medicines, including our medicine candidates. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payers. Further, the Bipartisan Budget Act of 2018, or the BBA, among other things, amends the ACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans (also known as the Medicare "Donut Hole"), and also increases in 2019 the percentage that a drug manufacturer must discount the cost of prescription drugs from 50 percent under current law to 70 percent. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our medicines.

Irish Law Matters

As we are an Irish-incorporated company, the following matters of Irish law are relevant to the holders of our ordinary shares.

Irish Restrictions on Import and Export of Capital. Except as indicated below, there are no restrictions imposed specifically on non-residents of Ireland dealing in Irish domestic securities, which includes ordinary shares of Irish companies. Dividends and redemption proceeds also continue to be freely transferable to non-resident holders of such securities. The Financial Transfers Act 1992 gives power to the Minister for Finance of Ireland to restrict financial transfers between Ireland and other countries and persons. Financial transfers are broadly defined and include all transfers that would be movements of capital or payments within the meaning of the treaties governing the member states of the EU. The acquisition or disposal of interests in shares issued by an Irish incorporated company and associated payments falls within this definition. In addition, dividends or payments on redemption or purchase of shares and payments on a liquidation of an Irish incorporated company would fall within this definition. The Criminal Justice (Terrorist Offences) Act 2005 (as amended) also gives the Minister of Finance of Ireland the power to take various measures, including the freezing or seizure of assets, in order to combat terrorism. At present the Financial Transfers Act 1992, certain EU regulations (as implemented into Irish law) and the Criminal Justice (Terrorist Offences) Act 2005 (as amended) prohibit financial transfers involving certain persons and entities associated with the ISIL (Da'esh) and Al-Qaida organizations, the late Slobodan Milosevic and associated persons, Republic of Guinea-Bissau, Myanmar/Burma, Belarus, certain persons indicted by the International Criminal Tribunal for the former Yugoslavia, the late Osama bin Laden, Al-Qaida, the Taliban of Afghanistan, Democratic Republic of Congo, Democratic People's Republic of Korea (North Korea), Iran, Iraq, Côte d'Ivoire, Lebanon, Liberia, Zimbabwe, South Sudan, Sudan, Somalia, Republic of Guinea, Afghanistan, Egypt, Eritrea, Libya, Syria, Tunisia, Burundi, the Central African Republic, Ukraine, Yemen, Bosnia and Herzegovina, certain known terrorists and terrorist groups, and countries that harbor certain terrorist groups, without the prior permission of the Central Bank of Ireland or the Minister of Finance (as applicable).

Any transfer of, or payment in respect of, a share or interest in a share involving the government of any country that is currently the subject of United Nations or EU sanctions, any person or body controlled by any of the foregoing, or by any person acting on behalf of the foregoing, may be subject to restrictions pursuant to such sanctions as implemented into Irish law.

Irish Taxes Applicable to U.S. Holders

Withholding Tax on Dividends. While we have no current plans to pay dividends, dividends on our ordinary shares would generally be subject to Irish Dividend Withholding Tax, or DWT, at the rate of 25 percent, unless an exemption applies.

Dividends on our ordinary shares that are owned by residents of the United States and held beneficially through the Depositary Trust Company, or DTC, will not be subject to DWT provided that the address of the beneficial owner of the ordinary shares in the records of the broker is in the United States.

Dividends on our ordinary shares that are owned by residents of the United States and held directly (outside of DTC) will not be subject to DWT provided that the shareholder has completed the appropriate Irish DWT form and this form remains valid. Such shareholders must provide the appropriate Irish DWT form to our transfer agent at least seven business days before the record date for the first dividend payment to which they are entitled.

If any shareholder who is resident in the United States receives a dividend subject to DWT, he or she should generally be able to make an application for a refund from the Irish Revenue Commissioners on the prescribed form (DWT Claim Form 1).

While the U.S./Ireland Double Tax Treaty contains provisions regarding withholding tax, due to the wide scope of the exemptions from DWT available under Irish domestic law, it would generally be unnecessary for a U.S. resident shareholder to rely on the treaty provisions.

Income Tax on Dividends. A shareholder who is neither resident nor ordinarily resident in Ireland and who is entitled to an exemption from DWT generally has no additional liability to Irish income tax or to the universal social charge on a dividend from us unless that shareholder holds our ordinary shares through a branch or agency in Ireland through which a trade is carried on.

A shareholder who is neither resident nor ordinarily resident in Ireland and who is not entitled to an exemption from DWT generally has no additional liability to Irish income tax or to the universal social charge on a dividend from us. The DWT deducted by us discharges the liability to Irish income tax and to the universal social charge. This however is not the case where the shareholder holds the ordinary shares through a branch or agency in Ireland through which a trade is carried on.

Irish Tax on Capital Gains. A shareholder who is neither resident nor ordinarily resident in Ireland and does not hold our ordinary shares in connection with a trade or business carried on by such shareholder in Ireland through a branch or agency should not be within the charge to Irish tax on capital gains on a disposal of our ordinary shares.

Capital Acquisitions Tax. Irish capital acquisitions tax, or CAT, is composed principally of gift tax and inheritance tax. CAT could apply to a gift or inheritance of our ordinary shares irrespective of the place of residence, ordinary residence or domicile of the parties. This is because our ordinary shares are regarded as property situated in Ireland as our share register must be held in Ireland. The person who receives the gift or inheritance has primary liability for CAT.

CAT is levied at a rate of 33 percent above certain tax-free thresholds. The appropriate tax-free threshold is dependent upon (i) the relationship between the donor and the donee and (ii) the aggregation of the values of previous gifts and inheritances received by the donee from persons within the same category of relationship for CAT purposes. Gifts and inheritances passing between spouses are exempt from CAT. Our shareholders should consult their own tax advisers as to whether CAT is creditable or deductible in computing any domestic tax liabilities.

Stamp Duty. Irish stamp duty (if any) may become payable in respect of ordinary share transfers. However, a transfer of our ordinary shares from a seller who holds shares through DTC to a buyer who holds the acquired shares through DTC will not be subject to Irish stamp duty. A transfer of our ordinary shares (i) by a seller who holds ordinary shares outside of DTC to any buyer, or (ii) by a seller who holds the ordinary shares through DTC to a buyer who holds the acquired ordinary shares outside of DTC, may be subject to Irish stamp duty (currently at the rate of 1 percent of the price paid or the market value of the ordinary shares acquired, if greater). The person accountable for payment of stamp duty is the buyer or, in the case of a transfer by way of a gift or for less than market value, all parties to the transfer.

A shareholder who holds ordinary shares outside of DTC may transfer those ordinary shares into DTC without giving rise to Irish stamp duty provided that the shareholder would be the beneficial owner of the related book-entry interest in those ordinary shares recorded in the systems of DTC (and in exactly the same proportions) as a result of the transfer and at the time of the transfer into DTC there is no sale of those book-entry interests to a third party being contemplated by the shareholder. Similarly, a shareholder who holds ordinary shares through DTC may transfer those ordinary shares out of DTC without giving rise to Irish stamp duty provided that the shareholder would be the beneficial owner of the ordinary shares (and in exactly the same proportions) as a result of the transfer, and at the time of the transfer out of DTC there is no sale of those ordinary shares to a third party being contemplated by the shareholder. In order for the share registrar to be satisfied as to the application of this Irish stamp duty treatment where relevant, the shareholder must confirm to us that the shareholder would be the beneficial owner of the related book-entry interest in those ordinary shares recorded in the systems of DTC (and in exactly the same proportions) (or vice-versa) as a result of the transfer and there is no agreement for the sale of the related book-entry interest or the ordinary shares or an interest in the ordinary shares, as the case may be, by the shareholder to a third party being contemplated.

Employees

As of December 31, 2019, we had approximately 1,200 full-time employees. Of our employees as of December 31, 2019, approximately 230 were engaged in development, regulatory and manufacturing activities, approximately 740 were engaged in sales and marketing and approximately 230 were engaged in administration, including business development, finance, legal, information systems, facilities and human resources. None of our employees are subject to a collective bargaining agreement. We consider our employee relations to be good.

Available Information

We make available free of charge on or through our internet website our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and all amendments to those reports as soon as reasonably practicable after such material is electronically filed with or furnished to the Securities and Exchange Commission. We also regularly post copies of our press releases as well as copies of presentations and other updates about our business on our website. Our website address is www.horizontherapeutics.com. The information contained in or that can be accessed through our website is not part of this Annual Report on Form 10-K. Information is also available through the Securities and Exchange Commission's website at www.sec.gov.

Item 1A. Risk Factors

Certain factors may have a material adverse effect on our business, financial condition and results of operations, and you should carefully consider them. Accordingly, in evaluating our business, we encourage you to consider the following discussion of risk factors in its entirety, in addition to other information contained in this report as well as our other public filings with the Securities and Exchange Commission, or SEC.

Risks Related to Our Business and Industry

Our ability to generate revenues from our medicines is subject to attaining significant market acceptance among physicians, patients and healthcare payers.

Our current medicines, and other medicines or medicine candidates that we may develop or acquire, may not attain market acceptance among physicians, patients, healthcare payers or the medical community. Some of our medicines have not been on the market for an extended period of time, which subjects us to numerous risks as we attempt to increase our market share. We believe that the degree of market acceptance and our ability to generate revenues from our medicines will depend on a number of factors, including:

- timing of market introduction of our medicines as well as competitive medicines;
- efficacy and safety of our medicines;
- continued projected growth of the markets in which our medicines compete;
- the extent to which physicians diagnose and treat the conditions that our medicines are approved to treat;
- prevalence and severity of any side effects;

- if and when we are able to obtain regulatory approvals for additional indications for our medicines;
- acceptance by patients, physicians and key specialists;
- availability of coverage and adequate reimbursement and pricing from government and other third-party payers;
- potential or perceived advantages or disadvantages of our medicines over alternative treatments, including cost of treatment and relative convenience and ease of administration;
- strength of sales, marketing and distribution support;
- the price of our medicines, both in absolute terms and relative to alternative treatments;
- impact of past and limitation of future medicine price increases;
- our ability to maintain a continuous supply of our medicines for commercial sale;
- the effect of current and future healthcare laws;
- the performance of third-party distribution partners, over which we have limited control; and
- medicine labeling or medicine insert requirements of the U.S. Food and Drug Administration, or FDA, or other regulatory authorities.

With respect to KRYSTEXXA, our ability to grow sales will be affected by the success of our sales, marketing and clinical strategies, which are intended to expand the patient population and usage of KRYSTEXXA. This includes our marketing efforts in nephrology and our studies designed to improve the response rate to KRYSTEXXA and to evaluate the use of KRYSTEXXA in kidney transplant patients. With respect to RAVICTI, which is approved to treat a very limited patient population, our ability to grow sales will depend in large part on our ability to transition urea cycle disorder, or UCD, patients from BUPHENYL or generic equivalents, which are comparatively much less expensive, to RAVICTI and to encourage patients and physicians to continue RAVICTI therapy once initiated. With respect to PROCYSBI, which is also approved to treat a very limited patient population, our ability to grow sales will depend in large part on our ability to transition patients from the first-generation immediate-release cysteamine therapy to PROCYSBI, to identify additional patients with nephropathic cystinosis and to encourage patients and physicians to continue therapy once initiated. With respect to ACTIMMUNE, while it is the only FDA-approved treatment for chronic granulomatous disease, or CGD, and severe, malignant osteopetrosis, or SMO, they are very rare conditions and, as a result, our ability to grow ACTIMMUNE sales will depend on our ability to identify additional patients and encourage patients and physicians to continue treatment once initiated. With respect to each of PENNSAID 2% w/w, or PENNSAID 2%, RAYOS, DUEXIS and VIMOVO, their higher cost compared to the generic or branded forms of their active ingredients alone may limit adoption by physicians, patients and healthcare payers. With respect to DUEXIS and VIMOVO, studies indicate that physicians do not commonly co-prescribe gastrointestinal, or GI, protective agents to high-risk patients taking nonsteroidal anti-inflammatory drugs, or NSAIDs. We believe this is due in part to a lack of awareness among physicians prescribing NSAIDs regarding the risk of NSAID-induced upper GI ulcers, in addition to the inconvenience of prescribing two separate medications and patient compliance issues associated with multiple prescriptions. If physicians remain unaware of, or do not otherwise believe in, the benefits of combining GI protective agents with NSAIDs, our market opportunity for DUEXIS and VIMOVO will be limited. Some physicians may also be reluctant to prescribe DUEXIS or VIMOVO due to the inability to vary the dose of ibuprofen and naproxen, respectively, or if they believe treatment with NSAIDs or GI protective agents other than those contained in DUEXIS and VIMOVO, including those of its competitors, would be more effective for their patients. With respect to TEPEZZA, sales will depend on market acceptance and adoption by physicians and healthcare payers, as well as the ability and willingness of physicians who do not have in-house infusion capability to refer patients to infusion sites of care. If our current medicines or any other medicine that we may seek approval for, or acquire, fail to attain market acceptance, we may not be able to generate significant revenue to achieve or sustain profitability, which would have a material adverse effect on our business, results of operations, financial condition and prospects (including, possibly, the value of our ordinary shares).

Our future prospects are highly dependent on our ability to successfully formulate and execute commercialization strategies for each of our medicines. Failure to do so would adversely impact our financial condition and prospects.

A substantial majority of our resources are focused on the commercialization of our current medicines. Our ability to generate significant medicine revenues and to achieve commercial success in the near-term will initially depend almost entirely on our ability to successfully commercialize these medicines in the United States.

With respect to our rare disease medicines, KRYSTEXXA, RAVICTI, PROCYSBI, ACTIMMUNE and TEPEZZA, our commercialization strategy includes efforts to increase awareness of the rare conditions that each medicine is designed to treat, enhancing efforts to identify target patients and in certain cases pursue opportunities for label expansion and more effective use through clinical trials. Our strategy with respect to KRYSTEXXA includes existing rheumatology account growth, new rheumatology account growth and accelerating nephrology growth, as well as development efforts to enhance response rates through combination treatment with methotrexate and to shorten the infusion time. With respect to RAVICTI and PROCYSBI, our strategy includes accelerating the transition of patients from first-generation therapies, increasing the diagnosis of the associated rare conditions through patient and physician outreach; and increasing compliance rates. Our commercialization strategy for TEPEZZA is focused on four pillars: establishing the market structure and simplifying the diagnosis and treatment of thyroid eye disease, or TED, for patients; educating the multiple stakeholders about TED and TEPEZZA; supporting the commercialization of TEPEZZA with our comprehensive approach and its patient-centric model; and facilitating access to TEPEZZA by establishing an infusion site-of-care referral process for treating physicians who may not have infusion capabilities.

We are focusing a significant portion of our commercial activities and resources on TEPEZZA, and we believe our ability to grow our long-term revenues, and a significant portion of the value of our company, relates to our ability to successfully commercialize TEPEZZA in the United States. As a newly-launched medicine for a disease that had no previously-approved treatments, successful commercialization of TEPEZZA is subject to many risks. There are numerous examples of unsuccessful product launches and failures to meet high expectations of market potential, including by pharmaceutical companies with more experience and resources than us. While we have established our commercial team and U.S. sales force, we will need to train and further develop the team in order to successfully coordinate the launch and commercialization of TEPEZZA. There are many factors that could cause the launch and commercialization of TEPEZZA to be unsuccessful, including a number of factors that are outside our control. Because no medicine has previously been approved by the FDA for the treatment of TED, it is especially difficult to estimate TEPEZZA's market potential or the time it will take to increase patient and physician awareness of TED and change current treatment paradigms. In addition, some physicians that are potential prescribers of TEPEZZA do not have the necessary infusion capabilities to administer the medicine and may not otherwise be able or willing to refer their patients to third-party infusion centers, which may discourage them from treating their patients with TEPEZZA. The commercial success of TEPEZZA depends on the extent to which patients and physicians accept and adopt TEPEZZA as a treatment for TED. For example, if the patient population suffering from TED is smaller than we estimate, if it proves difficult to identify TED patients or educate physicians as to the availability and potential benefits of TEPEZZA, or if physicians are unwilling to prescribe or patients are unwilling to take TEPEZZA, the commercial potential of TEPEZZA will be limited. We also do not know how physicians, patients and payers will respond to the pricing of TEPEZZA. Physicians may not prescribe TEPEZZA and patients may be unwilling to use TEPEZZA if coverage is not provided or reimbursement is inadequate to cover a significant portion of the cost. Further, the status of reimbursement codes for TEPEZZA could also affect reimbursement. J codes, Q codes and C codes are reimbursement codes maintained by the Centers for Medicare & Medicaid Services, or CMS, that are typically used to report injectable drugs that ordinarily cannot be self-administered. Initially, TEPEZZA will be reimbursed through a non-specific miscellaneous J code. The non-specific miscellaneous J code is used for a wide variety of products and health plans may have more difficulty determining the actual product used and billed for the patient. As a result, these claims must often be submitted with additional information and manually processed, which can create delays in claims processing times as well as increasing the likelihood for claim errors. These delays and claims errors may in turn slow adoption of TEPEZZA until a product-specific reimbursement code is issued by the CMS. Thus, significant uncertainty remains regarding the commercial potential of TEPEZZA. If the launch or commercialization of TEPEZZA is unsuccessful or perceived as disappointing, the price of our ordinary shares could decline significantly and long-term success of the medicine and our company could be harmed.

With respect to our inflammation medicines, PENNSAID 2%, DUEXIS, and VIMOVO, our strategy has included entering into rebate agreements with pharmacy benefit managers, or PBMs, for certain of our inflammation medicines where we believe the rebates and costs justify expanded formulary access for patients and ensuring patient assistance to these drugs when prescribed through our HorizonCares program. However, we cannot guarantee that we will be able to secure additional rebate agreements on commercially reasonable terms, that expected volume growth will sufficiently offset the rebates and fees paid to PBMs or that our existing agreements with PBMs will have the intended impact on formulary access. In addition, as the terms of our existing agreements with PBMs expire, we may not be able to renew the agreements on commercially favorable terms, or at all. For each of our inflammation medicines, we expect that our commercial success will depend on our sales and marketing efforts in the United States, reimbursement decisions by commercial payers, the expense we incur through our patient assistance program for fully bought down contracts and the rebates we pay to PBMs, as well as the impact of numerous efforts at federal, state and local levels to further reduce reimbursement and net pricing of inflammation medicines.

Our strategy for RAYOS in the United States is to focus on the rheumatology indications approved for RAYOS, including our collaboration with the Alliance for Lupus Research, to study the effect of RAYOS on the fatigue experienced by systemic lupus erythematosus, or SLE, patients.

If any of our commercial strategies are unsuccessful or we fail to successfully modify our strategies over time due to changing market conditions, our ability to increase market share for our medicines, grow revenues and to achieve and sustain profitability will be harmed.

In order to increase adoption and sales of our medicines, we will need to continue developing our commercial organization as well as recruit and retain qualified sales representatives.

Part of our strategy is to continue to build a biopharma company to successfully execute the commercialization of our medicines in the U.S. market, and in selected markets outside the United States where we have commercial rights. We may not be able to successfully commercialize our medicines in the United States or in any other territories where we have commercial rights. In order to commercialize any approved medicines, we must continue to build our sales, marketing, distribution, managerial and other non-technical capabilities. As of December 31, 2019, we had approximately 480 sales representatives in the field, consisting of approximately 75 orphan disease sales representatives (including approximately 50 TEPEZZA sales representatives), 170 rheumatology sales specialists and 235 inflammation sales representatives. We currently have limited resources compared to some of our competitors, and the continued development of our own commercial organization to market our medicines and any additional medicines we may acquire will be expensive and time-consuming. We also cannot be certain that we will be able to continue to successfully develop this capability.

As we continue to add medicines through development efforts and acquisition transactions, the members of our sales force may have limited experience promoting certain of our medicines. To the extent we employ an acquired entity’s sales forces to promote acquired medicines, we may not be successful in continuing to retain these employees and we otherwise will have limited experience marketing these medicines under our commercial organization. In addition, none of the members of our sales force have promoted TEPEZZA or any other medicine for the treatment of TED prior to the launch of TEPEZZA. We are required to expend significant time and resources to train our sales force to be credible and persuasive in convincing physicians to prescribe and pharmacists to dispense our medicines. In addition, we must train our sales force to ensure that a consistent and appropriate message about our medicines is being delivered to our potential customers. Our sales representatives may also experience challenges promoting multiple medicines when we call on physicians and their office staff. We have experienced, and may continue to experience, turnover of the sales representatives that we hired or will hire, requiring us to train new sales representatives. If we are unable to effectively train our sales force and equip them with effective materials, including medical and sales literature to help them inform and educate physicians about the benefits of our medicines and their proper administration and label indication, as well as our patient assistance programs, our efforts to successfully commercialize our medicines could be put in jeopardy, which could have a material adverse effect on our financial condition, share price and operations.

As a result of the evolving role of various constituents in the prescription decision making process, we focus on hiring sales representatives for our inflammation medicines and RAYOS with successful business to business experience. For example, we have faced challenges due to pharmacists switching a patient's intended prescription from DUEXIS and VIMOVO to a generic or over-the-counter brand of their active ingredients, despite such substitution being off-label in the case of DUEXIS and VIMOVO. We have faced similar challenges for PENNSAID 2% and RAYOS with respect to generic brands. While we believe the profile of our representatives is suited for this environment, we cannot be certain that our representatives will be able to successfully protect our market for PENNSAID 2%, DUEXIS, RAYOS and VIMOVO or that we will be able to continue attracting and retaining sales representatives with our desired profile and skills. We will also have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train and retain commercial personnel. To the extent we rely on additional third parties to commercialize any approved medicines, we may receive less revenue than if we commercialized these medicines ourselves. In addition, we may have little or no control over the sales efforts of any third parties involved in our commercialization efforts. In the event we are unable to successfully develop and maintain our own commercial organization or collaborate with a third-party sales and marketing organization, we may not be able to commercialize our medicines and medicine candidates and execute on our business plan.

Coverage and reimbursement may not be available, or reimbursement may be available at only limited levels, for our medicines, which could make it difficult for us to sell our medicines profitably or to successfully execute planned medicine price increases.

Market acceptance and sales of our medicines will depend in large part on global coverage and reimbursement policies and may be affected by future healthcare reform measures, both in the United States and other key international markets. Successful commercialization of our medicines will depend in part on the availability of governmental and third-party payer reimbursement for the cost of our medicines. Government health administration authorities, private health insurers and other organizations generally provide reimbursement for healthcare. In particular, in the United States, private health insurers and other third-party payers often provide reimbursement for medicines and services based on the level at which the government (through the Medicare or Medicaid programs) provides reimbursement for such treatments. In the United States, the European Union, or EU, and other significant or potentially significant markets for our medicines and medicine candidates, government authorities and third-party payers are increasingly attempting to limit or regulate the price of medicines and services, particularly for new and innovative medicines and therapies, which has resulted in lower average selling prices. Further, the increased scrutiny of prescription drug pricing practices and emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the EU will put additional pressure on medicine pricing, reimbursement and usage, which may adversely affect our medicine sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical reimbursement policies and pricing in general. These pressures may create negative reactions to any medicine price increases, or limit the amount by which we may be able to increase our medicine prices, which may adversely affect our medicine sales and results of operations.

We expect to experience pricing pressures in connection with the sale of our medicines due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative proposals relating to outcomes and quality. For example, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the ACA, increased the mandated Medicaid rebate from 15.1% to 23.1%, expanded the rebate to Medicaid managed care utilization and increased the types of entities eligible for the federal 340B drug discount program. As concerns continue to grow over the need for tighter oversight, there remains the possibility that the Health Resources and Services Administration or another agency under the U.S. Department of Health and Human Services, or HHS, will propose a similar regulation or that Congress will explore changes to the 340B program through legislation. For example, a bill was introduced in 2018 that would require hospitals to report their low-income utilization of the program. Further, the Centers for Medicare & Medicaid Services issued a final rule that would revise the Medicare hospital outpatient prospective payment system for calendar year 2019, including a new reimbursement methodology for drugs purchased under the 340B program for Medicare patients at the hospital setting and recently announced the same change for physician-based practices under 340B in 2019. Pursuant to the final rule, after January 1, 2019, manufacturers must calculate 340B program ceiling prices on a quarterly basis. Moreover, manufacturers could be subject to a $5,000 penalty for each instance where they knowingly and intentionally overcharge a covered entity under the 340B program. With respect to KRYSTEXXA, the "additional rebate" scheme of the 340B pricing rules, as applied to the historical pricing of KRYSTEXXA both before and after we acquired the medicine, have resulted in a 340B ceiling price of one penny. A material portion of KRYSTEXXA prescriptions (approximately 20 percent) are written by healthcare providers that are eligible for 340B drug pricing and therefore the reduction in 340B pricing to a penny has negatively impacted our net sales of KRYSTEXXA.

Patients are unlikely to use our medicines unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our medicines. Third-party payers may limit coverage to specific medicines on an approved list, also known as a formulary, which might not include all of the FDA-approved medicines for a particular indication. Moreover, a third-party payer's decision to provide coverage for a medicine does not imply that an adequate reimbursement rate will be approved. Additionally, one third-party payer's decision to cover a particular medicine does not ensure that other payers will also provide coverage for the medicine, or will provide coverage at an adequate reimbursement rate. Even though we have contracts with some PBMs in the United States, that does not guarantee that they will perform in accordance with the contracts, nor does that preclude them from taking adverse actions against us, which could materially adversely affect our operating results. In addition, the existence of such PBM contracts does not guarantee coverage by such PBM's contracted health plans or adequate reimbursement to their respective providers for our medicines. For example, some PBMs have placed certain of our medicines on their exclusion lists from time to time, which has resulted in a loss of coverage for patients whose healthcare plans have adopted these PBM lists. Additional healthcare plan formularies may also exclude our medicines from coverage due to the actions of certain PBMs, future price increases we may implement, our use of the HorizonCares program or other free medicine programs whereby we assist qualified patients with certain out-of-pocket expenditures for our medicine, including donations to patient assistance programs offered by charitable foundations, or any other co-pay programs, or other reasons. If our strategies to mitigate formulary exclusions are not effective, these events may reduce the likelihood that physicians prescribe our medicines and increase the likelihood that prescriptions for our medicines are not filled.

In light of such policies and the uncertainty surrounding proposed regulations and changes in the coverage and reimbursement policies of governments and third-party payers, we cannot be sure that coverage and reimbursement will be available for any of our medicines in any additional markets or for any other medicine candidates that we may develop. Also, we cannot be sure that reimbursement amounts will not reduce the demand for, or the price of, our medicines. If coverage and reimbursement are not available or are available only at limited levels, we may not be able to successfully commercialize our medicines.

There may be additional pressure by payers, healthcare providers, state governments, federal regulators and Congress, to use generic drugs that contain the active ingredients found in our medicines or any other medicine candidates that we may develop or acquire. If we fail to successfully secure and maintain coverage and adequate reimbursement for our medicines or are significantly delayed in doing so, we will have difficulty achieving market acceptance of our medicines and expected revenue and profitability which would have a material adverse effect on our business, results of operations, financial condition and prospects.

We may also experience pressure from payers as well as state and federal government authorities concerning certain promotional approaches that we may implement such as our HorizonCares program or any other co-pay programs. Certain state and federal enforcement authorities and members of Congress have initiated inquiries about co-pay assistance programs. Some state legislatures have been considering proposals that would restrict or ban co-pay coupons. For example, legislation was recently signed into law in California that would limit the use of co-pay coupons in cases where a lower cost generic drug is available and if individual ingredients in combination therapies are available over the counter at a lower cost. It is possible that similar legislation could be proposed and enacted in additional states. If we are unsuccessful with our HorizonCares program or any other co-pay programs, or we alternatively are unable to secure expanded formulary access through additional arrangements with PBMs or other payers, we would be at a competitive disadvantage in terms of pricing versus preferred branded and generic competitors. We may also experience financial pressure in the future which would make it difficult to support investment levels in areas such as managed care contract rebates, HorizonCares and other access tools.

Our medicines are subject to extensive regulation, and we may not obtain additional regulatory approvals for our medicines.

The clinical development, manufacturing, labeling, packaging, storage, recordkeeping, advertising, promotion, export, marketing and distribution and other possible activities relating to our medicines and our medicine candidates are, and will be, subject to extensive regulation by the FDA and other regulatory agencies. Failure to comply with FDA and other applicable regulatory requirements may, either before or after medicine approval, subject us to administrative or judicially imposed sanctions.

To market any drugs or biologics outside of the United States, we and current or future collaborators must comply with numerous and varying regulatory and compliance related requirements of other countries. Approval procedures vary among countries and can involve additional medicine testing and additional administrative review periods, including obtaining reimbursement and pricing approval in select markets. The time required to obtain approval in other countries might differ from that required to obtain FDA approval. The regulatory approval process in other countries may include all of the risks associated with FDA approval as well as additional, presently unanticipated, risks. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others.

Applications for regulatory approval, including a marketing authorization application, or MAA, for marketing new drugs in Europe, must be supported by extensive clinical and pre-clinical data, as well as extensive information regarding chemistry, manufacturing and controls, or CMC, to demonstrate the safety and effectiveness of the applicable medicine candidate. The number and types of pre-clinical studies and clinical trials that will be required for regulatory approval varies depending on the medicine candidate, the disease or the condition that the medicine candidate is designed to target and the regulations applicable to any particular medicine candidate. Despite the time and expense associated with pre-clinical and clinical studies, failure can occur at any stage, and we could encounter problems that cause us to repeat or perform additional pre-clinical studies, CMC studies or clinical trials. Regulatory authorities could delay, limit or deny approval of a medicine candidate for many reasons, including because they:

- may not deem a medicine candidate to be adequately safe and effective;
- may not find the data from pre-clinical studies, CMC studies and clinical trials to be sufficient to support a claim of safety and efficacy;
- may interpret data from pre-clinical studies, CMC studies and clinical trials significantly differently than we do;
- may not approve the manufacturing processes or facilities associated with our medicine candidates;
- may conclude that we have not sufficiently demonstrated long-term stability of the formulation for which we are seeking marketing approval;
- may change approval policies (including with respect to our medicine candidates' class of drugs) or adopt new regulations; or
- may not accept a submission due to, among other reasons, the content or formatting of the submission.

Even if we believe that data collected from our pre-clinical studies, CMC studies and clinical trials of our medicine candidates are promising and that our information and procedures regarding CMC are sufficient, our data may not be sufficient to support marketing approval by regulatory authorities, or regulatory interpretation of these data and procedures may be unfavorable. Even if approved, medicine candidates may not be approved for all indications requested and such approval may be subject to limitations on the indicated uses for which the medicine may be marketed, restricted distribution methods or other limitations. Our business and reputation may be harmed by any failure or significant delay in obtaining regulatory approval for the sale of any of our medicine candidates. We cannot predict when or whether regulatory approval will be obtained for any medicine candidate we develop.

The ultimate approval and commercial marketing of any of our medicines in additional indications or geographies is subject to substantial uncertainty. Failure to gain additional regulatory approvals would limit the potential revenues and value of our medicines and could cause our share price to decline.

We may be subject to penalties and litigation and large incremental expenses if we fail to comply with regulatory requirements or experience problems with our medicines.

Even after we achieve regulatory approvals, we are subject to ongoing obligations and continued regulatory review with respect to many operational aspects including our manufacturing processes, labeling, packaging, distribution, storage, adverse event monitoring and reporting, dispensation, advertising, promotion and recordkeeping. These requirements include submissions of safety and other post-marketing information and reports, ongoing maintenance of medicine registration and continued compliance with current good manufacturing practices, or cGMPs, good clinical practices, or GCPs, good pharmacovigilance practice, good distribution practices and good laboratory practices, or GLPs. If we, our medicines or medicine candidates, or the third-party manufacturing facilities for our medicines or medicine candidates fail to comply with applicable regulatory requirements, a regulatory agency may:

- impose injunctions or restrictions on the marketing, manufacturing or distribution of a medicine, suspend or withdraw medicine approvals, revoke necessary licenses or suspend medicine reimbursement;
- issue warning letters, show cause notices or untitled letters describing alleged violations, which may be publicly available;
- suspend any ongoing clinical trials or delay or prevent the initiation of clinical trials;
- delay or refuse to approve pending applications or supplements to approved applications we have filed;
- refuse to permit drugs or precursor or intermediary chemicals to be imported or exported to or from the United States;
- suspend or impose restrictions or additional requirements on operations, including costly new manufacturing quality or pharmacovigilance requirements;
- seize or detain medicines or require us to initiate a medicine recall; and/or
- commence criminal investigations and prosecutions.

Moreover, existing regulatory approvals and any future regulatory approvals that we obtain will be subject to limitations on the approved indicated uses and patient populations for which our medicines may be marketed, the conditions of approval, requirements for potentially costly, post-market testing and requirements for surveillance to monitor the safety and efficacy of the medicines. Physicians nevertheless may prescribe our medicines to their patients in a manner that is inconsistent with the approved label or that is off-label. Positive clinical trial results in any of our medicine development programs increase the risk that approved pharmaceutical forms of the same active pharmaceutical ingredients, or APIs, may be used off-label in those indications. If we are found to have improperly promoted off-label uses of approved medicines, we may be subject to significant sanctions, civil and criminal fines and injunctions prohibiting us from engaging in specified promotional conduct.

In addition, engaging in improper promotion of our medicines for off-label uses in the United States can subject us to false claims litigation under federal and state statutes. These false claims statutes in the United States include the federal False Claims Act, which allows any individual to bring a lawsuit against a pharmaceutical company on behalf of the federal government alleging submission of false or fraudulent claims or causing to present such false or fraudulent claims for payment by a federal program such as Medicare or Medicaid. Growth in false claims litigation has increased the risk that a pharmaceutical company will have to defend a false claim action, pay civil money penalties, settlement fines or restitution, agree to comply with burdensome reporting and compliance obligations and be excluded from Medicare, Medicaid and other federal and state healthcare programs.

The regulations, policies or guidance of regulatory agencies may change and new or additional statutes or government regulations may be enacted that could prevent or delay regulatory approval of our medicine candidates or further restrict or regulate post-approval activities. For example, in January 2014, the FDA released draft guidance on how drug companies can fulfill their regulatory requirements for post-marketing submission of interactive promotional media, and though the guidance provided insight into how the FDA views a company’s responsibility for certain types of social media promotion, there remains a substantial amount of uncertainty regarding internet and social media promotion of regulated medical products. We cannot predict the likelihood, nature or extent of adverse government regulation that may arise from pending or future legislation or administrative action, either in the United States or abroad. If we are unable to achieve and maintain regulatory compliance, we will not be permitted to market our drugs, which would materially adversely affect our business, results of operations and financial condition.

We have rights to medicines in certain jurisdictions but have no control over third parties that have rights to commercialize those medicines in other jurisdictions, which could adversely affect our commercialization of these medicines.

Following our sale of the rights to RAVICTI outside of North America and Japan to Medical Need Europe AB, part of the Immedica Group, or Immedica, in December 2018, Immedica has marketing and distribution rights to RAVICTI in those regions. Following our sale of the rights to PROCYSBI in the Europe, Middle East and Africa, or EMEA, regions to Chiesi Farmaceutici S.p.A., or Chiesi, in June 2017, or the Chiesi divestiture, Chiesi has marketing and distribution rights to PROCYSBI in the EMEA regions. Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.), or Nuvo, has retained its rights to PENNSAID 2% in territories outside of the United States. In March 2017, Nuvo announced that it had entered into an exclusive license agreement with Sayre Therapeutics PVT Ltd. to distribute, market and sell PENNSAID 2% in India, Sri Lanka, Bangladesh and Nepal, and in December 2017 Nuvo announced that it had entered into a license and distribution agreement with Gebro Pharma AG for the exclusive right to register, distribute, market and sell PENNSAID 2% in Switzerland and Liechtenstein. Grünenthal GmbH, or Grünenthal, acquired the rights to VIMOVO in territories outside of the United States, including the right to use the VIMOVO name and related trademark from AstraZeneca AB, or AstraZeneca, in October 2018. We have little or no control over Immedica's activities with respect to RAVICTI outside of North America and Japan, over Chiesi's activities with respect to PROCYSBI in the EMEA, over Nuvo's or its existing and future commercial partners' activities with respect to PENNSAID 2% outside of the United States, or over Grünenthal's activities with respect to VIMOVO outside the United States even though those activities could impact our ability to successfully commercialize these medicines. For example, Immedica or its assignees, Chiesi or its assignees, Nuvo or its assignees or Grünenthal or its assignees can make statements or use promotional materials with respect to RAVICTI, PROCYSBI, PENNSAID 2% or VIMOVO, respectively, outside of the United States that are inconsistent with our positioning of the medicines in the United States, and could sell RAVICTI, PROCYSBI, PENNSAID 2% or VIMOVO, respectively, in foreign countries at prices that are dramatically lower than the prices we charge in the United States. These activities and decisions, while occurring outside of the United States, could harm our commercialization strategy in the United States, in particular because Grünenthal is continuing to market VIMOVO outside the United States under the same VIMOVO brand name that we are using in the United States. In addition, medicine recalls or safety issues with these medicines outside the United States, even if not related to the commercial medicine we sell in the United States, could result in serious damage to the brand in the United States and impair our ability to successfully market them. We also rely on Immedica, Chiesi, Nuvo and Grünenthal or their assignees to provide us with timely and accurate safety information regarding the use of these medicines outside of the United States, as we have or will have limited access to this information ourselves.

We rely on third parties to manufacture commercial supplies of all of our medicines, and we currently intend to rely on third parties to manufacture commercial supplies of any other approved medicines. The commercialization of any of our medicines could be stopped, delayed or made less profitable if those third parties fail to provide us with sufficient quantities of medicine or fail to do so at acceptable quality levels or prices or fail to maintain or achieve satisfactory regulatory compliance.

The facilities used by our third-party manufacturers to manufacture our medicines and medicine candidates must be approved by the applicable regulatory authorities. We do not control the manufacturing processes of third-party manufacturers and are currently completely dependent on our third-party manufacturing partners. In addition, we are required to obtain Grünenthal's (formerly AstraZeneca) consent prior to engaging any third-party manufacturers for esomeprazole, one of the APIs in VIMOVO, other than the third-party manufacturer(s) used by Grünenthal or its affiliates or licensees. To the extent such manufacturers are unwilling or unable to manufacture esomeprazole for us on commercially acceptable terms, we cannot guarantee that Grünenthal would consent to our use of alternate sources of supply.

We rely on NOF Corporation, or NOF, as our exclusive supplier of the PEGylation agent that is a critical raw material in the manufacture of KRYSTEXXA. If NOF failed to supply such PEGylation agent, it may lead to KRYSTEXXA supply constraints. A key excipient used in PENNSAID 2% as a penetration enhancer is dimethyl sulfoxide, or DMSO. We and Nuvo, our exclusive supplier of PENNSAID 2%, rely on a sole proprietary form of DMSO for which we maintain a substantial safety stock. However, should this supply become inadequate, damaged, destroyed or unusable, we and Nuvo may not be able to qualify a second source. We rely on an exclusive supply agreement with Boehringer Ingelheim Biopharmaceuticals GmbH, or Boehringer Ingelheim Biopharmaceuticals, for manufacturing and supply of ACTIMMUNE. ACTIMMUNE is manufactured by starting with cells from working cell bank samples which are derived from a master cell bank. We and Boehringer Ingelheim Biopharmaceuticals separately store multiple vials of the master cell bank. In the event of catastrophic loss at our or Boehringer Ingelheim Biopharmaceuticals' storage facility, it is possible that we could lose multiple cell banks and have the manufacturing capacity of ACTIMMUNE severely impacted by the need to substitute or replace the cell banks. We rely on AGC Biologics A/S (formerly known as CMC Biologics A/S), or AGC Biologics, as our exclusive manufacturer of the TEPEZZA drug substance. If AGC Biologics failed to supply such drug substance, it may lead to TEPEZZA supply constraints.

If any of our third-party manufacturers cannot successfully manufacture material that conforms to our specifications and the applicable regulatory authorities' strict regulatory requirements, or pass regulatory inspection, they will not be able to secure or maintain regulatory approval for the manufacturing facilities. For example, BASF Corporation, or BASF, our manufacturer of one of the APIs in DUEXIS, ibuprofen in a direct compression blend called DC85, previously notified us that it was not able to supply DC85 due to a technical issue at its manufacturing facility in Bishop, Texas during 2018. During 2019, BASF has supplied us with a limited amount of DC85 and informed us of their intention to return to full supply. We consider our DUEXIS inventory on hand to be sufficient to meet current and future commercial requirements. However, we cannot guarantee that BASF's manufacturing facility will return to full operations or that we will be able to enter into a new supply agreement with BASF for DC85. In addition, we have no control over the ability of third-party manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or any other applicable regulatory authorities do not approve these facilities for the manufacture of our medicines or if they withdraw any such approval in the future, or if our suppliers or third-party manufacturers decide they no longer want to supply our primary active ingredients or manufacture our medicines, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our medicines. To the extent any third-party manufacturers that we engage with respect to our medicines are different from those currently being used for commercial supply in the United States, the FDA will need to approve the facilities of those third-party manufacturers used in the manufacture of our medicines prior to our sale of any medicine using these facilities.

Although we have entered into supply agreements for the manufacture and packaging of our medicines, our manufacturers may not perform as agreed or may terminate their agreements with us. We currently rely on single source suppliers for certain of our medicines. If our manufacturers terminate their agreements with us, we may have to qualify new back-up manufacturers. We rely on safety stock to mitigate the risk of our current suppliers electing to cease producing bulk drug product or ceasing to do so at acceptable prices and quality. However, we can provide no assurance that such safety stocks would be sufficient to avoid supply shortfalls in the event we have to identify and qualify new contract manufacturers.

The manufacture of medicines requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of medicines often encounter difficulties in production, particularly in scaling up and validating initial production. These problems include difficulties with production costs and yields, quality control, including stability of the medicine, quality assurance testing, shortages of qualified personnel, as well as compliance with strictly enforced federal, state and foreign regulations. Furthermore, if microbial, viral or other contaminations are discovered in the medicines or in the manufacturing facilities in which our medicines are made, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the contamination. We cannot assure that issues relating to the manufacture of any of our medicines will not occur in the future. Additionally, our manufacturers may experience manufacturing difficulties due to resource constraints or as a result of labor disputes or unstable political environments. If our manufacturers were to encounter any of these difficulties, or otherwise fail to comply with their contractual obligations, our ability to commercialize our medicines or provide any medicine candidates to patients in clinical trials would be jeopardized.

Any delay or interruption in our ability to meet commercial demand for our medicines will result in the loss of potential revenues and could adversely affect our ability to gain market acceptance for these medicines. In addition, any delay or interruption in the supply of clinical trial supplies could delay the completion of clinical trials, increase the costs associated with maintaining clinical trial programs and, depending upon the period of delay, require us to commence new clinical trials at additional expense or terminate clinical trials completely.

Failures or difficulties faced at any level of our supply chain could materially adversely affect our business and delay or impede the development and commercialization of any of our medicines or medicine candidates and could have a material adverse effect on our business, results of operations, financial condition and prospects.

We face significant competition from other biotechnology and pharmaceutical companies, including those marketing generic medicines and our operating results will suffer if we fail to compete effectively.

The biotechnology and pharmaceutical industries are intensely competitive. We have competitors both in the United States and international markets, including major multinational pharmaceutical companies, biotechnology companies and universities and other research institutions. Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff, experienced marketing and manufacturing organizations and well-established sales forces. Additional consolidations in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors and we will have to find new ways to compete and may have to potentially merge with or acquire other businesses to stay competitive. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or in-licensing on an exclusive basis, medicines that are more effective and/or less costly than our medicines.

While KRYSTEXXA faces limited direct competition, a number of competitors have medicines in Phase 1 or Phase 2 trials, including Selecta Biosciences Inc. which has presented Phase 2 clinical data and is conducting a six-month trial comparing their candidate that uses an immunomodulator to KRYSTEXXA alone. RAVICTI could face competition from a few medicine candidates that are in early-stage development, including a gene-therapy candidate by Ultragenyx Pharmaceutical Inc., a generic taste-masked formulation option of BUPHENYL by ACER Therapeutics Inc., and an enzyme replacement for a specific UCD subtype (ARG) by Aeglea Bio Therapeutics Inc. PROCYSBI faces competition from Cystagon (immediate-release cysteamine bitartrate capsules) for the treatment of cystinosis and Cystaran (cysteamine ophthalmic solution) for treatment of corneal crystal accumulation in patients with cystinosis. Additionally, we are also aware that AVROBIO, Inc. has an early-stage gene therapy candidate in development for the treatment of cystinosis. Although TEPEZZA does not face direct competition, other therapies, such as corticosteroids, have been used on an off-label basis to alleviate some of the symptoms of TED. While these therapies have not proved effective in treating the underlying disease, and carry with them significant side effects, their off-label use could reduce or delay treatment in the addressable patient population for TEPEZZA. Immunovant Inc. is also conducting clinical studies of a medicine candidate for the treatment of active TED, also referred to as Graves' ophthalmopathy. PENNSAID 2% faces competition from generic versions of diclofenac sodium topical solutions that are priced significantly less than the price we charge for PENNSAID 2%. The generic version of Voltaren Gel is the market leader in the topical NSAID category. Legislation enacted in most states in the United States allows, or in some instances mandates, that a pharmacist dispense an available generic equivalent when filling a prescription for a branded medicine, in the absence of specific instructions from the prescribing physician. DUEXIS and VIMOVO face competition from other NSAIDs, including Celebrex®, marketed by Pfizer Inc., and celecoxib, a generic form of the medicine marketed by other pharmaceutical companies. DUEXIS and VIMOVO also face significant competition from the separate use of NSAIDs for pain relief and GI protective medications to reduce the risk of NSAID-induced upper GI ulcers. Both NSAIDs and GI protective medications are available in generic form and may be less expensive to use separately than DUEXIS or VIMOVO, despite such substitution being off-label in the case of DUEXIS and VIMOVO. Because pharmacists often have economic and other incentives to prescribe lower-cost generics, if physicians prescribe PENNSAID 2%, DUEXIS, or VIMOVO, those prescriptions may not result in sales. If physicians do not complete prescriptions through our HorizonCares program or otherwise provide prescribing instructions prohibiting generic diclofenac sodium topical solutions as a substitute for PENNSAID 2%, the substitution of generic ibuprofen and famotidine separately as a substitution for DUEXIS or generic naproxen and branded Nexium® (esomeprazole) as a substitute for VIMOVO, sales of PENNSAID 2%, DUEXIS and VIMOVO may suffer despite any success we may have in promoting PENNSAID 2%, DUEXIS or VIMOVO to physicians. In addition, other medicine candidates that contain ibuprofen and famotidine in combination or naproxen and esomeprazole in combination, while not currently known or FDA approved, may be developed and compete with DUEXIS or VIMOVO, respectively, in the future.

We have also entered into settlement and license agreements that may allow certain of our competitors to sell generic versions of certain of our medicines in the United States, subject to the terms of such agreements. We granted (i) a non-exclusive license (that is only royalty-bearing in some circumstances) to manufacture and commercialize a generic version of DUEXIS in the United States after January 1, 2023, (ii) non-exclusive licenses to manufacture and commercialize generic versions of PENNSAID 2% in the United States after October 17, 2027, (iii) a non-exclusive license to manufacture and commercialize a generic version of RAYOS tablets in the United States after December 23, 2022, (iv) a non-exclusive license to manufacture and commercialize a generic version of VIMOVO in the United States after August 1, 2024, and (v) non-exclusive licenses to manufacture and commercialize generic versions of RAVICTI in the United States after July 1, 2025, or earlier under certain circumstances.

Patent litigation is currently pending in the United States District Court for the District of New Jersey against Actavis Laboratories UT, Inc., formerly known as Watson Laboratories, Inc., Actavis, Inc. and Actavis plc, or collectively Actavis, who intend to market a generic version of PENNSAID 2% prior to the expiration of certain of our patents listed in the FDA's Orange Book, or the Orange Book. These cases arise from Paragraph IV Patent Certification notice letters from Actavis advising it had filed an Abbreviated New Drug Application, or ANDA, with the FDA seeking approval to market a generic version of PENNSAID 2% before the expiration of the patents-in-suit.

Patent litigation is currently pending in the United States District Court for the District of New Jersey and the Court of Appeals for the Federal Circuit against Dr. Reddy's Laboratories Inc. and Dr. Reddy's Laboratories Ltd., or collectively Dr. Reddy's, who intends to market a generic version of VIMOVO before the expiration of certain of our patents listed in the Orange Book. The cases arise from Paragraph IV Patent Certification notice letters from Dr. Reddy's advising that it had filed an ANDA with the FDA seeking approval to market generic versions of VIMOVO before the expiration of the patents-in-suit. On July 30, 2019, the Federal Circuit Court of Appeals denied our request for a rehearing of the Court's invalidity ruling against the 6,926,907 and 8,557,285 patents for VIMOVO coordinated-release tablets. As a result, the District Court entered judgment in September 2019 invalidating the '907 and '285 patents, which ended any restriction against the FDA from granting final approval to Dr. Reddy's generic version of VIMOVO. On February 18, 2020, the FDA granted final approval for Dr. Reddy's generic version of VIMOVO. We anticipate that Dr. Reddy's will immediately launch its product at-risk notwithstanding the ongoing patent litigation. Patent litigation is currently pending in the United States District Court for the District of New Jersey against Ajanta Pharma LTD, or Ajanta, intending to market a generic version of VIMOVO before the expiration of certain of our patents listed in the Orange Book.

Patent litigation is currently pending in the United States District Court for the District of Delaware against Alkem Laboratories, Inc., or Alkem, who intends to market a generic version of DUEXIS prior to the expiration of certain of our patents listed in the Orange Book. This case arises from Paragraph IV Patent Certification notice letters from Alkem advising it had filed an ANDA with the FDA seeking approval to market a generic version of DUEXIS before the expiration of the patents-in-suit.

If we are unsuccessful in any of the VIMOVO cases, PENNSAID 2% cases or DUEXIS case, we will likely face generic competition with respect to VIMOVO, PENNSAID 2% and/or DUEXIS and sales of VIMOVO, PENNSAID 2% and/or DUEXIS will be substantially harmed.

ACTIMMUNE is the only medicine currently approved by the FDA specifically for the treatment of CGD and SMO. While there are additional or alternative approaches used to treat patients with CGD and SMO, there are currently no medicines on the market that compete directly with ACTIMMUNE. A widely accepted protocol to treat CGD in the United States is the use of concomitant "triple prophylactic therapy" comprising ACTIMMUNE, an oral antibiotic agent and an oral antifungal agent. However, the FDA-approved labeling for ACTIMMUNE does not discuss this "triple prophylactic therapy," and physicians may choose to prescribe one or both of the other modalities in the absence of ACTIMMUNE. Because of the immediate and life-threatening nature of SMO, the preferred treatment option for SMO is often to have the patient undergo a bone marrow transplant which, if successful, will likely obviate the need for further use of ACTIMMUNE in that patient. Likewise, the use of bone marrow transplants in the treatment of patients with CGD is becoming more prevalent, which could have a material adverse effect on sales of ACTIMMUNE and its profitability. We are aware of a number of research programs investigating the potential of gene therapy as a possible cure for CGD. Additionally, other companies may be pursuing the development of medicines and treatments that target the same diseases and conditions which ACTIMMUNE is currently approved to treat. As a result, it is possible that our competitors may develop new medicines that manage CGD or SMO more effectively, cost less or possibly even cure CGD or SMO. In addition, U.S. healthcare legislation passed in March 2010 authorized the FDA to approve biological products, known as biosimilars, that are similar to or interchangeable with previously approved biological products, like ACTIMMUNE, based upon potentially abbreviated data packages. Biosimilars are likely to be sold at substantially lower prices than branded medicines because the biosimilar manufacturer would not have to recoup the research and development and marketing costs associated with the branded medicine. Though we are not currently aware of any biosimilar under development, the development and commercialization of any competing medicines or the discovery of any new alternative treatment for CGD or SMO could have a material adverse effect on sales of ACTIMMUNE and its profitability.

BUPHENYL's composition of matter patent protection and orphan drug exclusivity have expired. Because BUPHENYL has no regulatory exclusivity or listed patents, there is nothing to prevent a competitor from submitting an ANDA for a generic version of BUPHENYL and receiving FDA approval. Generic versions of BUPHENYL to date have been priced at a discount relative to RAVICTI, and physicians, patients, or payers may decide that this less expensive alternative is preferable to RAVICTI. If this occurs, sales of RAVICTI could be materially reduced, but we would nevertheless be required to make royalty payments to Bausch Health Companies Inc. (formerly Ucyclyd Pharma, Inc.), or Bausch, and another external party, at the same royalty rates. While Bausch and its affiliates are generally contractually prohibited from developing or commercializing new medicines, anywhere in the world, for the treatment of UCD or hepatic encephalopathy, or HE, which are chemically similar to RAVICTI, they may still develop and commercialize medicines that compete with RAVICTI. For example, medicines approved for indications other than UCD and HE may still compete with RAVICTI if physicians prescribe such medicines off-label for UCD or HE. We are also aware that Recordati S.p.A (formerly known as Orphan Europe SARL), or Recordati, is conducting clinical trials of carglumic acid to assess the efficacy for acute hyperammonemia in some of the UCD enzyme deficiencies for which RAVICTI is approved for chronic treatment. Carglumic acid is approved for maintenance therapy for chronic hyperammonemia and to treat hyperammonemic crises in N-acetylglutamate synthase deficiency, a rare UCD subtype, and is sold under the name Carbaglu. If the results of this trial are successful and Recordati is able to complete development and obtain approval of Carbaglu to treat additional UCD enzyme deficiencies, RAVICTI may face additional competition from this compound.

The availability and price of our competitors' medicines could limit the demand, and the price we are able to charge, for our medicines. We will not successfully execute on our business objectives if the market acceptance of our medicines is inhibited by price competition, if physicians are reluctant to switch from existing medicines to our medicines, or if physicians switch to other new medicines or choose to reserve our medicines for use in limited patient populations.

In addition, established pharmaceutical companies may invest heavily to accelerate discovery and development of novel compounds or to acquire novel compounds that could make our medicines obsolete. Our ability to compete successfully with these companies and other potential competitors will depend largely on our ability to leverage our experience in clinical, regulatory and commercial development to:

- develop and acquire medicines that are superior to other medicines in the market;
- attract qualified clinical, regulatory, and sales and marketing personnel;
- obtain patent and/or other proprietary protection for our medicines and technologies;
- obtain required regulatory approvals; and
- successfully collaborate with pharmaceutical companies in the discovery, development and commercialization of new medicine candidates.

If we are unable to maintain or realize the benefits of orphan drug exclusivity, we may face increased competition with respect to certain of our medicines.

Under the Orphan Drug Act of 1983, the FDA may designate a medicine as an orphan drug if it is a drug intended to treat a rare disease or condition affecting fewer than 200,000 people in the United States. A company that first obtains FDA approval for a designated orphan drug for the specified rare disease or condition receives orphan drug marketing exclusivity for that drug for a period of seven years from the date of its approval. PROCYSBI has been granted orphan drug exclusivity by the FDA, which we expect will provide orphan drug marketing exclusivity in the United States until December 2020, with exclusivity for PROCYSBI extending to 2022 for patients ages one to six years. In addition, TEPEZZA has been granted orphan drug exclusivity for treatment of active (dynamic) phase Graves' ophthalmopathy, which we expect will provide orphan drug marketing exclusivity in the United States until January 2027. However, despite orphan drug exclusivity, the FDA can still approve another drug containing the same active ingredient and used for the same orphan indication if it determines that a subsequent drug is safer, more effective or makes a major contribution to patient care, and orphan exclusivity can be lost if the orphan drug manufacturer is unable to ensure that a sufficient quantity of the orphan drug is available to meet the needs of patients with the rare disease or condition. Orphan drug exclusivity may also be lost if the FDA later determines that the initial request for designation was materially defective. In addition, orphan drug exclusivity does not prevent the FDA from approving competing drugs for the same or similar indication containing a different active ingredient. If orphan drug exclusivity is lost and we were unable to successfully enforce any remaining patents covering the applicable medicine, we could be subject to generic competition and revenues from the medicine could decrease materially. In addition, if a subsequent drug is approved for marketing for the same or a similar indication as our medicines despite orphan drug exclusivity, we may face increased competition and lose market share with respect to these medicines.

If we cannot successfully implement our patient assistance programs or increase formulary access and reimbursement for our medicines in the face of increasing pressure to reduce the price of medications, the adoption of our medicines by physicians, patients and payers may decline.

There continues to be immense pressure from healthcare payers, PBMs and others to use less expensive or generic medicines or over-the-counter brands instead of certain branded medicines. For example, some PBMs have placed certain of our medicines on their exclusion lists from time to time, which has resulted in a loss of coverage for patients whose healthcare plans have adopted these PBM lists. Additional healthcare plans, including those that contract with these PBMs but use different formularies, may also choose to exclude our medicines from their formularies or restrict coverage to situations where a generic or over-the-counter medicine has been tried first. Many payers and PBMs also require patients to make co-payments for branded medicines, including many of our medicines, in order to incentivize the use of generic or other lower-priced alternatives instead. Legislation enacted in most states in the United States allows, or in some instances mandates, that a pharmacist dispenses an available generic equivalent when filling a prescription for a branded medicine, in the absence of specific instructions from the prescribing physician. Because our medicines (other than BUPHENYL and VIMOVO) do not currently have FDA-approved generic equivalents in the United States, we do not believe our medicines should be subject to mandatory generic substitution laws. We understand that some pharmacies may attempt to obtain physician authorization to switch prescriptions for DUEXIS or VIMOVO to prescriptions for multiple generic medicines with similar APIs to ensure payment for the medicine if the physician's prescription for the branded medicine is not immediately covered by the payer, despite such substitution being off-label in the case of DUEXIS and VIMOVO. If these limitations in coverage and other incentives result in patients refusing to fill prescriptions or being dissatisfied with the out-of-pocket costs of their medications, or if pharmacies otherwise seek and receive physician authorization to switch prescriptions, not only would we lose sales on prescriptions that are ultimately not filled, but physicians may be dissuaded from writing prescriptions for our medicines in the first place in order to avoid potential patient non-compliance or dissatisfaction over medication costs, or to avoid spending the time and effort of responding to pharmacy requests to switch prescriptions.

Part of our commercial strategy to increase adoption and access to our medicines in the face of these incentives to use generic alternatives is to offer physicians the opportunity to have patients fill prescriptions through independent pharmacies participating in our HorizonCares patient assistance program, including shipment of prescriptions to patients. We also have contracted with a third-party prescription clearinghouse that offers physicians a single point of contact for processing prescriptions through these independent pharmacies, reducing physician administrative costs, increasing the fill rates for prescriptions and enabling physicians to monitor refill activity. Through HorizonCares, financial assistance may be available to reduce eligible patients' out-of-pocket costs for prescriptions filled. Because of this assistance, eligible patients' out-of-pocket cost for our medicines when dispensed through HorizonCares may be significantly lower than such costs when our medicines are dispensed outside of the HorizonCares program. However, to the extent physicians do not direct prescriptions currently filled through traditional pharmacies, including those associated with or controlled by PBMs, to pharmacies participating in our HorizonCares program, we may experience a significant decline in PENNSAID 2%, DUEXIS and VIMOVO prescriptions. Our ability to increase utilization of our patient assistance programs will depend on physician and patient awareness and comfort with the programs, and we have limited ability to influence whether physicians use our patient assistance programs to prescribe our medicines or whether patients will agree to receive our medicines through our HorizonCares program. In addition, the HorizonCares program is not available to federal health care program (such as Medicare and Medicaid) beneficiaries. We have also contracted with certain PBMs and other payers to secure formulary status and reimbursement for certain of our inflammation medicines, which generally require us to pay administrative fees and rebates to the PBMs and other payers for qualifying prescriptions. While we have business relationships with two of the largest PBMs, Express Scripts, Inc., or Express Scripts, and CVS Caremark, as well as a rebate agreement with another PBM, Prime Therapeutics LLC, and we believe these agreements will secure formulary status for certain of our medicines, we cannot guarantee that we will be able to agree to terms with other PBMs and other payers, or that such terms will be commercially reasonable to us. Despite our agreements with PBMs, the extent of formulary status and reimbursement will ultimately depend to a large extent upon individual healthcare plan formulary decisions. If healthcare plans that contract with PBMs with which we have agreements do not adopt formulary changes recommended by the PBMs with respect to our medicines, we may not realize the expected access and reimbursement benefits from these agreements. In addition, we generally pay higher rebates for prescriptions covered under plans that adopt a PBM-chosen formulary than for plans that adopt custom formularies. Consequently, the success of our PBM contracting strategy will depend not only on our ability to expand formulary adoption among healthcare plans, but also upon the relative mix of healthcare plans that have PBM-chosen formularies versus custom formularies. If we are unable to realize the expected benefits of our contractual arrangements with the PBMs we may continue to experience reductions in net sales from our inflammation medicines and/or reductions in net pricing for our inflammation medicines due to increasing patient assistance costs. If we are unable to increase adoption of HorizonCares for filling prescriptions of our medicines and to secure formulary status and reimbursement through arrangements with PBMs and other payers, particularly with healthcare plans that use custom formularies, our ability to achieve net sales growth for our inflammation medicines would be impaired.

There has been negative publicity and inquiries from Congress and enforcement authorities regarding the use of specialty pharmacies and drug pricing. Our patient assistance programs are not involved in the prescribing of medicines and are solely to assist in ensuring that when a physician determines one of our medicines offers a potential clinical benefit to their patients and they prescribe one for an eligible patient, financial assistance may be available to reduce the patient's out-of-pocket costs. In addition, all pharmacies that fill prescriptions for our medicines are fully independent, including those that participate in HorizonCares. We do not own or possess any option to purchase an ownership stake in any pharmacy that distributes our medicines, and our relationship with each pharmacy is non-exclusive and arm's length. All of our sales are processed through pharmacies independent of us. Despite this, the negative publicity and interest from Congress and enforcement authorities regarding specialty pharmacies may result in physicians being less willing to participate in our patient assistance programs and thereby limit our ability to increase patient assistance and adoption of our medicines.

We may also encounter difficulty in forming and maintaining relationships with pharmacies that participate in our patient assistance programs. We currently depend on a limited number of pharmacies participating in HorizonCares to fulfill patient prescriptions under the HorizonCares program. If these HorizonCares participating pharmacies are unable to process and fulfill the volume of patient prescriptions directed to them under the HorizonCares program, our ability to maintain or increase prescriptions for our medicines will be impaired. The commercialization of our medicines and our operating results could be affected should any of the HorizonCares participating pharmacies choose not to continue participation in our HorizonCares program or by any adverse events at any of those HorizonCares participating pharmacies. For example, pharmacies that dispense our medicines could lose contracts that they currently maintain with managed care organizations, or MCOs, including PBMs. Pharmacies often enter into agreements with MCOs. They may be required to abide by certain terms and conditions to maintain access to MCO networks, including terms and conditions that could limit their ability to participate in patient assistance programs like ours. Failure to comply with the terms of their agreements with MCOs could result in a variety of penalties, including termination of their agreement, which could negatively impact the ability of those pharmacies to dispense our medicines and collect reimbursement from MCOs for such medicines.

The HorizonCares program may implicate certain federal and state laws related to, among other things, unlawful schemes to defraud, excessive fees for services, tortious interference with patient contracts and statutory or common law fraud. We have a comprehensive compliance program in place to address adherence with various laws and regulations relating to the selling, marketing and manufacturing of our medicines, as well as certain third-party relationships, including pharmacies. Specifically, with respect to pharmacies, the compliance program utilizes a variety of methods and tools to monitor and audit pharmacies, including those that participate in the HorizonCares program, to confirm their activities, adjudication and practices are consistent with our compliance policies and guidance. Despite our compliance efforts, to the extent the HorizonCares program is found to be inconsistent with applicable laws or the pharmacies that participate in our patient assistance programs do not comply with applicable laws, we may be required to restructure or discontinue such programs, terminate our relationship with certain pharmacies, or be subject to other significant penalties. In November 2015, we received a subpoena from the U.S. Attorney's Office for the Southern District of New York requesting documents and information related to our patient assistance programs and other aspects of our marketing and commercialization activities. We are unable to predict how long this investigation will continue or its outcome, but we have incurred and anticipate that we may continue to incur significant costs in connection with the investigation, regardless of the outcome. We may also become subject to similar investigations by other governmental agencies or Congress. The investigation by the U.S. Attorney's Office and any additional investigations of our patient assistance programs and sales and marketing activities may result in damages, fines, penalties, exclusion, additional reporting requirements and/or oversight or other administrative sanctions against us.

If the cost of maintaining our patient assistance programs increases relative to our sales revenues, we could be forced to reduce the amount of patient financial assistance that we offer or otherwise scale back or eliminate such programs, which could in turn have a negative impact on physicians' willingness to prescribe and patients' willingness to fill prescriptions of our medicines. While we believe that our arrangements with PBMs will result in broader inclusion of certain of our inflammation medicines on healthcare plan formularies, and therefore increase payer reimbursement and lower our cost of providing patient assistance programs, these arrangements generally require us to pay administrative and rebate payments to the PBMs and/or other payers and their effectiveness will ultimately depend to a large extent upon individual healthcare plan formulary decisions that are beyond the control of the PBMs. If our arrangements with PBMs and other payers do not result in increased prescriptions and reductions in our costs to provide our patient assistance programs that are sufficient to offset the administrative fees and rebate payments to the PBMs and/or other payers, our financial results may continue to be harmed.

If we are unable to successfully implement our commercial plans and facilitate adoption by patients and physicians of any approved medicines through our sales, marketing and commercialization efforts, then we will not be able to generate sustainable revenues from medicine sales which will have a material adverse effect on our business and prospects.

Our business operations may subject us to numerous commercial disputes, claims and/or lawsuits and such litigation may be costly and time-consuming and could materially and adversely impact our financial position and results of operations.

Operating in the pharmaceutical industry, particularly the commercialization of medicines, involves numerous commercial relationships, complex contractual arrangements, uncertain intellectual property rights, potential product liability and other aspects that create heightened risks of disputes, claims and lawsuits. In particular, we may face claims related to the safety of our medicines, intellectual property matters, employment matters, tax matters, commercial disputes, competition, sales and marketing practices, environmental matters, personal injury, insurance coverage and acquisition or divestiture-related matters. Any commercial dispute, claim or lawsuit may divert management's attention away from our business, we may incur significant expenses in addressing or defending any commercial dispute, claim or lawsuit, and we may be required to pay damage awards or settlements or become subject to equitable remedies that could adversely affect our operations and financial results.

We are currently in litigation with multiple generic drug manufacturers regarding intellectual property infringement. For example, we are currently involved in Hatch Waxman litigation with generic drug manufacturers related to DUEXIS, PENNSAID 2% and VIMOVO.

Similarly, from time to time we are involved in disputes with distributors, PBMs and licensing partners regarding our rights and performance of obligations under contractual arrangements. For example, we were previously in litigation with Express Scripts related to alleged breach of contract claims.

Litigation related to these disputes may be costly and time-consuming and could materially and adversely impact our financial position and results of operations if resolved against us.

A variety of risks associated with operating our business internationally could adversely affect our business.

In addition to our U.S. operations, we have operations in Ireland, Bermuda, the Grand Duchy of Luxembourg, or Luxembourg, Switzerland, Germany and in Canada. We face risks associated with our international operations, including possible unfavorable political, tax and labor conditions, which could harm our business. We are subject to numerous risks associated with international business activities, including:

- compliance with Irish laws and the maintenance of our Irish tax residency with respect to our overall corporate structure and administrative operations, including the need to generally hold meetings of our board of directors and make decisions in Ireland, which may make certain corporate actions more cumbersome, costly and time-consuming;
- difficulties in staffing and managing foreign operations;
- foreign government taxes, regulations and permit requirements;
- U.S. and foreign government tariffs, trade restrictions, price and exchange controls and other regulatory requirements;
- anti-corruption laws, including the Foreign Corrupt Practices Act, or the FCPA;
- economic weakness, including inflation, natural disasters, war, events of terrorism or political instability in particular foreign countries;
- fluctuations in currency exchange rates, which could result in increased operating expenses and reduced revenues, and other obligations related to doing business in another country;
- compliance with tax, employment, immigration and labor laws, regulations and restrictions for employees living or traveling abroad;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad;
- changes in diplomatic and trade relationships; and
- challenges in enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States.

Our business activities outside of the United States are subject to the FCPA and similar anti-bribery or anti-corruption laws, regulations or rules of other countries in which we operate. The FCPA and similar anti-corruption laws generally prohibit offering, promising, giving, or authorizing others to give anything of value, either directly or indirectly, to non-U.S. government officials in order to improperly influence any act or decision, secure any other improper advantage, or obtain or retain business. The FCPA also requires public companies to make and keep books and records that accurately and fairly reflect the transactions of the company and to devise and maintain an adequate system of internal accounting controls. As described above, our business is heavily regulated and therefore involves significant interaction with public officials, including officials of non-U.S. governments. Additionally, in many other countries, the health care providers who prescribe pharmaceuticals are employed by their government, and the purchasers of pharmaceuticals are government entities; therefore, any dealings with these prescribers and purchasers may be subject to regulation under the FCPA. Recently the SEC and the U.S. Department of Justice, or DOJ, have increased their FCPA enforcement activities with respect to pharmaceutical companies. In addition, under the Dodd–Frank Wall Street Reform and Consumer Protection Act, private individuals who report to the SEC original information that leads to successful enforcement actions may be eligible for a monetary award. We are engaged in ongoing efforts that are designed to ensure our compliance with these laws, including due diligence, training, policies, procedures and internal controls. However, there is no certainty that all employees and third-party business partners (including our distributors, wholesalers, agents, contractors, and other partners) will comply with anti-bribery laws. In particular, we do not control the actions of manufacturers and other third-party agents, although we may be liable for their actions. Violation of these laws may result in civil or criminal sanctions, which could include monetary fines, criminal penalties, and disgorgement of past profits, which could have a material adverse impact on our business and financial condition.

We are subject to tax audits around the world, and such jurisdictions may assess additional income tax against us. Although we believe our tax positions are reasonable, the final determination of tax audits could be materially different from our recorded income tax provisions and accruals. The ultimate results of an audit could have a material adverse effect on our operating results or cash flows in the period or periods for which that determination is made and could result in increases to our overall tax expense in subsequent periods.

These and other risks associated with our international operations may materially adversely affect our business, financial condition and results of operations.

If we fail to develop or acquire other medicine candidates or medicines, our business and prospects would be limited.

A key element of our strategy is to develop or acquire and commercialize a portfolio of other medicines or medicine candidates in addition to our current medicines, through business or medicine acquisitions. Because we do not engage in proprietary drug discovery, the success of this strategy depends in large part upon the combination of our regulatory, development and commercial capabilities and expertise and our ability to identify, select and acquire approved or clinically enabled medicine candidates for therapeutic indications that complement or augment our current medicines, or that otherwise fit into our development or strategic plans on terms that are acceptable to us. Identifying, selecting and acquiring promising medicines or medicine candidates requires substantial technical, financial and human resources expertise. Efforts to do so may not result in the actual acquisition or license of a particular medicine or medicine candidate, potentially resulting in a diversion of our management's time and the expenditure of our resources with no resulting benefit. If we are unable to identify, select and acquire suitable medicines or medicine candidates from third parties or acquire businesses at valuations and on other terms acceptable to us, or if we are unable to raise capital required to acquire businesses or new medicines, our business and prospects will be limited.

Moreover, any medicine candidate we acquire may require additional, time-consuming development or regulatory efforts prior to commercial sale or prior to expansion into other indications, including pre-clinical studies if applicable, and extensive clinical testing and approval by the FDA and applicable foreign regulatory authorities. All medicine candidates are prone to the risk of failure that is inherent in pharmaceutical medicine development, including the possibility that the medicine candidate will not be shown to be sufficiently safe and/or effective for approval by regulatory authorities. In addition, we cannot assure that any such medicines that are approved will be manufactured or produced economically, successfully commercialized or widely accepted in the marketplace or be more effective or desired than other commercially available alternatives.

In addition, if we fail to successfully commercialize and further develop our medicines, there is a greater likelihood that we will fail to successfully develop a pipeline of other medicine candidates to follow our existing medicines or be able to acquire other medicines to expand our existing portfolio, and our business and prospects would be harmed.

We have experienced growth and expanded the size of our organization substantially in connection with our acquisition transactions, and we may experience difficulties in managing this growth as well as potential additional growth in connection with future medicine, development program or company acquisitions.

As of December 31, 2013, we employed approximately 300 full-time employees as a consolidated entity. As of December 31, 2019, we employed approximately 1,200 full-time employees, including approximately 480 sales representatives, representing a substantial change to the size of our organization. We have also experienced, and may continue to experience, turnover of the sales representatives that we hired or will hire in connection with the commercialization of our medicines, requiring us to hire and train new sales representatives. Our management, personnel, systems and facilities currently in place may not be adequate to support anticipated growth, and we may not be able to retain or recruit qualified personnel in the future due to competition for personnel among pharmaceutical businesses.

As our commercialization plans and strategies continue to develop, we will need to continue to recruit and train sales and marketing personnel. Our ability to manage any future growth effectively may require us to, among other things:

- continue to manage and expand the sales and marketing efforts for our existing medicines;
- enhance our operational, financial and management controls, reporting systems and procedures;
- expand our international resources;
- successfully identify, recruit, hire, train, maintain, motivate and integrate additional employees;
- establish and increase our access to commercial supplies of our medicines and medicine candidates;
- expand our facilities and equipment; and
- manage our internal development efforts effectively while complying with our contractual obligations to licensors, licensees, contractors, collaborators, distributors and other third parties.

Our acquisitions have resulted in many changes, including significant changes in the corporate business and legal entity structure, the integration of other companies and their personnel with us, and changes in systems. We may encounter unexpected difficulties or incur unexpected costs, including:

- difficulties in achieving growth prospects from combining third-party businesses with our business;
- difficulties in the integration of operations and systems;
- difficulties in the assimilation of employees and corporate cultures;
- challenges in preparing financial statements and reporting timely results at both a statutory level for multiple entities and jurisdictions and at a consolidated level for public reporting;
- challenges in keeping existing physician prescribers and patients and increasing adoption of acquired medicines;
- difficulties in achieving anticipated cost savings, synergies, business opportunities and growth prospects from the combination;
- potential unknown liabilities, adverse consequences and unforeseen increased expenses associated with the transaction; and
- challenges in attracting and retaining key personnel.

If any of these factors impair our ability to continue to integrate our operations with those of any companies or businesses we acquire, we may not be able to realize the business opportunities, growth prospects and anticipated tax synergies from combining the businesses. In addition, we may be required to spend additional time or money on integration that otherwise would be spent on the development and expansion of our business.

We may not be successful in growing our commercial operations outside the United States, and could encounter other challenges in growing our commercial presence, including due to risks associated with political and economic instability, operating under different legal requirements and tax complexities. If we are unable to manage our commercial growth outside of the United States, our opportunities to expand sales in other countries will be limited or we may experience greater costs with respect to our ex-U.S. commercial operations.

We have also broadened our acquisition strategy to include development-stage assets or programs, which entails additional risk to us. For example, if we are unable to identify programs that ultimately result in approved medicines, we may spend material amounts of our capital and other resources evaluating, acquiring and developing medicines that ultimately do not provide a return on our investment. We have less experience evaluating development-stage assets and may be at a disadvantage compared to other entities pursuing similar opportunities. Regardless, development-stage programs generally have a high rate of failure and we cannot guarantee that any such programs will ultimately be successful. While we have significantly enhanced out research and development function over the last two years, we may need to enhance our clinical development and regulatory functions to properly evaluate and develop earlier-stage opportunities, which may include recruiting personnel that are knowledgeable in therapeutic areas we have not yet pursued. If we are unable to acquire promising development-stage assets or eventually obtain marketing approval for them, we may not be able to create a meaningful pipeline of new medicines and eventually realize a return on our investments.

Our management may also have to divert a disproportionate amount of its attention away from day-to-day activities and toward managing these growth and integration activities. Our future financial performance and our ability to execute on our business plan will depend, in part, on our ability to effectively manage any future growth and our failure to effectively manage growth could have a material adverse effect on our business, results of operations, financial condition and prospects.

Our prior medicine and company acquisitions and any other strategic transactions that we may pursue in the future could have a variety of negative consequences, and we may not realize the benefits of such transactions or attempts to engage in such transactions.

We have completed multiple medicine and company acquisitions and our strategy is to engage in additional strategic transactions with third parties, such as acquisitions of companies or divisions of companies and asset purchases of medicines, medicine candidates or technologies that we believe will complement or augment our existing business. We may also consider a variety of other business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and other investments. Any such transaction may require us to incur non-recurring and other charges, increase our near and long-term expenditures, pose significant integration challenges, create additional tax, legal, accounting and operational complexities in our business, require additional expertise, result in dilution to our existing shareholders and disrupt our management and business, which could harm our operations and financial results. For example, we assumed responsibility for the patent infringement litigation with respect to RAVICTI upon the closing of our acquisition of Hyperion Therapeutics, Inc., or Hyperion, and we have assumed responsibility for completing post-marketing clinical trials of RAVICTI that are required by the FDA, one of which is ongoing.

We are subject to contractual obligations under an amended and restated license agreement with the Regents of the University of California, San Diego, or UCSD, as amended, with respect to PROCYSBI. To the extent that we fail to perform our obligations under the agreement, UCSD may, with respect to applicable indications, terminate the license or otherwise cause the license to become non-exclusive. If this license was terminated, we would have no further right to use or exploit the related intellectual property, which would limit our ability to develop PROCYSBI in other indications, and could impact our ability to continue commercializing PROCYSBI in its approved indications.

We face significant competition in seeking appropriate strategic transaction opportunities and the negotiation process for any strategic transaction can be time-consuming and complex. In addition, we may not be successful in our efforts to engage in certain strategic transactions because our financial resources may be insufficient and/or third parties may not view our commercial and development capabilities as being adequate. We may not be able to expand our business or realize our strategic goals if we do not have sufficient funding or cannot borrow or raise additional capital. There is no assurance that following any of our recent acquisition transactions or any other strategic transaction, we will achieve the anticipated revenues, net income or other benefits that we believe justify such transactions. In addition, any failures or delays in entering into strategic transactions anticipated by analysts or the investment community could seriously harm our consolidated business, financial condition, results of operations or cash flow.

We may not be able to successfully maintain our current advantageous tax status and resulting tax rates, which could adversely affect our business and financial condition, results of operations and growth prospects.

Our parent company is incorporated in Ireland and has subsidiaries maintained in multiple jurisdictions, including Ireland, the United States, Switzerland, Luxembourg, Germany, Canada and Bermuda. We are able to achieve a favorable tax rate through the performance of certain functions and ownership of certain assets in tax-efficient jurisdictions, including Ireland and Bermuda, together with the use of intra-company service and transfer pricing agreements, each on an arm's length basis. Our effective tax rate may be different than experienced in the past due to numerous factors including, changes to the tax laws of jurisdictions that we operate in, the enactment of new tax treaties or changes to existing tax treaties, changes in the mix of our profitability from jurisdiction to jurisdiction, the implementation of the EU Anti-Tax Avoidance Directive (see further discussion below), the implementation of the Bermuda Economic Substance Act 2018 (effective December 31, 2018) and our inability to secure or sustain acceptable agreements with tax authorities (if applicable). Any of these factors could cause us to experience an effective tax rate significantly different from previous periods or our current expectations. Taxing authorities, such as the U.S. Internal Revenue Service, or IRS, actively audit and otherwise challenge these types of arrangements, and have done so in the pharmaceutical industry. We expect that these challenges will continue as a result of the recent increase in scrutiny and political attention on corporate tax structures. The IRS and/or the Irish tax authorities may challenge our structure and transfer pricing arrangements through an audit or lawsuit. Responding to or defending such a challenge could be expensive and consume time and other resources, and divert management's time and focus from operating our business. We cannot predict whether taxing authorities will conduct an audit or file a lawsuit challenging this structure, the cost involved in responding to any such audit or lawsuit, or the outcome. If we are unsuccessful in defending such a challenge, we may be required to pay taxes for prior periods, as well as interest, fines or penalties, and may be obligated to pay increased taxes in the future, any of which could require us to reduce our operating expenses, decrease efforts in support of our medicines or seek to raise additional funds, all of which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

The IRS may not agree with our conclusion that our parent company should be treated as a foreign corporation for U.S. federal income tax purposes following the combination of the businesses of Horizon Pharma, Inc., or HPI, our predecessor,and Vidara.

Although our parent company is incorporated in Ireland, the IRS may assert that it should be treated as a U.S. corporation (and, therefore, a U.S. tax resident) for U.S. federal income tax purposes pursuant to Section 7874 of the Internal Revenue Code of 1986, as amended, or the Code. A corporation is generally considered a tax resident in the jurisdiction of its organization or incorporation for U.S. federal income tax purposes. Because our parent company is an Irish incorporated entity, it would generally be classified as a foreign corporation (and, therefore, a non-U.S. tax resident) under these general rules. Section 7874 of the Code provides an exception pursuant to which a foreign incorporated entity may, in certain circumstances, be treated as a U.S. corporation for U.S. federal income tax purposes.

In July 2018, the IRS issued regulations under Section 7874. We do not believe that our classification as a foreign corporation for U.S. federal income tax purposes is affected by Section 7874 or the regulations thereunder, though the IRS may disagree.

Recent and future changes to U.S. and non-U.S. tax laws could materially adversely affect our company.

Under current law, we expect our parent company to be treated as a foreign corporation for U.S. federal income tax purposes. However, changes to the rules in Section 7874 of the Code or regulations promulgated thereunder or other guidance issued by the U.S. Department of the Treasury, or the U.S. Treasury, or the IRS could adversely affect our parent company's status as a foreign corporation for U.S. federal income tax purposes or the taxation of transactions between members of our group, and any such changes could have prospective or retroactive application. If our parent company is treated as a domestic corporation, more of our income will be taxed by the United States which may substantially increase our effective tax rate.

In addition, the Organization for Economic Co-operation and Development, or the OECD, released its Base Erosion and Profit Shifting project final report on October 5, 2015. This report provides the basis for international standards for corporate taxation that are designed to prevent, among other things, the artificial shifting of income to tax havens and low-tax jurisdictions, the erosion of the tax base through interest deductions on intra-company debt and the artificial avoidance of permanent establishments (i.e., tax nexus with a jurisdiction). Legislation to adopt these standards has been enacted or is currently under consideration in a number of jurisdictions. On June 7, 2017, several countries, including many countries that we operate and have subsidiaries in, participated in the signing ceremony adopting the OECD's Multilateral Convention to Implement Tax Treaty Related Measures to Prevent Base Erosion and Profit Shifting, commonly referred to as the MLI. The MLI came into effect on July 1, 2018. In January 2019, Ireland deposited the instrument of ratification of Ireland's MLI choices with the OECD. Ireland's MLI came into force on May 1, 2019, however the provisions in respect of withholding taxes and other taxes levied by Ireland did not come into effect for us until January 1, 2020 (with application also depending on whether the MLI has been ratified in other jurisdictions whose tax treaties with Ireland are affected). The MLI may modify affected tax treaties making it more difficult for us to obtain advantageous tax-treaty benefits. The number of affected tax treaties could eventually be in the thousands. As a result, our income may be taxed in jurisdictions where it is not currently taxed and at higher rates of tax than it is currently taxed, which may increase our effective tax rate.

The Irish Finance Act 2019, or Finance Act 2019, which was signed into law on December 22, 2019, introduced changes to Ireland's transfer pricing rules, which came into force with effect from January 1, 2020. The changes introduce the 2017 version of the OECD Transfer Pricing Guidelines, or 2017 OECD Guidelines, as the reference guidelines for Ireland's domestic transfer pricing regime. The 2017 OECD Guidelines were already applicable under Ireland's international tax treaties and therefore the introduction of these guidelines should only affect transactions with non-tax treaty countries. In addition to updating Irish tax law for the 2017 OECD Guidelines, these changes also extend the transfer pricing rules to certain non-trading transactions and to certain capital transactions. We have restructured certain intercompany arrangements, such that we do not expect there to be a material impact on our effective tax rate as a result of the introduction of these provisions.

On July 12, 2016, the Anti-Tax Avoidance Directive, or ATAD, was formally adopted by the Economic and Financial Affairs Council of the EU. The stated objective of the ATAD is to provide for the effective and swift coordinated implementation of anti-base erosion and profit shifting measures at EU level. Like all directives, the ATAD is binding as to the results it aims to achieve though EU Member States are free to choose the form and method of achieving those results. In addition, the ATAD contains a number of optional provisions that present an element of choice as to how it will be implemented into law. On December 25, 2018, the Finance Act 2018 was signed into Irish law, which introduced certain elements of the ATAD, such as the Controlled Foreign Company, or CFC, regime, into Irish law. The CFC regime became effective as of January 1, 2019. The ATAD also set out a high-level framework for the introduction of Anti-hybrid provisions. Finance Act 2019 introduced Anti-hybrid legislation in Ireland with effect from January 1, 2020. We do not expect these legislative changes to have a material impact on our effective tax rate. The timing of the introduction into Irish tax law of further ATAD measures, such as the interest limitation rules, is unclear. Although it is difficult at this stage to determine with precision the impact that these remaining provisions will have, their implementation could materially increase our effective tax rate.

On December 22, 2017, U.S. federal income tax legislation was signed into law (H.R. 1, "An Act to provide for reconciliation pursuant to titles II and V of the concurrent resolution on the budget for fiscal year 2018", informally titled the Tax Cuts and Jobs Act, or the Tax Act) that significantly revised the Code in the United States. The Tax Act, among other things, contained significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the tax deduction for interest expense to 30% of adjusted earnings (except for certain small businesses), implementation of a "base erosion anti-abuse tax" which requires U.S. corporations to make an alternative determination of taxable income without regard to tax deductions for certain payments to affiliates, taxation of certain non-U.S. corporations' earnings considered to be "global intangible low taxed income", or GILTI, repeal of the alternative minimum tax, or AMT, for corporations and changes to a taxpayer's ability to either utilize or refund the AMT credits previously generated, changes to the limitation on deductions for certain executive compensation particularly with respect to the removal of the previously allowed performance based compensation exception, changes in the attribution rules relating to shareholders of certain "controlled foreign corporations", limitation of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss carrybacks, one-time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing many business deductions and credits. For example, U.S. federal income tax law resulting in additional taxes owed by U.S. shareholders under the GILTI rules, together with the Tax Act's change to the attribution rules related to "controlled foreign corporations" may discourage U.S. investors from owning or acquiring 10% or greater of our outstanding ordinary shares, which other shareholders may have viewed as beneficial or may otherwise negatively impact the trading price of our ordinary shares. We are unable to predict what federal tax law may be proposed or enacted in the future or what effect such changes would have on our business, but such changes, to the extent they are brought into tax legislation, regulations, policies or practices, could affect our effective tax rates in the future in countries where we have operations and have an adverse effect on our overall tax rate in the future, along with increasing the complexity, burden and cost of tax compliance. We urge our shareholders to consult with their legal and tax advisors with respect to this legislation and the potential tax consequences of investing in or holding our ordinary shares.

On December 20, 2018, the U.S. Treasury issued Proposed Regulations under Section 267A of the Code, or Section 267A Proposed Regulations, to clarify certain aspects of Section 267A of the Code (commonly referred to as the "Anti-Hybrid Rules"). The Section 267A Proposed Regulations were the first administrative guidance on Section 267A of the Code and provided several rules which expanded the reach and scope of the Anti-Hybrid Rules particularly involving the payment of interest and royalties by certain branches, reverse hybrid entities, and other hybrid mismatch arrangements. While Section 267A of the Code does not appear to apply to us, we will assess the impact of the Anti-Hybrid Rules if and when the 267A Final Regulations are issued. To the extent that the Anti-Hybrid Rules under the 267A Final Regulations are applicable to us, such application could have a material impact on our effective tax rate.

On March 4, 2019, the U.S. Treasury issued Proposed Regulations under Section 250 of the Code, which provide guidance on both the computation of the deductions for GILTI and "foreign-derived intangible income", or FDII, and the determination of FDII. We do not expect to be subject to the GILTI inclusion nor is it expected that the potential FDII deduction would have a material impact on our effective tax rate.

If a United States person is treated as owning at least 10% of our ordinary shares, such holder may be subject to adverse U.S. federal income tax consequences.

If a United States person is treated as owning (directly, indirectly, or constructively) at least 10% of the value or voting power of our ordinary shares, such person may be treated as a "United States shareholder" with respect to each "controlled foreign corporation" in our group (if any). Because our group includes one or more U.S. subsidiaries, certain of our non-U.S. subsidiaries could be treated as controlled foreign corporations (regardless of whether or not we are treated as a controlled foreign corporation). A United States shareholder of a controlled foreign corporation may be required to report annually and include in its U.S. taxable income its pro rata share of "Subpart F income," "global intangible low-taxed income," and investments in U.S. property by controlled foreign corporations, regardless of whether we make any distributions. An individual that is a United States shareholder with respect to a controlled foreign corporation generally would not be allowed certain tax deductions or foreign tax credits that would be allowed to a United States shareholder that is a U.S. corporation. Failure to comply with these reporting and tax paying obligations may subject a United States shareholder to significant monetary penalties and may prevent the statute of limitations from starting with respect to such shareholder's U.S. federal income tax return for the year for which reporting was due. We cannot provide any assurances that we will assist investors in determining whether any of our non-U.S. subsidiaries is treated as a controlled foreign corporation or whether any investor is treated as a United States shareholder with respect to any such controlled foreign corporation or furnish to any United States shareholders information that may be necessary to comply with the aforementioned reporting and tax paying obligations. A United States investor should consult its advisors regarding the potential application of these rules to an investment in our ordinary shares.

If we are not successful in attracting and retaining highly qualified personnel, we may not be able to successfully implement our business strategy.

Our ability to compete in the highly competitive biotechnology and pharmaceuticals industries depends upon our ability to attract and retain highly qualified managerial, scientific and medical personnel. We are highly dependent on our management, sales and marketing and scientific and medical personnel, including our executive officers. In order to retain valuable employees at our company, in addition to salary and annual cash incentives, we provide a mix of performance stock units, or PSUs, that vest subject to attainment of specified corporate performance goals and continued services, stock options and restricted stock units, or RSUs, that vest over time subject to continued services. The value to employees of PSUs, stock options and RSUs will be significantly affected by movements in our share price that are beyond our control, and may at any time be insufficient to counteract more lucrative offers from other companies.

Despite our efforts to retain valuable employees, members of our management, sales and marketing, regulatory affairs, clinical development, medical affairs and development teams may terminate their employment with us on short notice. Although we have written employment arrangements with all of our employees, these employment arrangements generally provide for at-will employment, which means that our employees can leave our employment at any time, with or without notice. The loss of the services of any of our executive officers or other key employees and our inability to find suitable replacements could potentially harm our business, financial condition and prospects. We do not maintain "key man" insurance policies on the lives of these individuals or the lives of any of our other employees. Our success also depends on our ability to continue to attract, retain and motivate highly skilled junior, mid-level, and senior managers as well as junior, mid-level, and senior sales and marketing and scientific and medical personnel.

Many of the other biotechnology and pharmaceutical companies with whom we compete for qualified personnel have greater financial and other resources, different risk profiles and longer histories in the industry than we do. They also may provide more diverse opportunities and better chances for career advancement. Some of these characteristics may be more appealing to high quality candidates than that which we have to offer. If we are unable to continue to attract and retain high quality personnel, the rate and success at which we can develop and commercialize medicines and medicine candidates will be limited.

We are, with respect to our current medicines, and will be, with respect to any other medicine or medicine candidate for which we obtain FDA or EMA approval or which we acquire, subject to ongoing FDA or EMA obligations and continued regulatory review, which may result in significant additional expense. Additionally, any other medicine candidate, if approved by the FDA or EMA, could be subject to labeling and other restrictions and market withdrawal, and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our medicines.

Any regulatory approvals that we obtain for our medicine candidates may also be subject to limitations on the approved indicated uses for which the medicine may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials and surveillance to monitor the safety and efficacy of the medicine candidate. In addition, with respect to our current FDA-approved medicines (and with respect to our medicine candidates, if approved), the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for the medicine are subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMPs, GCPs, International Council for Harmonisation, or ICH, guidelines and GLPs, which are regulations and guidelines enforced by the FDA for all of our medicines in clinical development, for any clinical trials that we conduct post-approval.

In addition, the FDA closely regulates the marketing and promotion of drugs and biologics. The FDA does not regulate the behaviour of physicians in their choice of treatments. The FDA does, however, restrict manufacturers' promotional communications. A significant number of pharmaceutical companies have been the target of inquiries and investigations by various U.S. federal and state regulatory, investigative, prosecutorial and administrative entities in connection with the promotion of medicines for off-label uses and other sales practices. These investigations have alleged violations of various U.S. federal and state laws and regulations, including claims asserting antitrust violations, violations of the Food, Drug and Cosmetic Act, false claims laws, the Prescription Drug Marketing Act, anti-kickback laws, and other alleged violations in connection with the promotion of medicines for unapproved uses, pricing and Medicare and/or Medicaid reimbursement. While Congress has recently considered legislation that would modify or eliminate restrictions for off-label promotion, we do not have sufficient information to anticipate if the current regulatory environment will change.

Later discovery of previously unknown problems with a medicine, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on the marketing or manufacturing of the medicine, withdrawal of the medicine from the market, or voluntary or mandatory medicine recalls;
- refusal by the FDA to approve pending applications or supplements to approved applications filed by us or our strategic partners, or suspension or revocation of medicine license approvals;
- medicine seizure or detention, or refusal to permit the import or export of medicines; and
- injunctions, the imposition of civil or criminal penalties, or exclusion, debarment or suspension from government healthcare programs.

If we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would have a material adverse effect on our business, results of operations, financial condition and prospects.

We are subject to federal, state and foreign healthcare laws and regulations and implementation or changes to such healthcare laws and regulations could adversely affect our business and results of operations.

The United States and some foreign jurisdictions are considering or have enacted a number of legislative and regulatory proposals to regulate and to change the healthcare system in ways that could affect our ability to sell our medicines profitably. In the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs (including a number of proposals pertaining to prescription drugs, specifically), improving quality and/or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives.

If we are found to be in violation of any of these laws or any other federal or state regulations, we may be subject to civil and/or criminal penalties, damages, fines, exclusion, additional reporting requirements and/or oversight from federal health care programs and the restructuring of our operations. Any of these could have a material adverse effect on our business and financial results. Since many of these laws have not been fully interpreted by the courts, there is an increased risk that we may be found in violation of one or more of their provisions. Any action against us for violation of these laws, even if we ultimately are successful in our defense, will cause us to incur significant legal expenses and divert our management's attention away from the operation of our business.

There remain judicial and Congressional challenges to certain aspects of the ACA, as well as recent efforts by the Trump administration to repeal or replace certain aspects of the ACA. Since January 2017, President Trump has signed two Executive Orders and other directives designed to delay the implementation of certain provisions of the ACA. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the ACA. While Congress has not passed comprehensive repeal legislation, it has enacted laws that modify certain provisions of the ACA such as removing penalties, starting January 1, 2019, for not complying with the ACA's individual mandate to carry health insurance, and delaying the implementation of certain ACA-mandated fees, and increasing the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D. On December 14, 2018, a Texas U.S. District Court Judge ruled that the ACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the Tax Cuts and Jobs Act of 2017. While the Texas U.S. District Court Judge, as well as the Trump administration and CMS, have stated that the ruling will have no immediate effect pending appeal of the decision, it is unclear how this decision, subsequent appeals, and other efforts to repeal and replace the ACA will impact the ACA and our business.

Likewise, in the countries in the EU, legislators, policymakers and healthcare insurance funds continue to propose and implement cost-containing measures to keep healthcare costs down, due in part to the attention being paid to healthcare cost containment in the EU. Certain of these changes could impose limitations on the prices we will be able to charge for our products and any approved product candidates or the amounts of reimbursement available for these products from governmental agencies or third-party payers, may increase the tax obligations on pharmaceutical companies such as ours, or may facilitate the introduction of generic competition with respect to our products.

In addition, drug pricing by pharmaceutical companies has come under increased scrutiny. Specifically, there have been several recent state and U.S. Congressional inquiries, proposed federal and state legislation and state laws enacted designed to, among other things, bring more transparency to drug pricing by requiring drug companies to notify insurers and government regulators of price increases and provide an explanation of the reasons for the increase, reduce the out-of-pocket cost of prescription drugs, review the relationship between pricing and manufacturer patient programs, reduce the cost of drugs under Medicare, and reform government program reimbursement methodologies. For example, legislation signed into law in 2017 in California requires drug manufactures to provide advance notice and explanation to state regulators, health plans and insurers and PBMs for price increases of more than 16% over two years. Moreover, in May 2018, the Trump administration released its "Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs", or Blueprint. The Blueprint contains several potential regulatory actions and legislative recommendations aimed at lowering prescription drug prices including measures to promote innovation and competition for biologics, changes to Medicare Part D to give plan sponsors more leverage when negotiating prices with manufacturers and updating the Medicare drug-pricing dashboard to make price increases and generic competition more transparent. The recommendations in the Blueprint if enacted by Congress and HHS, could lead to changes to Medicare Parts B and D. Further, the Bipartisan Budget Act of 2018, among other things, amends the ACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole". The majority of our medicines are purchased by private payers, and much of the focus of pending legislation is on government program reimbursement. Most recently, the Office of Inspector General of HHS published a Proposed Rule in January 2019 that would, among other items, eliminate the current safe harbor protection under the Anti-Kickback Statute for pharmaceutical manufacturer rebates to Medicare Part D plans, Medicaid MCOs and the PBMs with which such entities contract. Although this Proposed Rule was withdrawn by the Administration, in July 2019 a similar provision was included in legislation currently being considered in the United States Senate. We cannot know what form any such action may take, the likelihood it would be executed, enacted, effectuated or implemented or the market's perception of how such legislation or regulation would affect us. Any reduction in reimbursement from government programs may result in a similar reduction in payments from private payers. The Trump administration's budget proposal for fiscal year 2020 contains further drug price control measures that could be enacted during the 2020 budget process, through regulation or other future legislation. In September 2019, Speaker of the House Nancy Pelosi introduced legislation that would in part, require the HHS Secretary to identify 250 drugs that "lack price competition" and therefore would be subject to government price negotiation. The proposal defines a drug that lacks price competition as a brand-name drug that does not have a generic or biosimilar competitor on the market. Under the proposal, the HHS Secretary would directly negotiate with drug manufacturers to establish a maximum fair price. In December 2019, the Further Consolidated Appropriations Act was signed into law which included the Creating and Restoring Equal Access to Equivalent Samples Act, or CREATES Act. The CREATES Act allows generic drug manufacturers to bring suit against a brand name manufacturer to compel the provision of brand samples if the generic manufacturer has made a request for samples and the brand manufacturer fails to deliver sufficient quantities of the sample on commercially reasonable, market-based terms within 31 days of receipt of the request. The United States Senate is also considering legislation that would, among other changes to Medicare reimbursement, require manufacturers to report to the HHS Secretary information to justify price increases. The HHS would make the price justification information available to the public. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our current medicines and/or those for which we may receive regulatory approval in the future.

We are subject, directly or indirectly, to federal and state healthcare fraud and abuse, transparency laws and false claims laws. Prosecutions under such laws have increased in recent years and we may become subject to such litigation. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

In the United States, we are subject directly, or indirectly or through our customers, to various state and federal fraud and abuse and transparency laws, including, without limitation, the federal Anti-Kickback Statute, the federal False Claims Act, civil monetary penalty statutes prohibiting beneficiary inducements, and similar state and local laws, federal and state privacy and security laws, sunshine laws, government price reporting laws, and other fraud laws. Some states, such as Massachusetts, make certain reported information public. In addition, there are state and local laws that require pharmaceutical representatives to be licensed and comply with codes of conduct, transparency reporting, and other obligations. Collectively, these laws may affect, among other things, our current and proposed sales, marketing and educational programs, as well as other possible relationships with customers, pharmacies, physicians, payers, and patients. We are subject to similar laws in the EU/European Economic Area, including the EU General Data Protection Regulation (2016/679), or GDPR, under which fines of up to €20.0 million or up to 4% of the annual global turnover of the infringer, whichever is greater, could be imposed for significant non-compliance.

Compliance with these laws, including the development of a comprehensive compliance program, is difficult, costly and time consuming. Because of the breadth of these laws and the narrowness of available statutory and regulatory exemptions, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Moreover, state governmental agencies may propose or enact laws and regulations that extend or contradict federal requirements. These risks may be increased where there are evolving interpretations of applicable regulatory requirements, such as those applicable to manufacturer co-pay programs. Pharmaceutical manufacturer co-pay programs, including pharmaceutical manufacturer donations to patient assistance programs offered by charitable foundations, are the subject of ongoing litigation, enforcement actions and settlements (involving other manufacturers and to which we are not a party) and evolving interpretations of applicable regulatory requirements and certain state laws, and any change in the regulatory or enforcement environment regarding such programs could impact our ability to offer such programs. If we are unsuccessful with our HorizonCares programs, any other co-pay programs, we would be at a competitive disadvantage in terms of pricing versus preferred branded and generic competitors, or be subject to significant penalties. We are engaged in various business arrangements with current and potential customers, and we can give no assurance that such arrangements would not be subject to scrutiny under such laws, despite our efforts to properly structure such arrangements. Even if we structure our programs with the intent of compliance with such laws, there can be no certainty that we would not need to defend our business activities against enforcement or litigation. Further, we cannot give any assurances that prior business activities or arrangements of other companies that we acquire will not be scrutinized or subject to enforcement or litigation.

There has also been a trend of increased federal and state regulation of payments made to physicians and other healthcare providers. The ACA, among other things, imposed reporting requirements on drug manufacturers for payments made by them to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. In November 2019, HHS published a final 2020 Physician Fee Schedule rule which for calendar year 2021, expands the definition of “covered recipients” for which reporting of payments and transfers is required, to include physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists and certified nurse midwives. Failure to submit required information may result in significant civil monetary penalties.

On March 5, 2019, we received a civil investigative demand, or CID, from the DOJ pursuant to the Federal False Claims Act regarding assertions that certain of our payments to PBMs were potentially in violation of the Anti-Kickback Statute. The CID requests certain documents and information related to our payments to PBMs, pricing and our patient assistance program regarding DUEXIS, VIMOVO and PENNSAID 2%. We are cooperating with the investigation. While we believe that our payments and programs are compliant with the Anti-Kickback Statute, no assurance can be given as to the timing or outcome of the DOJ’s investigation, or that it will not result in a material adverse effect on our business.

We are unable to predict whether we could be subject to other actions under any of these or other healthcare laws, or the impact of such actions. If we are found to be in violation of, or to encourage or assist the violation by third parties of any of the laws described above or other applicable state and federal fraud and abuse laws, we may be subject to penalties, including administrative, civil and criminal penalties, damages, fines, withdrawal of regulatory approval, imprisonment, exclusion from government healthcare reimbursement programs, contractual damages, reputational harm, diminished profits and future earnings, injunctions and other associated remedies, or private “qui tam” actions brought by individual whistleblowers in the name of the government, and the curtailment or restructuring of our operations, all of which could have a material adverse effect on our business and results of operations. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management’s attention from the operation of our business.

Our medicines or any other medicine candidate that we develop may cause undesirable side effects or have other properties that could delay or prevent regulatory approval or commercialization, result in medicine re-labeling or withdrawal from the market or have a significant impact on customer demand.

Undesirable side effects caused by any medicine candidate that we develop could result in the denial of regulatory approval by the FDA or other regulatory authorities for any or all targeted indications, or cause us to evaluate the future of our development programs. With respect to KRYSTEXXA, the most commonly reported serious adverse reactions in the pivotal trial were gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis, exacerbation of pre-existing congestive heart failure and vomiting. With respect to RAVICTI, the most common side effects are diarrhea, nausea, decreased appetite, gas, vomiting, high blood levels of ammonia, headache, tiredness and dizziness. The most common adverse events reported in a Phase 2 clinical trial of PENNSAID 2% were application site reactions, such as dryness, exfoliation, erythema, pruritus, pain, induration, rash and scabbing. With respect to PROCYSBI, the most common side effects include vomiting, nausea, abdominal pain, breath odor, diarrhea, skin odor, fatigue, rash and headache. In our two Phase 3 clinical trials with DUEXIS, the most commonly reported treatment-emergent adverse events were nausea, dyspepsia, diarrhea, constipation and upper respiratory tract infection. The most common side effects observed in pivotal trials for ACTIMMUNE were “flu-like” or constitutional symptoms such as fever, headache, chills, myalgia and fatigue. The most commonly reported treatment-emergent adverse events in the Phase 3 clinical trials with RAYOS included flare in rheumatoid arthritis related symptoms, abdominal pain, nasopharyngitis, headache, flushing, upper respiratory tract infection, back pain and weight gain. In Phase 3 endoscopic registration clinical trials with VIMOVO, the most commonly reported treatment-emergent adverse events were erosive gastritis, dyspepsia, gastritis, diarrhea, gastric ulcer, upper abdominal pain, nausea and upper respiratory tract infection. In our Phase 3 clinical trial evaluating TEPEZZA for the treatment of active TED, the most commonly reported treatment-emergent adverse events were muscle spasms, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dysgeusia, headache and dry skin.

The FDA or other regulatory authorities may also require, or we may undertake, additional clinical trials to support the safety profile of our medicines or medicine candidates.

In addition, if we or others identify undesirable side effects caused by our medicines or any other medicine candidate that we may develop that receives marketing approval, or if there is a perception that the medicine is associated with undesirable side effects:

- regulatory authorities may require the addition of labeling statements, such as a “black box” warning or a contraindication;
- regulatory authorities may withdraw their approval of the medicine or place restrictions on the way it is prescribed;
- we may be required to change the way the medicine is administered, conduct additional clinical trials or change the labeling of the medicine or implement a risk evaluation and mitigation strategy; and
- we may be subject to increased exposure to product liability and/or personal injury claims.

If any of these events occurred with respect to our medicines, our ability to generate significant revenues from the sale of these medicines would be significantly harmed.

We rely on third parties to conduct our pre-clinical and clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines or if they experience regulatory compliance issues, we may not be able to obtain regulatory approval for or commercialize our medicine candidates and our business could be substantially harmed.

We have agreements with third-party contract research organizations, or CROs, to conduct our clinical programs, including those required for post-marketing commitments, and we expect to continue to rely on CROs for the completion of on-going and planned clinical trials. We may also have the need to enter into other such agreements in the future if we were to develop other medicine candidates or conduct clinical trials in additional indications for our existing medicines. We also rely heavily on these parties for the execution of our clinical studies and control only certain aspects of their activities. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol. We, our CROs and our academic research organizations are required to comply with current GCP or ICH regulations. The FDA enforces these GCP or ICH regulations through periodic inspections of trial sponsors, principal investigators and trial sites. If we or our CROs or collaborators fail to comply with applicable GCP or ICH regulations, the data generated in our clinical trials may be deemed unreliable and our submission of marketing applications may be delayed or the FDA may require us to perform additional clinical trials before approving our marketing applications. We cannot assure that, upon inspection, the FDA will determine that any of our clinical trials comply or complied with GCP or ICH regulations. In addition, our clinical trials must be conducted with medicine produced under cGMP regulations, and may require a large number of test subjects. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. Moreover, our business may be implicated if any of our CROs or collaborators violates federal or state fraud and abuse or false claims laws and regulations or privacy and security laws. We must also obtain certain third-party institutional review board, or IRB, and ethics committee approvals in order to conduct our clinical trials. Delays by IRBs and ethics committees in providing such approvals may delay our clinical trials.

If any of our relationships with these third-party CROs or collaborators terminate, we may not be able to enter into similar arrangements on commercially reasonable terms, or at all. If CROs or collaborators do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our medicines and medicine candidates. As a result, our results of operations and the commercial prospects for our medicines and medicine candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed.

Switching or adding additional CROs or collaborators can involve substantial cost and require extensive management time and focus. In addition, there is a natural transition period when a new CRO or collaborator commences work. As a result, delays may occur, which can materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our CROs and collaborators, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition or prospects.

Clinical development of drugs and biologics involves a lengthy and expensive process with an uncertain outcome, and results of earlier studies and trials may not be predictive of future trial results.

Clinical testing is expensive and can take many years to complete, and its outcome is uncertain. Failure can occur at any time during the clinical trial process. The results of pre-clinical studies and early clinical trials of potential medicine candidates may not be predictive of the results of later-stage clinical trials. Medicine candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through pre-clinical studies and initial clinical testing. For example, in December 2016, we announced that the Phase 3 trial, Safety, Tolerability and Efficacy of ACTIMMUNE Dose Escalation in Friedreich's ataxia, evaluating ACTIMMUNE for the treatment of Friedreich's ataxia did not meet its primary endpoint. Additionally, we discontinued our ACTIMMUNE investigator-initiated trials in oncology to focus on our strategic pipeline where we see more promise and long-term intellectual property.

We may experience delays in clinical trials or investigator-initiated studies. We do not know whether any additional clinical trials will be initiated in the future, begin on time, need to be redesigned, enroll patients on time or be completed on schedule, if at all. Clinical trials can be delayed for a variety of reasons, including delays related to:

- obtaining regulatory approval to commence a trial;
- reaching agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;

- obtaining IRB or ethics committee approval at each site;
- recruiting suitable patients to participate in a trial;
- having patients complete a trial or return for post-treatment follow-up;
- clinical sites dropping out of a trial;
- adding new sites; or
- manufacturing sufficient quantities of medicine candidates for use in clinical trials.

Patient enrollment, a significant factor in the timing of clinical trials, is affected by many factors including the size and nature of the patient population, the proximity of patients to clinical sites, the eligibility criteria for the trial, the design of the clinical trial, competing clinical trials and clinicians' and patients' perceptions as to the potential advantages of the medicine candidate being studied in relation to other available therapies, including any new drugs or biologics that may be approved for the indications we are investigating.

We could encounter delays if prescribing physicians encounter unresolved ethical issues associated with enrolling patients in clinical trials of our medicine candidates in lieu of prescribing existing treatments that have established safety and efficacy profiles. Further, a clinical trial may be suspended or terminated by us, our collaborators, the FDA or other regulatory authorities due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a medicine candidate, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. If we experience delays in the completion of, or if we terminate, any clinical trial of our medicine candidates, the commercial prospects of our medicine candidates will be harmed, and our ability to generate medicine revenues from any of these medicine candidates will be delayed. In addition, any delays in completing our clinical trials will increase our costs, slow down our medicine development and approval process and jeopardize our ability to commence medicine sales and generate revenues.

Moreover, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and receive compensation in connection with such services. Under certain circumstances, we may be required to report some of these relationships to the FDA. The FDA may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected interpretation of the study. The FDA may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing applications by the FDA and may ultimately lead to the denial of marketing approval of one or more of our medicine candidates.

Any of these occurrences may harm our business, financial condition, results of operations and prospects significantly. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our medicine candidates.

Business interruptions could seriously harm our future revenue and financial condition and increase our costs and expenses.

Our operations could be subject to earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics and other natural or man-made disasters or business interruptions. While we carry insurance for certain of these events and have implemented disaster management plans and contingencies, the occurrence of any of these business interruptions could seriously harm our business and financial condition and increase our costs and expenses. We conduct significant management operations at both our global headquarters located in Dublin, Ireland and our U.S. office located in Lake Forest, Illinois. If our Dublin or Lake Forest offices were affected by a natural or man-made disaster or other business interruption, our ability to manage our domestic and foreign operations could be impaired, which could materially and adversely affect our results of operations and financial condition. We currently rely, and intend to rely in the future, on third-party manufacturers and suppliers to produce our medicines and third-party logistics partners to ship our medicines. Our ability to obtain commercial supplies of our medicines could be disrupted and our results of operations and financial condition could be materially and adversely affected if the operations of these third-party suppliers or logistics partners were affected by a man-made or natural disaster or other business interruption. The ultimate impact of such events on us, our significant suppliers and our general infrastructure is unknown.

We are dependent on information technology systems, infrastructure and data, which exposes us to data security risks.

We are dependent upon our own or third-party information technology systems, infrastructure and data, including mobile technologies, to operate our business. The multitude and complexity of our computer systems may make them vulnerable to service interruption or destruction, disruption of data integrity, malicious intrusion, or random attacks. Likewise, data privacy or security incidents or breaches by employees or others may pose a risk that sensitive data, including our intellectual property, trade secrets or personal information of our employees, patients, customers or other business partners may be exposed to unauthorized persons or to the public. Cyberattacks are increasing in their frequency, sophistication and intensity. Cyberattacks could include the deployment of harmful malware, denial-of-service, social engineering and other means to affect service reliability and threaten data confidentiality, integrity and availability. Our business partners face similar risks and any security breach of their systems could adversely affect our security posture. A security breach or privacy violation that leads to disclosure or modification of or prevents access to patient information, including personally identifiable information or protected health information, could harm our reputation, compel us to comply with federal and/or state breach notification laws and foreign law equivalents, subject us to mandatory corrective action, require us to verify the correctness of database contents and otherwise subject us to litigation or other liability under laws and regulations that protect personal data, any of which could disrupt our business and/or result in increased costs or loss of revenue. Moreover, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information, trade secrets or other intellectual property.

Despite significant efforts to create security barriers to the above described threats, it is impossible for us to entirely mitigate these risks. We may be unable to anticipate or prevent techniques used to obtain unauthorized access or to compromise our systems because they change frequently and are generally not detected until after an incident has occurred. In addition, a cybersecurity event could result in significant increases in costs, including costs for remediating the effects of such an event, fines imposed by regulators, lost revenues due to decrease in customer trust and network downtime, increases in insurance premiums due to cybersecurity incidents and damages to our reputation because of any such incident. While we have invested, and continue to invest, in the protection of our data and information technology infrastructure, there can be no assurance that our efforts will prevent service interruptions, or identify vulnerabilities or breaches in our systems, that could adversely affect our business and operations and/or result in the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm to us. In addition, our liability insurance may not be sufficient in type or amount to cover us against claims related to security breaches, cyberattacks and other related breaches.

We are subject to extensive laws and regulations related to data privacy, and our failure to comply with these laws and regulations could harm our business.

We are subject to laws and regulations governing data privacy and the protection of personal information. These laws and regulations govern our processing of personal data, including the collection, access, use, analysis, modification, storage, transfer, security breach notification, destruction and disposal of personal data. There are foreign and state law versions of these laws and regulations to which we are currently and/or may in the future, be subject. For example, the collection and use of personal health data in the EU is governed by the GDPR. The GDPR, which is wide-ranging in scope, imposes several requirements relating to the consent of the individuals to whom the personal data relates, the information provided to the individuals, the security and confidentiality of the personal data, data breach notification and the use of third-party processors in connection with the processing of personal data. The GDPR also imposes strict rules on the transfer of personal data out of the EU to the United States, provides an enforcement authority and imposes potentially large monetary penalties for noncompliance. The GDPR requirements apply not only to third-party transactions, but also to transfers of information within our company, including employee information. The GDPR and similar data privacy laws of other jurisdictions place significant responsibilities on us and create potential liability in relation to personal data that we or our third-party service providers process, including in clinical trials conducted in the United States and EU. In addition, we expect that there will continue to be new proposed laws, regulations and industry standards relating to privacy and data protection in the United States, the EU and other jurisdictions, and we cannot determine the impact such future laws, regulations and standards may have on our business.

Additionally, the California Consumer Privacy Act, or CCPA, went into effect on January 1, 2020. The CCPA has been dubbed the first "GDPR-like" law in the United States since it creates new individual privacy rights for consumers (as that word is broadly defined in the law) and places increased privacy and security obligations on entities handling personal data of consumers or households. The CCPA requires covered companies to provide new disclosures to California consumers (as that word is broadly defined in the CCPA), provide such consumers new ways to opt-out of certain sales of personal information, and allow for a new cause of action for data breaches. It remains unclear how the CCPA will be interpreted, but as currently written, it will likely impact our business activities and exemplifies the vulnerability of our business to not only cyber threats but also the evolving regulatory environment related to personal data and protected health information. As we expand our operations and trials (both preclinical or clinical), the CCPA may increase our compliance costs and potential liability. Some observers have noted that the CCPA could mark the beginning of a trend toward more stringent privacy legislation in the United States. Other states are beginning to pass similar laws.

Compliance with these and any other applicable privacy and data security laws and regulations is a rigorous and time-intensive process, and we may be required to put in place additional mechanisms ensuring compliance with the new data protection rules. If we fail to comply with any such laws or regulations, we may face significant fines and penalties that could adversely affect our business, financial condition and results of operations. Furthermore, the laws are not consistent, and compliance in the event of a widespread data breach is costly.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our medicines.

We face an inherent risk of product liability claims as a result of the commercial sales of our medicines and the clinical testing of our medicine candidates. For example, we may be sued if any of our medicines or medicine candidates allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the medicine, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our medicines and medicine candidates. Even a successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for our medicines or medicine candidates that we may develop;
- injury to our reputation;
- withdrawal of clinical trial participants;
- initiation of investigations by regulators;
- costs to defend the related litigation;

- a diversion of management's time and resources;
- substantial monetary awards to trial participants or patients;
- medicine recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- exhaustion of any available insurance and our capital resources; and
- the inability to commercialize our medicines or medicine candidates.

Our inability to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of medicines we develop. We currently carry product liability insurance covering our clinical studies and commercial medicine sales in the amount of $125.0 million in the aggregate. Although we maintain such insurance, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. If we determine that it is prudent to increase our product liability coverage due to the on-going commercialization of our current medicines in the United States, and/or the potential commercial launches of any of our medicines in additional markets or for additional indications, we may be unable to obtain such increased coverage on acceptable terms or at all. Our insurance policies also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We will have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts.

Our business involves the use of hazardous materials, and we and our third-party manufacturers must comply with environmental laws and regulations, which can be expensive and restrict how we do business.

Our third-party manufacturers' activities involve the controlled storage, use and disposal of hazardous materials owned by us, including the components of our medicine candidates and other hazardous compounds. We and our manufacturers are subject to federal, state and local as well as foreign laws and regulations governing the use, manufacture, storage, handling and disposal of these hazardous materials. Although we believe that the safety procedures utilized by our third-party manufacturers for handling and disposing of these materials comply with the standards prescribed by these laws and regulations, we cannot eliminate the risk of accidental contamination or injury from these materials. In the event of an accident, state, federal or foreign authorities may curtail the use of these materials and interrupt our business operations. We currently only maintain hazardous materials insurance coverage related to our South San Francisco facility. If we are subject to any liability as a result of our third-party manufacturers' activities involving hazardous materials, our business and financial condition may be adversely affected. In the future we may seek to establish longer-term third-party manufacturing arrangements, pursuant to which we would seek to obtain contractual indemnification protection from such third-party manufacturers potentially limiting this liability exposure.

Our employees, independent contractors, principal investigators, consultants, vendors, distributors and CROs may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk that our employees, independent contractors, principal investigators, consultants, vendors, distributors and CROs may engage in fraudulent or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct or unauthorized activities that violate FDA regulations, including those laws that require the reporting of true, complete and accurate information to the FDA, manufacturing standards, federal and state healthcare fraud and abuse laws and regulations, and laws that require the true, complete and accurate reporting of financial information or data. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Misconduct by our employees and other third parties may also include the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. We have adopted a Code of Business Conduct and Ethics, but it is not always possible to identify and deter misconduct by our employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs and imprisonment.

Risks Related to our Financial Position and Capital Requirements

We have incurred significant operating losses.

We have financed our operations primarily through equity and debt financings and have incurred significant operating losses. We recorded operating income of $126.6 million for the year ended December 31, 2019, operating income of $37.9 million for the year ended December 31, 2018 and an operating loss of $339.4 million for the year ended December 31, 2017. We recorded net income of $573.0 million for the year ended December 31, 2019, a net loss of $38.4 million for the year ended December 31, 2018 and a net loss of $350.1 million for the year ended December 31, 2017. As of December 31, 2019, we had an accumulated deficit of $605.7 million. Our prior losses have resulted principally from costs incurred in our development activities for our medicines and medicine candidates, commercialization activities related to our medicines, costs associated with our acquisition transactions and costs associated with derivative liability accounting. Our prior losses, combined with possible future losses, have had and will continue to have an adverse effect on our shareholders' equity and working capital. While we anticipate that we will generate operating profits in the future, whether we can accomplish this will depend on the revenues we generate from the sale of our medicines being sufficient to cover our operating expenses.

We have limited sources of revenues and significant expenses. We cannot be certain that we will achieve or sustain profitability, which would depress the market price of our ordinary shares and could cause our investors to lose all or a part of their investment.

Our ability to achieve and sustain profitability depends upon our ability to generate sales of our medicines. The commercialization of our medicines has been primarily in the United States. We may never be able to successfully commercialize our medicines or develop or commercialize other medicines in the United States, which we believe represents our most significant commercial opportunity. Our ability to generate future revenues depends heavily on our success in:

- continued commercialization of our existing medicines and any other medicine candidates for which we obtain approval;
- securing additional foreign regulatory approvals for our medicines in territories where we have commercial rights; and
- developing, acquiring and commercializing a portfolio of other medicines or medicine candidates in addition to our current medicines.

Even if we do generate additional medicine sales, we may not be able to achieve or sustain profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the market price of our ordinary shares and could impair our ability to raise capital, expand our business, diversify our medicine offerings or continue our operations.

We may need to obtain additional financing to fund additional acquisitions.

Our operations have consumed substantial amounts of cash since inception. We expect to continue to spend substantial amounts to:

- commercialize our existing medicines in the United States, including the substantial expansion of our sales force in recent years;
- complete the regulatory approval process, and any future required clinical development related thereto, for our medicines and medicine candidates;
- potentially acquire other businesses or additional complementary medicines or medicines that augment our current medicine portfolio, including costs associated with refinancing debt of acquired companies;
- satisfy progress and milestone payments under our existing and future license, collaboration and acquisition agreements; and
- conduct clinical trials with respect to potential additional indications, as well as conduct post-marketing requirements and commitments, with respect to our medicines and medicines we acquire.

While we believe that our existing cash and cash equivalents will be sufficient to fund our operations based on our current expectations of continued revenue growth, we may need to raise additional funds if we choose to expand our commercialization or development efforts more rapidly than presently anticipated, if we develop or acquire additional medicines or acquire companies, or if our revenue does not meet expectations.

We cannot be certain that additional funding will be available on acceptable terms, or at all. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of one or more of our medicines or medicine candidates or one or more of our other research and development initiatives, or delay, cut back or abandon our plans to grow the business through acquisitions. We also could be required to:

- seek collaborators for one or more of our current or future medicine candidates at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available; or
- relinquish or license on unfavorable terms our rights to technologies or medicine candidates that we would otherwise seek to develop or commercialize ourselves.

In addition, if we are unable to secure financing to support future acquisitions, our ability to execute on a key aspect of our overall growth strategy would be impaired.

Any of the above events could significantly harm our business, financial condition and prospects.

We have incurred a substantial amount of debt, which could adversely affect our business, including by restricting our ability to engage in additional transactions or incur additional indebtedness, and prevent us from meeting our debt obligations.

As of December 31, 2019, we had $1,352.8 million book value, or $1,418.0 million aggregate principal amount of indebtedness, including $418.0 million in secured indebtedness. In March 2019, we received $200.0 million of commitments under a new revolving credit facility under our credit agreement. In December 2019, we borrowed approximately $418.0 million aggregate principal amount of loans pursuant to an amendment to our credit agreement to refinance the then outstanding senior secured term loans of approximately $418.0 million under our credit agreement. In July 2019, we issued $600.0 million aggregate principal amount of 5.500% Senior Notes due 2027, or the 2027 Senior Notes. In March 2015, we issued $400.0 million aggregate principal amount of 2.50% Exchangeable Senior Notes due 2022, or the Exchangeable Senior Notes. Accordingly, we have a significant amount of debt outstanding on a consolidated basis.

This substantial level of debt could have important consequences to our business, including, but not limited to:

- reducing the benefits we expect to receive from our prior and any future acquisition transactions;
- making it more difficult for us to satisfy our obligations;
- requiring a substantial portion of our cash flows from operations to be dedicated to the payment of principal and interest on our indebtedness, therefore reducing our ability to use our cash flows to fund acquisitions, capital expenditures, and future business opportunities;
- exposing us to the risk of increased interest rates to the extent of any future borrowings, including borrowings under our credit agreement, at variable rates of interest;

- making it more difficult for us to satisfy our obligations with respect to our indebtedness, including our outstanding notes, our credit agreement, and any failure to comply with the obligations of any of our debt instruments, including restrictive covenants and borrowing conditions, could result in an event of default under the agreements governing such indebtedness;
- increasing our vulnerability to, and reducing our flexibility to respond to, changes in our business or general adverse economic and industry conditions;
- limiting our ability to obtain additional financing for working capital, capital expenditures, debt service requirements, acquisitions, and general corporate or other purposes and increasing the cost of any such financing;
- limiting our flexibility in planning for, or reacting to, changes in our business and the industry in which we operate; and placing us at a competitive disadvantage as compared to our competitors, to the extent they are not as highly leveraged and who, therefore, may be able to take advantage of opportunities that our leverage may prevent us from exploiting; and
- restricting us from pursuing certain business opportunities.

The credit agreement and the indenture governing the 2027 Senior Notes impose, and the terms of any future indebtedness may impose, various covenants that limit our ability and/or the ability of our restricted subsidiaries' (as designated under such agreements) to, among other things, pay dividends or distributions, repurchase equity, prepay junior debt and make certain investments, incur additional debt and issue certain preferred stock, incur liens on assets, engage in certain asset sales, consolidate with or merge or sell all or substantially all of our assets, enter into transactions with affiliates, designate subsidiaries as unrestricted subsidiaries, and allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to us.

Our ability to obtain future financing and engage in other transactions may be restricted by these covenants. In addition, any credit ratings will impact the cost and availability of future borrowings and our cost of capital. Our ratings at any time will reflect each rating organization's then opinion of our financial strength, operating performance and ability to meet our debt obligations. There can be no assurance that we will achieve a particular rating or maintain a particular rating in the future. A reduction in our credit ratings may limit our ability to borrow at acceptable interest rates. If our credit ratings were downgraded or put on watch for a potential downgrade, we may not be able to sell additional debt securities or borrow money in the amounts, at the times or interest rates or upon the more favorable terms and conditions that might otherwise be available. Any impairment of our ability to obtain future financing on favorable terms could have an adverse effect on our ability to refinance any of our then-existing debt and may severely restrict our ability to execute on our business strategy, which includes the continued acquisition of additional medicines or businesses.

We may not be able to generate sufficient cash to service all of our indebtedness and may be forced to take other actions to satisfy our obligations under our indebtedness, which may not be successful.

Our ability to make scheduled payments under or to refinance our debt obligations depends on our financial condition and operating performance, which is subject to prevailing economic, industry and competitive conditions and to certain financial, business and other factors beyond our control. Our ability to generate cash flow to meet our payment obligations under our debt may also depend on the successful implementation of our operating and growth strategies. Any refinancing of our debt could be at higher interest rates and may require us to comply with more onerous covenants, which could further restrict our business operations. We cannot assure that we will maintain a level of cash flows from operating activities sufficient to pay the principal, premium, if any, and interest on our indebtedness.

If our cash flows and capital resources are insufficient to fund our debt service obligations, we may be forced to reduce or delay capital expenditures, sell assets or business operations, seek additional capital or restructure or refinance our indebtedness. We cannot ensure that we would be able to take any of these actions, that these actions would be successful and permit us to meet our scheduled debt service obligations or that these actions would be permitted under the terms of existing or future debt agreements, including the indenture that governs the 2027 Senior Notes and the credit agreement. In addition, any failure to make payments of interest and principal on our outstanding indebtedness on a timely basis would likely result in a reduction of our credit rating, which could harm our ability to incur additional indebtedness.

If we cannot make scheduled payments on our debt, we will be in default and, as a result:

- our debt holders could declare all outstanding principal and interest to be due and payable;
- the administrative agent and/or the lenders under the credit agreement could foreclose against the assets securing the borrowings then outstanding; and
- we could be forced into bankruptcy or liquidation, which could result in you losing your investment.

We generally have broad discretion in the use of our cash and may not use it effectively.

Our management has broad discretion in the application of our cash, and investors will be relying on the judgment of our management regarding the use of our cash. Our management may not apply our cash in ways that ultimately increase the value of any investment in our securities. We expect to use our existing cash to fund commercialization activities for our medicines, to potentially fund additional medicine, medicine candidate or business acquisitions, to potentially fund additional regulatory approvals of certain of our medicines, to potentially fund development, life cycle management or manufacturing activities of our medicines and medicine candidates, to potentially fund share repurchases, and for working capital, milestone payments, capital expenditures and general corporate purposes. We may also invest our cash in short-term, investment-grade, interest-bearing securities. These investments may not yield a favorable return to our shareholders. If we do not invest or apply our cash in ways that enhance shareholder value, we may fail to achieve expected financial results, which could cause the price of our ordinary shares to decline.

Our ability to use net operating loss carryforwards and certain other tax attributes to offset U.S. income taxes may be limited.

Under Sections 382 and 383 of the Code, if a corporation undergoes an "ownership change" (generally defined as a greater than 50 percent change (by value) in its equity ownership over a three-year period), the corporation's ability to use pre-change net operating loss carryforwards and other pre-change tax attributes to offset post-change income may be limited. We continue to carry forward our annual limitation resulting from an ownership change date of August 2, 2012. The limitation on pre-change net operating losses incurred prior to the August 2, 2012 change date is approximately $7.7 million for 2020 through 2028. In addition, we recognized $32.2 million of federal net operating losses, $2.2 million of state net operating losses and $9.5 million of federal tax credits following our acquisition of River Vision Development Corp. These acquired federal net operating losses and tax credits are subject to an annual limitation of $2.6 million. The net operating loss carryforward and tax credit carryforward limitations are cumulative such that any use of the carryforwards below the limitations in one year will result in a corresponding increase in the limitations for the subsequent tax year. Under the Tax Act, U.S. federal net operating losses incurred in taxable years ending after December 31, 2017 may be carried forward indefinitely, but the deductibility of federal net operating losses generated in taxable years beginning after December 31, 2017 is limited to 80 percent of the current year's taxable income. It remains uncertain if and to what extent various U.S. states will conform to the Tax Act.

Following certain acquisitions of a U.S. corporation by a foreign corporation, Section 7874 of the Code limits the ability of the acquired U.S. corporation and its U.S. affiliates to utilize U.S. tax attributes such as net operating losses to offset U.S. taxable income resulting from certain transactions. Based on the limited guidance available, we expect this limitation is applicable for approximately ten years following the Vidara Merger with respect to certain intra-company transactions. As a result, we or our other U.S. affiliates may not be able to utilize U.S. tax attributes to offset U.S. taxable income or U.S. tax liability respectively, if any, resulting from certain intra-company taxable transactions during such period. Notwithstanding this limitation, we expect that we will be able to fully use our U.S. net operating losses and tax credits prior to their expiration. As a result of this limitation, however, it may take Horizon Therapeutics USA, Inc. (formerly known as Horizon Pharma USA, Inc. and as the successor to HPI) longer to use its net operating losses and tax credits. Moreover, contrary to these expectations, it is possible that the limitation under Section 7874 of the Code on the utilization of U.S. tax attributes could prevent us from fully utilizing our U.S. tax attributes prior to their expiration if we do not generate sufficient taxable income or tax obligations.

Any limitation on our ability to use our net operating loss and tax credit carryforwards, including the carryforwards of companies that we acquire, will likely increase the taxes we would otherwise pay in future years if we were not subject to such limitations.

Unstable market and economic conditions may have serious adverse consequences on our business, financial condition and share price.

From time to time, global credit and financial markets have experienced extreme disruptions, including severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates, and uncertainty about economic stability. Our general business strategy may be adversely affected by any such economic downturn, volatile business environment and continued unpredictable and unstable market conditions. If the equity and credit markets deteriorate, it may make any necessary debt or equity financing more difficult to complete, more costly, and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and share price and could require us to delay or abandon commercialization or development plans. There is a risk that one or more of our current service providers, manufacturers and other partners may not survive an economic down-turn, which could directly affect our ability to attain our operating goals on schedule and on budget.

The United Kingdom's referendum to leave the EU and the United Kingdom's exit from the EU on January 31, 2020, or "Brexit," has caused and may continue to cause disruptions to capital and currency markets worldwide. The full impact of Brexit, however, remains uncertain. Pursuant to the formal withdrawal arrangements agreed to between the United Kingdom and the EU, the United Kingdom will be subject to a transition period, or Transition Period, until December 31, 2020, during which EU rules will continue to apply. Negotiations between the United Kingdom and the EU are expected to continue in relation to the customs and trading relationship between the United Kingdom and the EU following the expiry of the Transition Period. During this period of negotiation and afterwards, our results of operations and access to capital may be negatively affected by interest rate, exchange rate and other market and economic volatility, as well as political uncertainty. Brexit may also have a detrimental effect on our customers, distributors and suppliers, which would, in turn, adversely affect our revenues and financial condition.

At December 31, 2019, we had $1,076.3 million of cash and cash equivalents consisting of cash and money market funds. While we are not aware of any downgrades, material losses, or other significant deterioration in the fair value of our cash equivalents since December 31, 2019, no assurance can be given that deterioration in conditions of the global credit and financial markets would not negatively impact our current portfolio of cash equivalents or our ability to meet our financing objectives. Dislocations in the credit market may adversely impact the value and/or liquidity of marketable securities owned by us.

If the London Inter-Bank Offered Rate, or LIBOR, is discontinued, interest payments under our credit agreement may be calculated using another reference rate.

In July 2017, the Chief Executive of the United Kingdom Financial Conduct Authority, or FCA, which regulates LIBOR, announced that the FCA intends to phase out the use of LIBOR by the end of 2021. In addition, the U.S. Federal Reserve, in conjunction with the Alternative Reference Rates Committee, a steering committee comprised of large U.S. financial institutions, is considering replacing U.S. dollar LIBOR with the Secured Overnight Financing Rate, or SOFR, a new index calculated by short-term repurchase agreements, backed by Treasury securities. Although there have been certain issuances utilizing SOFR, it is unknown whether this or any other alternative reference rate will attain market acceptance as a replacement for LIBOR. LIBOR is used as a benchmark rate throughout our credit agreement, and our credit agreement does not address all circumstances in which LIBOR ceases to be published. There remains uncertainty regarding the future utilization of LIBOR and the nature of any replacement rate, and any potential effects of the transition away from LIBOR on us are not known. The transition process may involve, among other things, increased volatility and illiquidity in markets for instruments that currently rely on LIBOR and may result in increased borrowing costs, the effectiveness of related transactions such as hedges, uncertainty under applicable documentation, including the credit agreement, or difficult and costly processes to amend such documentation. As a result, our ability to refinance our credit agreement or other indebtedness or to hedge our exposure to floating rate instruments may be impaired, which would adversely affect the operations of our business.

Changes in accounting rules or policies may affect our financial position and results of operations.

Accounting principles generally accepted in the United States, or GAAP, and related implementation guidelines and interpretations can be highly complex and involve subjective judgments. Changes in these rules or their interpretation, the adoption of new guidance or the application of existing guidance to changes in our business could significantly affect our financial position and results of operations. In addition, our operation as an Irish company with multiple subsidiaries in different jurisdictions adds additional complexity to the application of GAAP and this complexity will be exacerbated further if we complete additional strategic transactions. Changes in the application of existing rules or guidance applicable to us or our wholly owned subsidiaries could significantly affect our consolidated financial position and results of operations.

Covenants under the indenture governing our 2027 Senior Notes and our credit agreement may restrict our business and operations in many ways, and if we do not effectively manage our covenants, our financial conditions and results of operations could be adversely affected.

The indenture governing the 2027 Senior Notes and the credit agreement impose various covenants that limit our ability and/or our restricted subsidiaries' ability to, among other things:

- pay dividends or distributions, repurchase equity, prepay, redeem or repurchase certain debt and make certain investments;
- incur additional debt and issue certain preferred stock;
- provide guarantees in respect of obligations of other persons;
- incur liens on assets;
- engage in certain asset sales;
- merge, consolidate with or sell all or substantially all of our assets to another person;
- enter into transactions with affiliates;
- sell assets and capital stock of our subsidiaries;
- enter into agreements that restrict distributions from our subsidiaries;
- designate subsidiaries as unrestricted subsidiaries; and
- allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to us.

These covenants may:

- limit our ability to borrow additional funds for working capital, capital expenditures, acquisitions or other general business purposes;
- limit our ability to use our cash flow or obtain additional financing for future working capital, capital expenditures, acquisitions or other general business purposes;
- require us to use a substantial portion of our cash flow from operations to make debt service payments;
- limit our flexibility to plan for, or react to, changes in our business and industry;
- place us at a competitive disadvantage compared to less leveraged competitors; and
- increase our vulnerability to the impact of adverse economic and industry conditions.

If we are unable to successfully manage the limitations and decreased flexibility on our business due to our significant debt obligations, we may not be able to capitalize on strategic opportunities or grow our business to the extent we would be able to without these limitations.

Our failure to comply with any of the covenants could result in a default under the credit agreement or the indenture governing the 2027 Senior Notes, which could permit the administrative agent or the trustee, as applicable, or permit the lenders or the holders of the 2027 Senior Notes to cause the administrative agent or the trustee, as applicable, to declare all or part of any outstanding senior secured term loans or revolving loans, or the 2027 Senior Notes to be immediately due and payable or to exercise any remedies provided to the administrative agent or the trustee, including, in the case of the credit agreement proceeding against the collateral granted to secure our obligations under the credit agreement. An event of default under the credit agreement or the indenture governing the 2027 Senior Notes could also lead to an event of default under the terms of the other agreements and the indenture governing our Exchangeable Senior Notes. Any such event of default or any exercise of rights and remedies by our creditors could seriously harm our business.

If intangible assets that we have recorded in connection with our acquisition transactions become impaired, we could have to take significant charges against earnings.

In connection with the accounting for our various acquisition transactions, we have recorded significant amounts of intangible assets. Under GAAP, we must assess, at least annually and potentially more frequently, whether the value of goodwill has been impaired. Amortizing intangible assets will be assessed for impairment in the event of an impairment indicator. For example, during the year ended December 31, 2018, we recorded an impairment of $33.6 million to fully write off the book value of developed technology related to PROCYSBI in Canada and Latin America. Such impairment and any reduction or other impairment of the value of goodwill or other intangible assets will result in a charge against earnings, which could materially adversely affect our results of operations and shareholders' equity in future periods.

Risks Related to Our Intellectual Property

If we are unable to obtain or protect intellectual property rights related to our medicines and medicine candidates, we may not be able to compete effectively in our markets.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our medicines and medicine candidates. The strength of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions and can be uncertain. The patent applications that we own may fail to result in issued patents with claims that cover our medicines in the United States or in other foreign countries. If this were to occur, early generic competition could be expected against our current medicines and other medicine candidates in development. There is no assurance that all potentially relevant prior art relating to our patents and patent applications has been found, which prior art can invalidate a patent or prevent a patent from issuing based on a pending patent application. In particular, because the APIs in RAYOS, DUEXIS, PENNSAID 2% and VIMOVO have been on the market as separate medicines for many years, it is possible that these medicines have previously been used off-label in such a manner that such prior usage would affect the validity of our patents or our ability to obtain patents based on our patent applications. In addition, claims directed to dosing and dose adjustment may be substantially less likely to issue in light of the Supreme Court decision in *Mayo Collaborative Services v. Prometheus Laboratories, Inc*., where the court held that claims directed to methods of determining whether to adjust drug dosing levels based on drug metabolite levels in the red blood cells were not patent eligible because they were directed to a law of nature. This decision may have wide-ranging implications on the validity and scope of pharmaceutical method claims.

Even if patents do successfully issue, third parties may challenge their validity, enforceability or scope, which may result in such patents being narrowed or invalidated.

Patent litigation is currently pending in the United States District Court for the District of New Jersey against Actavis, who intend to market a generic version of PENNSAID 2% prior to the expiration of certain of our patents listed in the Orange Book. These cases arise from Paragraph IV Patent Certification notice letters from Actavis advising they had filed an ANDA with the FDA seeking approval to market a generic version of PENNSAID 2% before the expiration of the patents-in-suit. For a more detailed description of the PENNSAID 2% litigation, see Note 16, *Legal Proceedings*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K.

Patent litigation is currently pending in the United States District Court for the District of New Jersey and the Court of Appeals for the Federal Circuit against Dr. Reddy's intending to market a generic version of VIMOVO before the expiration of certain of our patents listed in the Orange Book. The cases arise from Paragraph IV Patent Certification notice letters from Dr. Reddy's, advising that it had filed an ANDA with the FDA seeking approval to market generic versions of VIMOVO before the expiration of the patents-in-suit. On July 30, 2019, the Federal Circuit Court of Appeals denied our request for a rehearing of the Court's invalidity ruling against the 6,926,907 and 8,557,285 patents for VIMOVO coordinated-release tablets. As a result, the District Court entered judgment in September 2019 invalidating the '907 and '285 patents, which ended any restriction against the FDA from granting final approval to Dr. Reddy's generic version of VIMOVO. On February 18, 2020, the FDA granted final approval for Dr. Reddy's generic version of VIMOVO. We anticipate that Dr. Reddy's will immediately launch its product at-risk notwithstanding the ongoing patent litigation. Patent litigation is currently pending in the United States District Court for the District of New Jersey against Ajanta intending to market a generic version of VIMOVO before the expiration of certain of our patents listed in the Orange Book. For a more detailed description of the VIMOVO litigation, see Note 16, *Legal Proceedings*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K.

Patent litigation is currently pending in the United States District Court for the District of Delaware against Alkem, who intends to market a generic version of DUEXIS prior to the expiration of certain of our patents listed in the Orange Book. This case arises from Paragraph IV Patent Certification notice letters from Alkem advising it had filed an ANDA with the FDA seeking approval to market a generic version of DUEXIS before the expiration of the patents-in-suit. For a more detailed description of the DUEXIS litigation, see Note 16, Legal Proceedings, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K.

We intend to vigorously defend our intellectual property rights relating to our medicines, but we cannot predict the outcome of the DUEXIS case, the PENNSAID 2% cases and the VIMOVO cases. Any adverse outcome in these matters or any new generic challenges that may arise could result in one or more generic versions of our medicines being launched before the expiration of the listed patents, which could adversely affect our ability to successfully execute our business strategy to increase sales of our medicines, and would negatively impact our financial condition and results of operations, including causing a significant decrease in our revenues and cash flows.

Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property or prevent others from designing around our claims. If the patent applications we hold with respect to our medicines fail to issue or if their breadth or strength of protection is threatened, it could dissuade companies from collaborating with us to develop them and threaten our ability to commercialize our medicines. We cannot offer any assurances about which, if any, patents will issue or whether any issued patents will be found not invalid and not unenforceable or will go unthreatened by third parties. Since patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we were the first to file any patent application related to our medicines or any other medicine candidates. Furthermore, if third parties have filed such patent applications, an interference proceeding in the United States can be provoked by a third-party or instituted by us to determine which party was the first to invent any of the subject matter covered by the patent claims of our applications.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable, processes for which patents are difficult to enforce and any other elements of our drug discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. Although we expect all of our employees to assign their inventions to us, and all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques.

Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. For example, if the issuance, in a given country, of a patent to us, covering an invention, is not followed by the issuance, in other countries, of patents covering the same invention, or if any judicial interpretation of the validity, enforceability, or scope of the claims in, or the written description or enablement in, a patent issued in one country is not similar to the interpretation given to the corresponding patent issued in another country, our ability to protect our intellectual property in those countries may be limited. Changes in either patent laws or in interpretations of patent laws in the United States and other countries may materially diminish the value of our intellectual property or narrow the scope of our patent protection. If we are unable to prevent material disclosure of the non-patented intellectual property related to our technologies to third parties, and there is no guarantee that we will have any such enforceable trade secret protection, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, results of operations and financial condition.

Third-party claims of intellectual property infringement may prevent or delay our development and commercialization efforts.

Our commercial success depends in part on us avoiding infringement of the patents and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions and inter party reexamination proceedings before the United States Patent and Trademark Office, or the U.S. PTO. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which our collaborators are developing medicine candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our medicine candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our medicines and/or any other medicine candidates. Because patent applications can take many years to issue, there may be currently pending patent applications, which may later result in issued patents that our medicine candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our medicine candidates, any molecules formed during the manufacturing process or any final medicine itself, the holders of any such patents may be able to block our ability to commercialize such medicine candidate unless we obtained a license under the applicable patents, or until such patents expire. Similarly, if any third-party patent were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or methods of use, including combination therapy, the holders of any such patent may be able to block our ability to develop and commercialize the applicable medicine candidate unless we obtained a license or until such patent expires. In either case, such a license may not be available on commercially reasonable terms or at all.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our medicine candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties or redesign our infringing medicines, which may be impossible or require substantial time and monetary expenditure. We cannot predict whether any such license would be available at all or whether it would be available on commercially reasonable terms. Furthermore, even in the absence of litigation, we may need to obtain licenses from third parties to advance our research or allow commercialization of our medicine candidates, and we have done so from time to time. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. In that event, we would be unable to further develop and commercialize one or more of our medicine candidates, which could harm our business significantly. We cannot provide any assurances that third-party patents do not exist which might be enforced against our medicines, resulting in either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties.

If we fail to comply with our obligations in the agreements under which we license rights to technology from third parties, we could lose license rights that are important to our business.

We are party to a number of technology licenses that are important to our business and expect to enter into additional licenses in the future. For example, we rely on a license from Bausch with respect to technology developed by Bausch in connection with the manufacturing of RAVICTI. The purchase agreement under which Hyperion purchased the rights to RAVICTI contains obligations to pay Bausch regulatory and sales milestone payments relating to RAVICTI, as well as royalties on the net sales of RAVICTI. On May 31, 2013, when Hyperion acquired BUPHENYL under a restated collaboration agreement with Bausch, Hyperion received a license to use some of the manufacturing technology developed by Bausch in connection with the manufacturing of BUPHENYL. The restated collaboration agreement also contains obligations to pay Bausch regulatory and sales milestone payments, as well as royalties on net sales of BUPHENYL. If we fail to make a required payment to Bausch and do not cure the failure within the required time period, Bausch may be able to terminate the license to use its manufacturing technology for RAVICTI and BUPHENYL. If we lose access to the Bausch manufacturing technology, we cannot guarantee that an acceptable alternative method of manufacture could be developed or acquired. Even if alternative technology could be developed or acquired, the loss of the Bausch technology could still result in substantial costs and potential periods where we would not be able to market and sell RAVICTI and/or BUPHENYL. We also license intellectual property necessary for commercialization of RAVICTI from an external party. This party may be entitled to terminate the license if we breach the agreement, including failure to pay required royalties on net sales of RAVICTI, or we do not meet specified diligence obligations in our development and commercialization of RAVICTI, and we do not cure the failure within the required time period. If the license is terminated, it may be difficult or impossible for us to continue to commercialize RAVICTI, which would have a material adverse effect on our business, financial condition and results of operations.

We also license rights to know-how and trademarks for ACTIMMUNE from Genentech Inc., or Genentech. Genentech may terminate the agreement upon our material default, if not cured within a specified period of time. Genentech may also terminate the agreement in the event of our bankruptcy or insolvency. Upon such a termination of the agreement, all intellectual property rights conveyed to us under the agreement, including the rights to the ACTIMMUNE trademark, revert to Genentech. If we fail to comply with our obligations under this agreement, we could lose the ability to market and distribute ACTIMMUNE, which would have a material adverse effect on our business, financial condition and results of operations.

We are subject to contractual obligations under our amended and restated license agreement with UCSD, as amended, with respect to PROCYSBI. If one or more of these licenses was terminated, we would have no further right to use or exploit the related intellectual property, which would limit our ability to develop PROCYSBI in other indications, and could impact our ability to continue commercializing PROCYSBI in its approved indications.

We also hold an exclusive license to patents and technology from Duke University, or Duke, and Mountain View Pharmaceuticals, Inc., or MVP, covering KRYSTEXXA. Duke and MVP may terminate the license if we commit fraud or for our willful misconduct or illegal conduct. Duke and MVP may also terminate the license upon our material breach of the agreement, if not cured within a specified period of time, or upon written notice if we have committed two or more material breaches under the agreement. Duke and MVP may also terminate the license in the event of our bankruptcy or insolvency. If the license is terminated, it may be impossible for us to continue to commercialize KRYSTEXXA, which would have a material adverse effect on our business, financial condition and results of operations.

We hold an exclusive license to Vectura Group plc's, or Vectura, proprietary technology and know-how covering the delayed-release of corticosteroids relating to RAYOS. If we fail to comply with our obligations under our agreement with Vectura or our other license agreements, or if we are subject to a bankruptcy, the licensor may have the right to terminate the license, in which event we would not be able to market medicines covered by the license, including RAYOS.

We hold an exclusive, worldwide license from F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., or Roche, to patents and know-how for TEPEZZA. We also have exclusive sub-licenses for rights licensed to Roche for TEPEZZA by certain third-party licensors. Roche may have the right to terminate the license upon our breach, if not cured within a specified period of time. Roche may also terminate the license in the event of our bankruptcy or insolvency, or if we challenge the validity of Roche's patents. If the license is terminated for our breach or based on our challenging the validity of Roche's patents, then all rights and licenses granted to us by Roche would also terminate, and we may be required to assign and transfer to Roche certain filings and approvals, trademarks, and data in our possession necessary for the development and commercialization of TEPEZZA, and assign clinical trial agreements to the extent permitted. We may also be required to grant Roche an exclusive license under our patents and know-how for TEPEZZA, and to manufacture and supply TEPEZZA to Roche for a transitional period. We also have a license of patent rights to TEPEZZA under a license agreement with Lundquist Institute (formerly known as Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center), or Lundquist. Lundquist has the right to terminate the license agreement upon our material breach, if not cured within a specified period of time, or in the event of our bankruptcy or insolvency. If one or more of these licenses is terminated, it may be impossible for us to continue to commercialize TEPEZZA, which would have a material adverse effect on our business, financial condition and results of operations.

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our patents or the patents of our licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that one of our patents, or a patent of one of our licensors, is not valid or is unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing.

There are numerous post grant review proceedings available at the U.S. PTO (including inter partes review, post-grant review and ex-parte reexamination) and similar proceedings in other countries of the world that could be initiated by a third-party that could potentially negatively impact our issued patents.

Interference proceedings provoked by third parties or brought by us may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our collaborators or licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our ordinary shares.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees on any issued patent are due to be paid to the U.S. PTO and foreign patent agencies in several stages over the lifetime of the patent. The U.S. PTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we or licensors that control the prosecution and maintenance of our licensed patents fail to maintain the patents and patent applications covering our medicine candidates, our competitors might be able to enter the market, which would have a material adverse effect on our business.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties.

We employ individuals who were previously employed at other biotechnology or pharmaceutical companies. We may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed confidential information of our employees' former employers or other third parties. We may also be subject to claims that former employers or other third parties have an ownership interest in our patents. Litigation may be necessary to defend against these claims. There is no guarantee of success in defending these claims, and even if we are successful, litigation could result in substantial cost and be a distraction to our management and other employees.

Risks Related to Ownership of Our Ordinary Shares

The market price of our ordinary shares historically has been volatile and is likely to continue to be volatile, and you could lose all or part of any investment in our ordinary shares.

The trading price of our ordinary shares has been volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. In addition to the factors discussed in this "Risk Factors" section and elsewhere in this report, these factors include:

- our failure to successfully execute our commercialization strategy with respect to our approved medicines, particularly our commercialization of our medicines in the United States;
- actions or announcements by third-party or government payers with respect to coverage and reimbursement of our medicines;
- disputes or other developments relating to intellectual property and other proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our medicines and medicine candidates;
- unanticipated serious safety concerns related to the use of our medicines;
- adverse regulatory decisions;
- changes in laws or regulations applicable to our business, medicines or medicine candidates, including but not limited to clinical trial requirements for approvals or tax laws;
- inability to comply with our debt covenants and to make payments as they become due;
- inability to obtain adequate commercial supply for any approved medicine or inability to do so at acceptable prices;
- developments concerning our commercial partners, including but not limited to those with our sources of manufacturing supply;
- our decision to initiate a clinical trial, not to initiate a clinical trial or to terminate an existing clinical trial;
- adverse results or delays in clinical trials;

- our failure to successfully develop and/or acquire additional medicine candidates or obtain approvals for additional indications for our existing medicine candidates;
- introduction of new medicines or services offered by us or our competitors;
- overall performance of the equity markets, including the pharmaceutical sector, and general political and economic conditions;
- failure to meet or exceed revenue and financial projections that we may provide to the public;
- actual or anticipated variations in quarterly operating results;
- failure to meet or exceed the estimates and projections of the investment community;
- inaccurate or significant adverse media coverage;
- publication of research reports about us or our industry or positive or negative recommendations or withdrawal of research coverage by securities analysts;
- our inability to successfully enter new markets;
- the termination of a collaboration or the inability to establish additional collaborations;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us or our competitors;
- our inability to maintain an adequate rate of growth;
- ineffectiveness of our internal controls or our inability to otherwise comply with financial reporting requirements;
- adverse U.S. and foreign tax exposure;
- additions or departures of key management, commercial or regulatory personnel;
- issuances of debt or equity securities;
- significant lawsuits, including patent or shareholder litigation;
- changes in the market valuations of similar companies to us;
- sales of our ordinary shares by us or our shareholders in the future;
- trading volume of our ordinary shares;
- effects of natural or man-made catastrophic events or other business interruptions; and
- other events or factors, many of which are beyond our control.

In addition, the stock market in general, and The Nasdaq Global Select Market and the stock of biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may adversely affect the market price of our ordinary shares, regardless of our actual operating performance.

We have never declared or paid dividends on our share capital and we do not anticipate paying dividends in the foreseeable future.

We have never declared or paid any cash dividends on our ordinary shares. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future, including due to limitations that are currently imposed by our credit agreement and the indenture governing the 2027 Senior Notes. Any return to shareholders will therefore be limited to the increase, if any, of our ordinary share price.

We have incurred and will continue to incur significant increased costs as a result of operating as a public company and our management will be required to devote substantial time to compliance initiatives.

As a public company, we have incurred and will continue to incur significant legal, accounting and other expenses that we did not incur as a private company. In particular, the Sarbanes-Oxley Act of 2000, or the Sarbanes-Oxley Act, as well as rules subsequently implemented by the SEC and the Nasdaq Stock Market, Inc., or Nasdaq, impose significant requirements on public companies, including requiring establishment and maintenance of effective disclosure and financial controls and changes in corporate governance practices. These rules and regulations have substantially increased our legal and financial compliance costs and have made some activities more time-consuming and costly. These effects are exacerbated by our transition to an Irish company and the integration of numerous acquired businesses and operations into our historical business and operating structure. If these requirements divert the attention of our management and personnel from other business concerns, they could have a material adverse effect on our business, financial condition and results of operations. The increased costs will continue to decrease our net income or increase our net loss, and may require us to reduce costs in other areas of our business or increase the prices of our medicines or services. For example, these rules and regulations make it more difficult and more expensive for us to obtain and maintain director and officer liability insurance. We cannot predict or estimate the amount or timing of additional costs that we may incur to respond to these requirements. The impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers. If we fail to comply with the continued listing requirements of Nasdaq, our ordinary shares could be delisted from The Nasdaq Global Select Market, which would adversely affect the liquidity of our ordinary shares and our ability to obtain future financing.

The Sarbanes-Oxley Act requires, among other things, that we maintain effective internal controls for financial reporting and disclosure controls and procedures. In particular, we are required to perform annual system and process evaluation and testing of our internal controls over financial reporting to allow management to report on the effectiveness of our internal controls over financial reporting, as required by Section 404 of the Sarbanes-Oxley Act, or Section 404. Our independent registered public accounting firm is also required to deliver a report on the effectiveness of our internal control over financial reporting. Our testing, or the testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses. Our compliance with Section 404 requires that we incur substantial expense and expend significant management efforts, particularly because of our Irish parent company structure and international operations. If we are not able to comply with the requirements of Section 404 or if we or our independent registered public accounting firm identify deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses, the market price of our ordinary shares could decline and we could be subject to sanctions or investigations by Nasdaq, the SEC or other regulatory authorities, which would require additional financial and management resources.

New laws and regulations as well as changes to existing laws and regulations affecting public companies, including the provisions of the Sarbanes-Oxley Act and rules adopted by the SEC and by Nasdaq, would likely result in increased costs as we respond to their requirements.

Sales of a substantial number of our ordinary shares in the public market could cause our share price to decline.

If our existing shareholders sell, or indicate an intention to sell, substantial amounts of our ordinary shares in the public market, the trading price of such ordinary shares could decline. In addition, our ordinary shares that are either subject to outstanding options and restricted stock units or reserved for future issuance under our employee benefit plans are or may become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules and the Securities Act of 1933, as amended, or the Securities Act. If these additional ordinary shares are sold, or if it is perceived that they will be sold, in the public market, the trading price of our ordinary shares could decline.

In addition, any conversion or exchange of our Exchangeable Senior Notes, whether pursuant to their terms or pursuant to privately negotiated transactions between the issuer and/or us and a holder of such securities, could depress the market price for our ordinary shares.

Future sales and issuances of our ordinary shares, securities convertible into our ordinary shares or rights to purchase ordinary shares or convertible securities could result in additional dilution of the percentage ownership of our shareholders and could cause our share price to decline.

Additional capital may be needed in the future to continue our planned operations. To the extent we raise additional capital by issuing equity securities or securities convertible into or exchangeable for ordinary shares, our shareholders may experience substantial dilution. We may sell ordinary shares, and we may sell convertible or exchangeable securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell such ordinary shares, convertible or exchangeable securities or other equity securities in subsequent transactions, existing shareholders may be materially diluted. New investors in such subsequent transactions could gain rights, preferences and privileges senior to those of holders of ordinary shares. We also maintain equity incentive plans, including our Amended and Restated 2014 Equity Incentive Plan, 2014 Non-Employee Equity Plan, as amended, and 2014 Employee Share Purchase Plan, as amended, and intend to grant additional ordinary share awards under these and future plans, which will result in additional dilution to our existing shareholders.

Irish law differs from the laws in effect in the United States and may afford less protection to holders of our securities.

It may not be possible to enforce court judgments obtained in the United States against us in Ireland based on the civil liability provisions of the U.S. federal or state securities laws. In addition, there is some uncertainty as to whether the courts of Ireland would recognize or enforce judgments of U.S. courts obtained against us or our directors or officers based on the civil liabilities provisions of the U.S. federal or state securities laws or hear actions against us or those persons based on those laws. We have been advised that the United States currently does not have a treaty with Ireland providing for the reciprocal recognition and enforcement of judgments in civil and commercial matters. Therefore, a final judgment for the payment of money rendered by any U.S. federal or state court based on civil liability, whether or not based solely on U.S. federal or state securities laws, would not automatically or necessarily be enforceable in Ireland.

As an Irish company, we are governed by the Irish Companies Act 2014 (as amended), which differs in some material respects from laws generally applicable to U.S. corporations and shareholders, including, among others, differences relating to interested director and officer transactions and shareholder lawsuits. Likewise, the duties of directors and officers of an Irish company generally are owed to the company only. Shareholders of Irish companies generally do not have a personal right of action against directors or officers of the company and may exercise such rights of action on behalf of the company only in limited circumstances. Accordingly, holders of our securities may have more difficulty protecting their interests than would holders of securities of a corporation incorporated in a jurisdiction of the United States.

Provisions of our articles of association, and Irish law could delay or prevent a takeover of us by a third party.

Our articles of association could delay, defer or prevent a third-party from acquiring us, despite the possible benefit to our shareholders, or otherwise adversely affect the price of our ordinary shares. For example, our articles of association:

- impose advance notice requirements for shareholder proposals and nominations of directors to be considered at shareholder meetings;
- stagger the terms of our board of directors into three classes; and
- require the approval of a supermajority of the voting power of the shares of our share capital entitled to vote generally at a meeting of shareholders to amend or repeal our articles of association.

In addition, several mandatory provisions of Irish law could prevent or delay an acquisition of us. For example, Irish law does not permit shareholders of an Irish public limited company to take action by written consent with less than unanimous consent. We are also subject to various provisions of Irish law relating to mandatory bids, voluntary bids, requirements to make a cash offer and minimum price requirements, as well as substantial acquisition rules and rules requiring the disclosure of interests in our ordinary shares in certain circumstances.

These provisions may discourage potential takeover attempts, discourage bids for our ordinary shares at a premium over the market price or adversely affect the market price of, and the voting and other rights of the holders of, our ordinary shares. These provisions could also discourage proxy contests and make it more difficult for you and our other shareholders to elect directors other than the candidates nominated by our board of directors, and could depress the market price of our ordinary shares.

Any attempts to take us over will be subject to Irish Takeover Rules and subject to review by the Irish Takeover Panel.

We are subject to the Irish Takeover Rules, under which our board of directors will not be permitted to take any action which might frustrate an offer for our ordinary shares once it has received an approach which may lead to an offer or has reason to believe an offer is imminent.

A transfer of our ordinary shares may be subject to Irish stamp duty.

In certain circumstances, the transfer of shares in an Irish incorporated company will be subject to Irish stamp duty, which is a legal obligation of the buyer. This duty is currently charged at the rate of 1.0 percent of the price paid or the market value of the shares acquired, if higher. Because our ordinary shares are traded on a recognized stock exchange in the United States, an exemption from this stamp duty is available to transfers by shareholders who hold ordinary shares beneficially through brokers, which in turn hold those shares through the Depositary Trust Company, or DTC, to holders who also hold through DTC. However, a transfer by or to a record holder who holds ordinary shares directly in his, her or its own name could be subject to this stamp duty. We, in our absolute discretion and insofar as the Irish Companies Act 2014 (as amended) or any other applicable law permit, may, or may provide that one of our subsidiaries will pay Irish stamp duty arising on a transfer of our ordinary shares on behalf of the transferee of such ordinary shares. If stamp duty resulting from the transfer of ordinary shares which would otherwise be payable by the transferee is paid by us or any of our subsidiaries on behalf of the transferee, then in those circumstances, we will, on our behalf or on behalf of such subsidiary (as the case may be), be entitled to (i) seek reimbursement of the stamp duty from the transferee, (ii) set-off the stamp duty against any dividends payable to the transferee of those ordinary shares and (iii) claim a first and permanent lien on the ordinary shares on which stamp duty has been paid by us or such subsidiary for the amount of stamp duty paid. Our lien shall extend to all dividends paid on those ordinary shares.

Dividends paid by us may be subject to Irish dividend withholding tax.

In certain circumstances, as an Irish tax resident company, we will be required to deduct Irish dividend withholding tax (currently at the rate of 20%) from dividends paid to our shareholders. Shareholders that are resident in the United States, EU countries (other than Ireland) or other countries with which Ireland has signed a tax treaty (whether the treaty has been ratified or not) generally should not be subject to Irish withholding tax so long as the shareholder has provided its broker, for onward transmission to our qualifying intermediary or other designated agent (in the case of shares held beneficially), or our or its transfer agent (in the case of shares held directly), with all the necessary documentation by the appropriate due date prior to payment of the dividend. However, some shareholders may be subject to withholding tax, which could adversely affect the price of our ordinary shares.

If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, our share price and trading volume could decline.

The trading market for our ordinary shares will depend in part on the research and reports that securities or industry analysts publish about us or our business. If one or more of the analysts who cover us downgrade our rating or publish inaccurate or unfavorable research about our business, our share price could decline. If one or more of these analysts cease coverage of our company or fail to publish reports on our company regularly, demand for our ordinary shares could decrease, which might cause our share price and trading volume to decline.

Securities class action litigation could divert our management's attention and harm our business and could subject us to significant liabilities.

The stock markets have from time to time experienced significant price and volume fluctuations that have affected the market prices for the equity securities of pharmaceutical companies. These broad market fluctuations may cause the market price of our ordinary shares to decline. In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology and biopharma companies have experienced significant stock price volatility in recent years. For example, following declines in our stock price, two federal securities class action lawsuits were filed in March 2016 against us and certain of our current and former officers alleging violations of the Securities Exchange Act of 1934, as amended, which lawsuits were dismissed by the plaintiffs in June 2018. Even if we are successful in defending any similar claims that may be brought in the future, such litigation could result in substantial costs and may be a distraction to our management, and may lead to an unfavorable outcome that could adversely impact our financial condition and prospects.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Location	Approximate Square Footage	Lease Expiry Date
Dublin, Ireland	18,900	November 4, 2029
Lake Forest, Illinois	160,000	March 31, 2031
Novato, California	61,000	August 31, 2021
South San Francisco, California	20,000	January 31, 2030
Chicago, Illinois	9,200	December 31, 2028
Mannheim, Germany	4,800	December 31, 2020
Other	12,400	May 31, 2020 to September 15, 2022

The above table does not include details of an agreement to lease entered into on October 14, 2019, relating to approximately 63,000 square feet of office space under construction in Dublin, Ireland. Lease commencement will begin when construction of the offices are completed by the lessor and we have access to begin the construction of leasehold improvements. We expect to incur leasehold improvement costs during 2020 and 2021 in order to prepare the building for occupancy.

In February 2020, we purchased a three-building campus in Deerfield, Illinois, for total cash consideration of $115.0 million. The Deerfield campus totals 70 acres and consists of more than 650,000 square feet of office space. We expect to move to the Deerfield campus in the second half of 2020 and market our Lake Forest office for sub-lease. We expect to make significant capital expenditures during 2020 in order to prepare the Deerfield campus for occupancy.

Item 3. Legal Proceedings

For a description of our legal proceedings, see Note 16 of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K.

Item 4. Mine Safety Disclosures

None.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Information

Our ordinary shares trade on The Nasdaq Global Select Market under the trading symbol "HZNP".

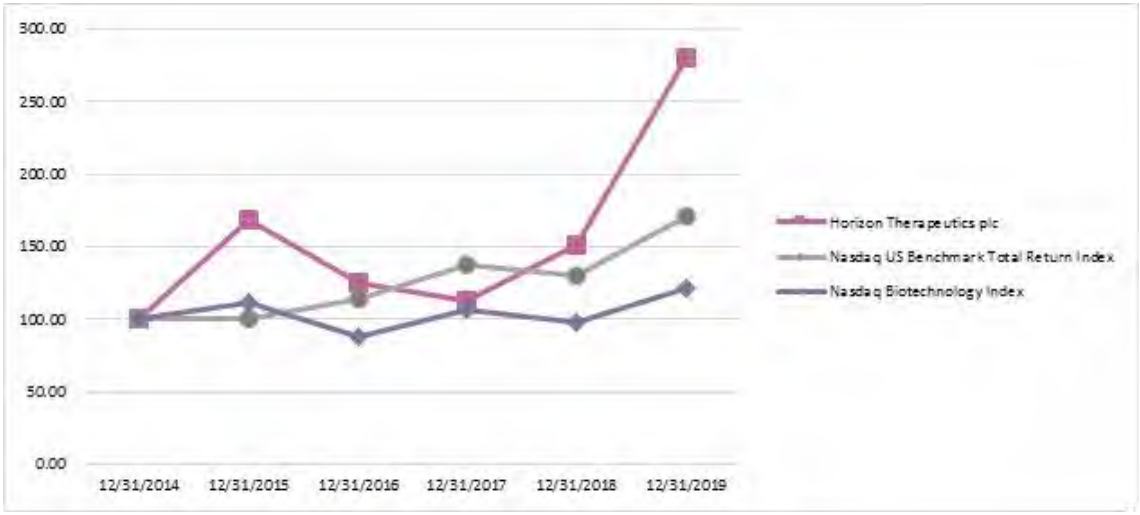
Holders of Record

The closing price of our ordinary shares on February 19, 2020 was $36.06. As of February 19, 2020, there were approximately eleven holders of record of our ordinary shares. Because almost all of our ordinary shares are held by brokers, nominees and other institutions on behalf of shareholders, we are unable to estimate the total number of shareholders represented by these record holders.

Performance Graph

The following graph shows a comparison from December 31, 2014, through December 31, 2019, of the cumulative total return for (i) our ordinary shares, (ii) the Nasdaq Biotechnology Index and (iii) the Nasdaq U.S. Benchmark Total Return Index.

Information set forth in the graph below represents the performance of our ordinary shares from December 31, 2014, through December 31, 2019. The graph assumes an initial investment of $100 on December 31, 2014. The comparisons in the graph are required by the Securities and Exchange Commission and are not intended to forecast or be indicative of possible future performance of our ordinary shares.



	12/31/2014	12/31/2015	12/31/2016	12/31/2017	12/31/2018	12/31/2019
Cumulative Returns						
Horizon Therapeutics plc	$ 100.00	$ 168.11	$ 125.52	$ 113.27	$ 151.59	$ 280.84
Nasdaq Biotechnology Index	100.00	111.77	87.91	106.92	97.45	121.92
Nasdaq U.S. Benchmark Total Return Index	100.00	100.48	113.55	137.83	130.33	170.96

The foregoing graph and table are furnished solely with this report, and are not filed with this report, and shall not be deemed incorporated by reference into any other filing under the Securities Act of 1933, as amended, or the Securities Act, or the Securities Exchange Act of 1934, as amended, whether made by us before or after the date hereof, regardless of any general incorporation language in any such filing, except to the extent we specifically incorporate this material by reference into any such filing.

Dividend Policy

We have never declared or paid cash dividends on our common equity. We currently intend to retain all available funds and any future earnings to support operations and finance the growth and development of our business and do not intend to pay cash dividends on our ordinary shares for the foreseeable future. Under Irish law, dividends may only be paid, and share repurchases and redemptions must generally be funded only out of, "distributable reserves". In addition, our ability to pay cash dividends is currently prohibited by the terms of our credit agreement with Citibank, N.A., as administrative and collateral agent and our $600.0 million aggregate principal amount of 5.5% Senior Notes due 2027, subject to customary exceptions. Any future determination as to the payment of dividends will, subject to Irish legal requirements, be at the sole discretion of our board of directors and will depend on our financial condition, results of operations, capital requirements and other factors our board of directors deems relevant.

Securities Authorized for Issuance under Equity Compensation Plans

See Item 12 of Part III of this Annual Report on Form 10-K regarding information about securities authorized for issuance under our equity compensation plans.

Recent Sales of Unregistered Securities

There were no unregistered sales of equity securities by us during the year ended December 31, 2019.

Issuer Repurchases of Equity Securities

None.

Irish Law Matters

See *Irish Law Matters* included in Item 1 of Part I of this Annual Report on Form 10-K.

Item 6. Selected Financial Data

The selected statement of comprehensive income (loss) data and selected statement of cash flows data for the years ended December 31, 2019, 2018 and 2017, and the selected balance sheet data as of December 31, 2019 and 2018 have been derived from our audited financial statements included elsewhere in this Annual Report on Form 10-K. The selected statement of comprehensive income (loss) data and selected statement of cash flows data for the years ended December 31, 2016 and 2015, and the selected balance sheet data as of December 31, 2017, 2016 and 2015 have been derived from audited financial statements which are not included in this Annual Report on Form 10-K.

Our historical results are not necessarily indicative of future results. The selected financial data should be read in conjunction with "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our financial statements and related notes included elsewhere in this Annual Report on Form 10-K.

On May 7, 2015, we completed our acquisition of Hyperion Therapeutics, Inc., on January 13, 2016, we completed our acquisition of Crealta Holdings LLC and on October 25, 2016, we completed our acquisition of Raptor Pharmaceutical Corp. The financial data presented below include the results of operations of the acquired Hyperion, Crealta and Raptor businesses from the applicable dates of acquisition.

	As of December 31,				
	2019	2018	2017	2016	2015
	(in thousands)				
Selected Balance Sheet Data					
Cash and cash equivalents	$ 1,076,287	$ 958,712	$ 751,368	$ 509,055	$ 859,616
Working capital	962,934	837,129	526,905	389,147	706,209
Total assets [3][6]	4,436,034	3,941,962	3,961,472	4,054,897	2,941,407
Total debt, net	1,352,841	1,896,684	1,901,655	1,807,493	1,136,756
Accumulated deficit [1][2][3][6]	(605,682)	(1,178,769)	(1,141,975)	(798,135)	(651,043)
Total shareholders' equity [1][2][3][6]	2,185,449	1,190,106	1,101,452	1,313,665	1,343,289

	For the Years Ended December 31,				
	2019	2018	2017	2016	2015
	(in thousands, except per share data)				
Selected Statement of Comprehensive Income (Loss) Data					
Net sales	$ 1,300,029	$ 1,207,570	$ 1,056,231	$ 981,120	$ 757,044
Cost of goods sold [6]	362,175	391,301	493,368	366,405	194,516
Gross profit [6]	937,854	816,269	562,863	614,715	562,528
Loss before benefit for income taxes [6]	(20,224)	(83,132)	(458,811)	(199,918)	(107,726)
Net income (loss) [6]	573,020	(38,380)	(350,125)	(147,092)	60,411
Net income (loss) per ordinary share – basic [6]	3.13	(0.23)	(2.15)	(0.92)	0.41
Net income (loss) per ordinary share – diluted [6] [7]	2.90	(0.23)	(2.15)	(0.92)	0.39
Selected Statement of Cash Flows Data					
Net cash provided by operating activities [5]	$ 426,332	$ 194,543	$ 284,340	$ 369,456	$ 249,536
Net cash provided by (used in) investing activities [4]	(17,857)	27,653	(102,185)	(1,370,646)	(1,049,299)
Net cash (used in) provided by financing activities [5]	(290,446)	(16,596)	54,276	657,074	1,442,481

(1) On January 1, 2017, we adopted Accounting Standards Update or ASU No. 2016-09, *Improvements to Employee Share-Based Payment Accounting*, on a modified retrospective basis and recorded a decrease of $7.2 million in net deferred tax liabilities and a corresponding decrease in accumulated deficit during the year ended December 31, 2017.

(2) On January 1, 2018, we adopted ASU No. 2016-16, *Income Taxes*, on a modified retrospective basis through a cumulative-effect adjustment to retained earnings and we reclassified $9.3 million of unrecognized deferred charges directly to retained earnings.

(3) On January 1, 2018, we adopted ASU No. 2014-09, *Revenue from Contracts with Customers*, on a modified retrospective basis and we reclassified $11.3 million of deferred revenue directly to retained earnings. In addition, as a result of the adoption of ASU No. 2014-09, we now present all allowances for medicine returns in accrued expenses on the consolidated balance sheets. This resulted in a reclassification of $37.9 million, $15.2 million and $14.5 million, respectively, of allowances for medicine returns from "accounts receivable, net" to "accrued expenses" in the consolidated balance sheets at December 31, 2017, 2016 and 2015.

(4) On January 1, 2018, we adopted ASU No. 2016-18, Statement of Cash Flows (Topic 230): Restricted Cash. This resulted in movements in restricted cash of $0.6 million, $5.2 million and $1.1 million in the consolidated statement of cash flows for the years ended December 31, 2017, 2016 and 2015, respectively, no longer being included in "net cash provided by (used in) investing activities".

(5) On January 1, 2018, we adopted ASU No. 2016-15, Statement of Cash Flows (Topic 230): Classification of Certain Cash Receipts and Cash Payments. This resulted in a reclassification of $4.1 million and $55.4 million outflow in the consolidated statement of cash flows for the years ended December 31, 2017 and 2015, respectively, from "net cash provided by operating activities" to "net cash (used in) provided by financing activities".

(6) Effective January 1, 2019, we retrospectively changed our accounting for business combinations and we now record acquired intangible assets and their related third-party contingent royalties on a net basis, or the New Method. We changed our accounting principle on the basis that the use of the New Method is preferable primarily due to improved comparability with our peers. The impact of the accounting change resulted in adjustments to the consolidated financial statements as of and for the years ended December 31, 2018, 2017, 2016 and 2015, and the revised amounts are presented above. See Note 1 of the Notes to the Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K, for further detail of the impact of the accounting change.

(7) During the year ended December 31, 2019, we prospectively applied the if-converted method to our 2.50% Exchangeable Senior Notes due 2022 when determining the diluted net income (loss) per share.

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and the related notes appearing at the end of this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. You should read the "Risk Factors" section of this Annual Report on Form 10-K for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

The discussion below contains "forward-looking statements," as defined in Section 21E of the Securities Exchange Act of 1934, as amended, that reflect our current expectations regarding our future growth, results of operations, business strategy and plans, financial condition, cash flows, performance, development plans and timelines, business prospects and opportunities, as well as assumptions made by, and information currently available to, our management. We have tried to identify forward-looking statements by using words such as "anticipate," "believe," "plan," "expect," "intend," "will," and similar expressions, but these words are not the exclusive means of identifying forward-looking statements. These statements are based on information currently available to us and are subject to various risks, uncertainties, and other factors, including, but not limited to, those matters discussed in Item 1A. "Risk Factors" in Part I of this Annual Report on Form 10-K, that could cause our actual growth, results of operations, business strategy and plans, financial condition, cash flows, performance, business prospects and opportunities to differ materially from those expressed in, or implied by, these statements. Except as expressly required by the federal securities laws, we undertake no obligation to update such factors or to publicly announce the results of any of the forward-looking statements contained herein to reflect future events, developments, or changed circumstances, or for any other reason.

Unless otherwise indicated or the context otherwise requires, references to "we", "us", "our" and "Horizon" refer to Horizon Therapeutics plc (formerly known as Horizon Pharma plc) and its consolidated subsidiaries.

When accounting for business combinations under ASC Topic 805, Business Combinations, we previously separately identified and recorded at fair value intangible assets acquired and their related third-party contingent royalties at the date of acquisition. Third-party contingent royalties are royalties payable to parties other than sellers of the businesses. Effective January 1, 2019, we retrospectively changed our accounting for business combinations and we now record acquired intangible assets and their related third-party contingent royalties on a net basis, or the New Method. We changed our accounting principle on the basis that the use of the New Method is preferable primarily due to improved comparability with our peers. We adjusted the accompanying consolidated balance sheet as at December 31, 2018, the consolidated statement of comprehensive income (loss) for the years ended December 31, 2018 and 2017 and the consolidated statement of cash flows for the years ended December 31, 2018 and 2017 to reflect this change in accounting. There was no impact on total operating, investing or financing cash flows for any period. In addition, there was no impact from the change in accounting principle on our previously reported adjusted EBITDA, non-GAAP net income and non-GAAP diluted earnings per share for any prior period.

OUR BUSINESS

We are focused on researching, developing and commercializing medicines that address critical needs for people impacted by rare and rheumatic diseases. Our pipeline is purposeful: we apply scientific expertise and courage to bring clinically meaningful therapies to patients. We believe science and compassion must work together to transform lives.

On January 21, 2020, the U.S. Food and Drug Administration, or FDA, approved TEPEZZA™ (teprotumumab-trbw), for the treatment of thyroid eye disease, or TED, a serious, progressive and vision-threatening rare autoimmune condition.

During 2019, our two reportable segments were (i) the orphan and rheumatology segment and (ii) the inflammation segment (previously the primary care segment). We report net sales and segment operating income for each segment. Effective in the first quarter of 2020, we (i) reorganized our commercial operations and moved responsibility for RAYOS® to the inflammation segment and (ii) renamed the orphan and rheumatology segment the orphan segment. With the approval of TEPEZZA in the first quarter of 2020, net sales generated by this medicine will be reported as part of the renamed orphan segment.

As of December 31, 2019, our marketed medicine portfolio consisted of the following:

Orphan and Rheumatology
KRYSTEXXA® (pegloticase injection), for intravenous infusion
RAVICTI® (glycerol phenylbutyrate) oral liquid
PROCYSBI® (cysteamine bitartrate) delayed-release capsules, for oral use
ACTIMMUNE® (interferon gamma-1b) injection, for subcutaneous use
RAYOS (prednisone) delayed-release tablets
BUPHENYL® (sodium phenylbutyrate) tablets and powder
QUINSAIR™ (levofloxacin) solution for inhalation
Inflammation
PENNSAID® (diclofenac sodium topical solution) 2% w/w, or PENNSAID 2%, for topical use
DUEXIS® (ibuprofen/famotidine) tablets, for oral use
VIMOVO® (naproxen/esomeprazole magnesium) delayed-release tablets, for oral use

Acquisitions and Divestitures

Since January 1, 2017, we completed the following acquisitions and divestitures:

- On June 28, 2019, we sold our rights to MIGERGOT to Cosette Pharmaceuticals, Inc., for an upfront payment and potential additional contingent consideration payments, or the MIGERGOT transaction.
- Effective January 1, 2019, we amended our license and supply agreements with Jagotec AG and Skyepharma AG, which are affiliates of Vectura Group plc, or Vectura. Under these amendments, we agreed to transfer all economic benefits of LODOTRA® in Europe to Vectura.
- On December 28, 2018, we sold our rights to RAVICTI and AMMONAPS (known as BUPHENYL in the United States) outside of North America and Japan to Medical Need Europe AB, part of the Immedica Group, or Immedica, and such transaction, the Immedica transaction. We previously distributed RAVICTI and AMMONAPS through a commercial partner in Europe and other non-U.S. markets. We have retained the rights to RAVICTI and BUPHENYL in North America and Japan.
- On June 30, 2017, we completed our acquisition of certain rights to interferon gamma-1b from Boehringer Ingelheim International GmbH, or Boehringer Ingelheim International, in all territories outside of the United States, Canada and Japan. Interferon gamma-1b is known as IMUKIN outside of the United States, Canada and Japan. On July 24, 2018, we sold the rights to IMUKIN in all territories outside of the United States, Canada and Japan to Clinigen Group plc, or Clinigen, for an upfront payment and a potential additional contingent consideration payment, that was subsequently received in September 2019, or the IMUKIN sale.
- On June 23, 2017, we sold our European subsidiary that owned the marketing rights to PROCYSBI (cysteamine bitartrate) delayed-release capsules and QUINSAIR (levofloxacin inhalation solution) in Europe, the Middle East and Africa, or EMEA, regions, or the Chiesi divestiture, to Chiesi Farmaceutici S.p.A., or Chiesi.
- On May 8, 2017, we completed our acquisition of River Vision Development Corp., or River Vision, which added the late development-stage rare disease biologic medicine candidate TEPEZZA to our research and development pipeline. In January 2020, the FDA approved TEPEZZA for the treatment of TED.

The consolidated financial statements presented herein include the results of operations of the acquired businesses from the applicable dates of acquisition. See Note 4 of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K, for further details of our acquisitions and divestitures.

Strategy

Horizon today is a leading biopharma company focused on rare diseases, delivering innovative therapies to patients and generating value for our shareholders. Our strategy is to maximize the benefit and value of our key growth drivers KRYSTEXXA and TEPEZZA, both rare disease medicines, and expand our pipeline for sustainable growth. We believe our strategy allows more patients to benefit from our on-market medicines, as well as from medicines we develop as part of our pipeline. Our vision is to build healthier communities, urgently and responsibly, which in turn, we believe, generates value to our many stakeholders, including our shareholders.

On May 2, 2019, our shareholders approved changing our name from "Horizon Pharma Public Limited Company" to "Horizon Therapeutics Public Limited Company". We believe the new name better reflects our long-term strategy to develop and commercialize innovative new medicines to address rare diseases with very few effective treatment options.

Orphan and Rheumatology

As of December 31, 2019, our orphan and rheumatology segment consisted of our medicines KRYSTEXXA, RAVICTI, PROCYSBI, ACTIMMUNE, BUPHENYL, QUINSAIR and RAYOS. In January 2020, the FDA approved TEPEZZA for the treatment of TED. With the exception of RAYOS, all are orphan medicines for rare diseases.

KRYSTEXXA is the only approved medicine indicated for the treatment of uncontrolled gout, or gout that is refractory (unresponsive) to conventional therapies. We are focused on optimizing and maximizing the peak sales potential of KRYSTEXXA through our patient-centric commercialization efforts as well as investing in education, patient and physician outreach that demonstrates the benefits KRYSTEXXA offers in treating uncontrolled gout.

Three areas are driving growth for KRYSTEXXA: an increase in new and existing accounts; accelerating uptake by nephrologists; and growth in the adoption of the use of KRYSTEXXA with the immunomodulator methotrexate to improve the KRYSTEXXA response rate in patients with uncontrolled gout.

Immunomodulation is one of the clinical development programs we are investing in to evaluate ways to increase the number of patients who can benefit from KRYSTEXXA. Our registrational MIRROR randomized controlled trial, or RCT, is evaluating the co-administration of KRYSTEXXA with methotrexate, the immunomodulator most often used by rheumatologists, to increase the durability of response for uncontrolled gout patients. The MIRROR RCT, which we initiated in mid-2019, was preceded by the MIRROR open-label study, which was initiated in 2018 and completed in 2019. The recently announced positive topline results of the MIRROR open-label study signify to us the value of continuing our research into the benefits of this immunomodulation approach. We are also investing to expand the use of KRYSTEXXA among nephrologists by providing additional data about the effectiveness of KRYSTEXXA in treating uncontrolled gout with its kidney-friendly mechanism of action. In October 2019, we initiated our PROTECT open-label study to evaluate the use of KRYSTEXXA in adult uncontrolled gout patients who have undergone a kidney transplant, a population that was not originally studied in the KRYSTEXXA pivotal trials. We also plan to initiate a proof of concept study in 2020 to evaluate the impact of administering KRYSTEXXA over a shorter infusion time, which could improve the experience and convenience for patients. We believe KRYSTEXXA represents a significant driver of growth for Horizon.

TEPEZZA is the first and only FDA-approved medicine for the treatment of TED, a serious, progressive and vision-threatening rare autoimmune condition. TEPEZZA obtained FDA approval in early 2020, after an accelerated review of the medicine and its statistically significant Phase 3 data. Our commercialization strategy for the medicine, which we recently launched, has four components: (i) establishing the market structure and simplifying the diagnosis and treatment of TED for patients; (ii) educating the multiple stakeholders about TED, the benefits of TEPEZZA and the urgency to diagnose and treat; (iii) supporting the TEPEZZA launch with our comprehensive approach and including a high-touch, patient-centric model; and (iv) facilitating access to TEPEZZA and establishing a referral process for treating physicians who may not have infusion capabilities. During 2019, we invested significantly in TEPEZZA in preparation for its potential U.S. launch, driving awareness in the medical and patient community about TED and establishing a potential pathway for treatment.

Our clinical strategy for TEPEZZA is to evaluate additional indications for the medicine. Scientific literature suggests that the mechanism of action of TEPEZZA, which is to block the insulin-like growth factor-1 receptor, could have an impact on fibrotic processes. As such, we expect to initiate an exploratory TEPEZZA study in the first half of 2020 in diffuse cutaneous scleroderma, a rare fibrotic disease with no treatment options. The objective of the exploratory trial is to evaluate objective biomarker and clinical endpoints to inform potential subsequent larger and longer duration clinical trials.

Our strategy for RAVICTI, our medicine for the treatment of urea cycle disorders, is to drive growth through increased awareness and diagnosis of urea cycle disorders; to drive conversion to RAVICTI from older-generation nitrogen scavengers, such as generic forms of sodium phenylbutyrate based on the medicine’s differentiated benefits; to position RAVICTI as the first line of therapy; and to increase compliance rates.

Our strategy for PROCYSBI, our medicine for the treatment of nephropathic cystinosis, is to drive conversion of patients from older-generation immediate-release capsules of cysteamine bitartrate; to increase the use of the medicine by diagnosed but untreated patients; to identify previously undiagnosed patients who are suitable for treatment; to position PROCYSBI as a first line of therapy; and to increase compliance rates.

Our strategy with respect to ACTIMMUNE, our medicine for the treatment of chronic granulomatous disease, includes increasing awareness and diagnosis of chronic granulomatous disease and increasing compliance rates.

We also market the rheumatology medicine RAYOS. As of December 31, 2019, RAYOS was included in the orphan and rheumatology segment. Effective in the first quarter of 2020, we (i) reorganized our commercial operations and moved responsibility for RAYOS to the inflammation segment and (ii) renamed the orphan and rheumatology segment the orphan segment. With the approval of TEPEZZA in the first quarter of 2020, net sales generated by this medicine will be reported as part of the renamed orphan segment.

Inflammation

As of December 31, 2019, our inflammation segment consisted of our medicines PENNSAID 2%, DUEXIS and VIMOVO. Our strategy for our inflammation medicines is to educate physicians about these clinically differentiated medicines and the benefits they offer. Patients are able to fill prescriptions for these medicines through pharmacies participating in our HorizonCares patient assistance program, as well as other pharmacies. We offer discount card and other programs to patients under which the patient receives a discount on his or her prescription. In certain circumstances when a patient's prescription is rejected by a managed care vendor, we will pay for the full cost of the prescription. In addition, we have entered into business arrangements with pharmacy benefit managers, or PBMs, and other payers to secure formulary status and reimbursement of our inflammation medicines. The business arrangements with the PBMs generally require us to pay administrative fees and rebates to the PBMs and other payers for qualifying prescriptions. Effective in the first quarter of 2020, we moved our medicine RAYOS, which is not an orphan medicine, to the inflammation segment.

Patent litigation is currently pending in the United States District Court for the District of New Jersey and the Court of Appeals for the Federal Circuit against Dr. Reddy's Laboratories Inc. and Dr. Reddy's Laboratories Ltd., or collectively Dr. Reddy's, who intends to market a generic version of VIMOVO before the expiration of certain of our patents listed in the Orange Book. The cases arise from Paragraph IV Patent Certification notice letters from Dr. Reddy's advising that it had filed an ANDA with the FDA seeking approval to market generic versions of VIMOVO before the expiration of the patents-in-suit. On July 30, 2019, the Federal Circuit Court of Appeals denied our request for a rehearing of the Court's invalidity ruling against the 6,926,907 and 8,557,285 patents for VIMOVO coordinated-release tablets. As a result, the District Court entered judgment in September 2019 invalidating the '907 and '285 patents, which ended any restriction against the FDA from granting final approval to Dr. Reddy's generic version of VIMOVO. On February 18, 2020, the FDA granted final approval for Dr. Reddy's generic version of VIMOVO. We anticipate that Dr. Reddy's will immediately launch its product at-risk notwithstanding the ongoing patent litigation. Patent litigation is currently pending in the United States District Court for the District of New Jersey against Ajanta Pharma LTD, or Ajanta, intending to market a generic version of VIMOVO before the expiration of certain of our patents listed in the Orange Book. If we are unsuccessful in any of the VIMOVO cases, we will likely face generic competition with respect to VIMOVO and sales of VIMOVO will be substantially harmed.

We market all of our medicines in the United States through our field sales forces, which numbered approximately 480 representatives as of December 31, 2019.

RESULTS OF OPERATIONS

Year Ended December 31, 2019 Compared to Year Ended December 31, 2018

Consolidated Results

	For the Years Ended December 31,		
	2019	2018	Change
	(in thousands)		
Net sales	$ 1,300,029	$ 1,207,570	$ 92,459
Cost of goods sold	362,175	391,301	(29,126)
Gross profit	**937,854**	**816,269**	**121,585**
Operating expenses:			
Research and development	103,169	82,762	20,407
Selling, general and administrative	697,111	692,485	4,626
Loss (gain) on sale of assets	10,963	(42,985)	53,948
Impairment of long-lived assets	—	46,096	(46,096)
Total operating expenses	**811,243**	**778,358**	**32,885**
Operating income	**126,611**	**37,911**	**88,700**
Other expense, net:			
Interest expense, net	(87,089)	(121,692)	34,603
Loss on debt extinguishment	(58,835)	—	(58,835)
Foreign exchange gain (loss)	33	(192)	225
Other (expense) income, net	(944)	841	(1,785)
Total other expense, net	**(146,835)**	**(121,043)**	**(25,792)**
Loss before benefit for income taxes	**(20,224)**	**(83,132)**	**62,908**
Benefit for income taxes	(593,244)	(44,752)	(548,492)
Net income (loss)	**$ 573,020**	**$ (38,380)**	**$ 611,400**

Net sales. Net sales increased $92.4 million, or 8%, to $1,300.0 million during the year ended December 31, 2019, from $1,207.6 million during the year ended December 31, 2018. The increase in net sales during the year ended December 31, 2019 was primarily due to an increase in net sales in our orphan and rheumatology segment of $98.1 million, offset by a decrease in net sales in our inflammation segment of $5.7 million.

The following table presents a summary of total net sales attributed to geographic sources for the years ended December 31, 2019 and 2018 (in thousands, except percentages):

	Year Ended December 31, 2019		Year Ended December 31, 2018	
	Amount	% of Total Net Sales	Amount	% of Total Net Sales
United States	$ 1,292,419	99%	$ 1,186,519	98%
Rest of world	7,610	1%	21,051	2%
Total net sales	**$ 1,300,029**		**$ 1,207,570**	

The following table reflects the components of net sales for the years ended December 31, 2019 and 2018 (in thousands, except percentages):

	Year Ended December 31,		Change	Change
	2019	2018	$	%
KRYSTEXXA	$ 342,379	$ 258,920	$ 83,459	32%
RAVICTI	228,755	226,650	2,105	1%
PROCYSBI	161,941	154,895	7,046	5%
ACTIMMUNE	107,302	105,563	1,739	2%
RAYOS	78,595	61,067	17,528	29%
BUPHENYL	9,806	21,810	(12,004)	(55)%
QUINSAIR	817	504	313	62%
LODOTRA	—	2,067	(2,067)	(100)%
Orphan and Rheumatology segment net sales	**$ 929,595**	**$ 831,476**	**$ 98,119**	**12%**
PENNSAID 2%	200,756	190,206	10,550	6%
DUEXIS	115,750	114,672	1,078	1%
VIMOVO	52,106	67,646	(15,540)	(23)%
MIGERGOT	1,822	3,570	(1,748)	(49)%
Inflammation segment net sales	**$ 370,434**	**$ 376,094**	**$ (5,660)**	**(2)%**
Total net sales	**$ 1,300,029**	**$ 1,207,570**	**$ 92,459**	**8%**

Orphan and Rheumatology

KRYSTEXXA. Net sales increased $83.5 million, or 32%, to $342.4 million during the year ended December 31, 2019, from $258.9 million during the year ended December 31, 2018. Net sales increased by approximately $73.9 million due to volume growth and approximately $9.6 million due to higher net pricing.

RAVICTI. Net sales increased $2.1 million, or 1%, to $228.7 million during the year ended December 31, 2019, from $226.6 million during the year ended December 31, 2018. Net sales in the United States increased by approximately $5.2 million, which was composed of an increase of approximately $21.9 million due to higher sales volume, partially offset by a decrease of approximately $16.7 million resulting from lower net pricing. Net sales outside the United States decreased by approximately $3.1 million as a result of the Immedica transaction on December 28, 2018.

PROCYSBI. Net sales increased $7.0 million, or 5%, to $161.9 million during the year ended December 31, 2019, from $154.9 million during the year ended December 31, 2018. The increase in net sales was composed of an increase of approximately $9.0 million due to volume growth, partially offset by a decrease of $2.0 million resulting from lower net pricing.

ACTIMMUNE. Net sales increased $1.7 million, or 2%, to $107.3 million during the year ended December 31, 2019, from $105.6 million during the year ended December 31, 2018. Net sales increased by approximately $4.2 million due to higher net pricing, partially offset by a decrease of approximately $2.5 million resulting from lower sales volume.

RAYOS. Net sales increased $17.5 million, or 29%, to $78.5 million during the year ended December 31, 2019, from $61.0 million during the year ended December 31, 2018. Net sales increased by approximately $29.9 million resulting from higher net pricing primarily due to lower utilization of our patient assistance programs, partially offset by a decrease of approximately $12.4 million due to lower sales volume.

BUPHENYL. Net sales decreased $12.0 million, or 55%, to $9.8 million during the year ended December 31, 2019, from $21.8 million during the year ended December 31, 2018. Net sales decreased primarily as a result of the Immedica transaction in December 2018.

LODOTRA. Effective January 1, 2019, we amended our license and supply agreements with Jagotec AG and Skyepharma AG, which are affiliates of Vectura. Under these amendments, we agreed to transfer all economic benefits of LODOTRA in Europe to Vectura during an initial transition period, with full rights transferring to Vectura when certain transfer activities have been completed. Effective January 1, 2019, we ceased recording LODOTRA net sales.

Inflammation

PENNSAID 2%. Net sales increased $10.6 million, or 6%, to $200.8 million during the year ended December 31, 2019, from $190.2 million during the year ended December 31, 2018. Net sales increased by approximately $47.2 million resulting from higher net pricing primarily due to lower utilization of our patient assistance programs, partially offset by a decrease of approximately $36.6 million resulting from lower sales volume.

DUEXIS. Net sales increased $1.1 million, or 1%, to $115.8 million during the year ended December 31, 2019, from $114.7 million during the year ended December 31, 2018. Net sales increased by approximately $18.1 million resulting from higher net pricing primarily due to lower utilization of our patient assistance programs, partially offset by a decrease of approximately $17.0 million resulting from lower sales volume.

VIMOVO. Net sales decreased $15.5 million, or 23%, to $52.1 million during the year ended December 31, 2019, from $67.6 million during the year ended December 31, 2018. Net sales decreased by approximately $17.8 million due to lower sales volume, partially offset by an increase of approximately $2.3 million resulting from higher net pricing primarily due to lower utilization of our patient assistance programs.

MIGERGOT. Net sales decreased $1.8 million, or 49%, to $1.8 million during the year ended December 31, 2019, from $3.6 million during the year ended December 31, 2018. On June 28, 2019, we sold our rights to MIGERGOT.

The table below reconciles our gross to net sales for the years ended December 31, 2019 and 2018 (in millions, except percentages):

	Year Ended December 31, 2019		Year Ended December 31, 2018	
	Amount	% of Gross Sales	Amount	% of Gross Sales
Gross sales	$ 3,911.8	100%	$ 4,264.5	100%
Adjustments to gross sales:				
Prompt pay discounts	(71.4)	(1.8)%	(75.1)	(1.8)%
Medicine returns	(26.5)	(0.7)%	(25.1)	(0.6)%
Co-pay and other patient assistance	(1,519.7)	(38.8)%	(1,970.4)	(46.2)%
Commercial rebates and wholesaler fees	(479.5)	(12.3)%	(589.6)	(13.8)%
Government rebates and chargebacks	(514.7)	(13.2)%	(396.7)	(9.3)%
Total adjustments	**(2,611.8)**	**(66.8)%**	**(3,056.9)**	**(71.7)%**
Net sales	**$ 1,300.0**	**33.2%**	**$ 1,207.6**	**28.3%**

During the year ended December 31, 2019, co-pay and other patient assistance costs, as a percentage of gross sales, decreased to 38.8% from 46.2% during the year ended December 31, 2018, primarily due to lower utilization of our patient assistance programs.

During the year ended December 31, 2019, government rebates and chargebacks, as a percentage of gross sales, increased to 13.2% from 9.3% during the year ended December 31, 2018, primarily as a result of an increased proportion of orphan and rheumatology medicines sold. Government rebates and chargebacks as a percentage of gross sales are typically higher for medicines in the orphan and rheumatology segment compared to medicines in the inflammation segment.

On a quarter-to-quarter basis, our net sales have traditionally been lower in first half of the year, particularly in the first quarter, with the second half of the year representing a greater share of overall net sales each year. This is due to annual managed care plan changes and the re-setting of patients' medical insurance deductibles at the beginning of each year, resulting in higher co-pay and other patient assistance costs as patients meet their annual medical insurance deductibles during the first and second quarters, and higher net sales in the second half of the year after patients meet their deductibles and healthcare plans reimburse a greater portion of the total cost of our medicines.

Cost of Goods Sold. Cost of goods sold decreased $29.1 million to $362.2 million during the year ended December 31, 2019, from $391.3 million during the year ended December 31, 2018. As a percentage of net sales, cost of goods sold was 28% during the year ended December 31, 2019, compared to 32% during the year ended December 31, 2018. The decrease in cost of goods sold was primarily attributable to a $17.0 million decrease in inventory step-up expense.

Because inventory step-up expense is acquisition-related, will not continue indefinitely and has a significant effect on our gross profit, gross margin percentage and net income (loss) for all affected periods, we disclose balance sheet and income statement amounts related to inventory step-up within the Notes to the Consolidated Financial Statements. The decrease in inventory step-up expense of $17.0 million recorded to cost of goods sold during the year ended December 31, 2019 compared to the prior year was primarily related to KRYSTEXXA, inventory step-up being fully expensed by March 31, 2018, resulting in no significant inventory step-up expense being recorded during the year ended December 31, 2019.

Research and Development Expenses. Research and development expenses increased $20.4 million to $103.2 million during the year ended December 31, 2019, from $82.8 million during the year ended December 31, 2018. The increase was primarily attributable to total upfront and progress payments of $6.0 million incurred under our collaboration agreement with HemoShear Therapeutics, LLC, or HemoShear, and a milestone payment of $3.0 million made to Roche relating to the TEPEZZA BLA submission to the FDA. In addition, employee-related costs increased by $6.5 million, TEPEZZA-related external costs increased by $3.3 million and KRYSTEXXA-related external costs increased by $1.6 million during the year ended December 31, 2019 compared to December 31, 2018.

Selling, General and Administrative Expenses. Selling, general and administrative expenses increased $4.6 million to $697.1 million during the year ended December 31, 2019, from $692.5 million during the year ended December 31, 2018. The increase was primarily attributable to an increase in employee costs of $17.6 million, partially offset by a decrease of $14.0 million in legal fees and litigation settlements.

Loss (Gain) on sale of assets. During the year ended December 31, 2019, we sold our rights to MIGERGOT for cash proceeds of $6.0 million, and we recorded a loss of $11.0 million on the sale.

During the year ended December 31, 2018, we completed the sale of rights to RAVICTI and AMMONAPS outside of North America and Japan for cash proceeds of $35.0 million, and we recorded a gain of $30.7 million on the sale. Additionally, we completed the IMUKIN sale for cash proceeds of $9.5 million, with a potential additional contingent consideration payment and we recorded a gain of $12.3 million on the sale. The contingent consideration payment of €3.0 million ($3.3 million when converted using a Euro-to-Dollar exchange rate at the date of receipt of 1.0991) was received in September 2019.

Impairment of Long-Lived Assets. During the year ended December 31, 2018, we recorded an impairment of $33.6 million to fully write off the book value of developed technology related to PROCYSBI in Canada and Latin America due primarily to lower anticipated future net sales based on a Patented Medicine Prices Review Board, or PMPRB, review. We also recorded an impairment of $10.6 million during the year ended December 31, 2018, to fully write off the book value of developed technology related to LODOTRA as result of amendments to our license and supply agreements with Jagotec AG and Skyepharma AG, which are affiliates of Vectura. Under these amendments, effective January 1, 2019, we agreed to transfer all economic benefits of LODOTRA in Europe to Vectura during an initial transition period, with full rights transferring to Vectura when certain transfer activities have been completed. These transfer activities are ongoing. We ceased recording LODOTRA revenue from January 1, 2019.

Interest Expense, Net. Interest expense, net, decreased $34.6 million to $87.1 million during the year ended December 31, 2019, from $121.7 million during the year ended December 31, 2018. The decrease was primarily due to a decrease in debt interest expense of $27.9 million, primarily related to the decrease in the principal amount of our term loans, repayment of our 6.625% Senior Notes due 2023, or the 2023 Senior Notes, in May 2019 and in August 2019, repayment of our 8.750% Senior Notes due 2024, or the 2024 Senior Notes, and an increase in interest income of $6.5 million.

Loss on Debt Extinguishment. During the year ended December 31, 2019, we recorded a loss on debt extinguishment of $58.8 million in the consolidated statements of comprehensive income (loss), which reflected the early redemption premiums and the write-off of the deferred financing fees and debt discount fees related to the prepayment of $775.0 million of our 2023 Senior Notes and our 2024 Senior Notes, and the write-off of the deferred financing fees and debt discount fees related to the $400.0 million of term loan repayments.

Benefit for Income Taxes. During the year ended December 31, 2019, we recorded a benefit for income taxes of $593.2 million compared to $44.8 million during the year ended December 31, 2018. The benefit for income taxes recorded during the year ended December 31, 2019, was primarily attributable to the recognition of a $553.3 million deferred tax asset resulting from an intra-company transfer of intellectual property assets to an Irish subsidiary.

Information by Segment

See Note 11, *Segment and Other Information*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K for a reconciliation of our segment operating income to our total loss before benefit for income taxes for the years ended December 31, 2019 and 2018.

Orphan and Rheumatology

The following table reflects our orphan and rheumatology net sales and segment operating income for the years ended December 31, 2019 and 2018 (in thousands, except percentages).

	For the Year Ended December 31,			
	2019	2018	Change	% Change
Net sales	$ 929,595	$ 831,476	$ 98,119	12%
Segment operating income	306,333	290,014	16,319	6%

The increase in orphan and rheumatology net sales during the year ended December 31, 2019 is described in the *Consolidated Results* section above.

Segment operating income. Orphan and rheumatology segment operating income increased $16.3 million to $306.3 million during the year ended December 31, 2019, from $290.0 million during the year ended December 31, 2018. The increase was primarily attributable to an increase in net sales of $98.1 million as described above, partially offset by an increase in selling, general and administrative expenses of $69.4 million. The increase in selling, general and administrative expenses was mainly due to an increase in costs to prepare for the U.S. launch of TEPEZZA.

Inflammation

The following table reflects our inflammation net sales and segment operating income for the years ended December 31, 2019 and 2018 (in thousands, except percentages).

	For the Year Ended December 31,			
	2019	2018	Change	% Change
Net sales	$ 370,434	$ 376,094	$ (5,660)	(2)%
Segment operating income	174,869	160,447	14,422	9%

The decrease in inflammation net sales during the year ended December 31, 2019 is described in the *Consolidated Results* section above.

Segment operating income. Inflammation segment operating income increased $14.4 million to $174.8 million during the year ended December 31, 2019, from $160.4 million during the year ended December 31, 2018. The increase was primarily attributable to a decrease in selling, general and administrative expenses of $18.6 million offset by a decrease in net sales of $5.7 million as described above. The decrease in selling, general and administrative expenses was mainly due to lower sample and patient assistance program administration expenses.

Year Ended December 31, 2018 Compared to Year Ended December 31, 2017

Consolidated Results

	For the Years Ended December 31,		
	2018	2017	Change
	(in thousands)		
Net sales	$ 1,207,570	$ 1,056,231	$ 151,339
Cost of goods sold	391,301	493,368	(102,067)
Gross profit	**816,269**	**562,863**	**253,406**
Operating expenses			
Research and development	82,762	224,962	(142,200)
Selling, general and administrative	692,485	655,093	37,392
Impairment of long-lived assets	46,096	22,270	23,826
Gain on sale of asset	(42,985)	—	(42,985)
Total operating expenses	**778,358**	**902,325**	**(123,967)**
Operating income (loss)	**37,911**	**(339,462)**	**377,373**
Other expense, net:			
Interest expense, net	(121,692)	(126,523)	4,831
Foreign exchange loss	(192)	(260)	68
Gain on divestiture	—	7,965	(7,965)
Loss on debt extinguishment	—	(978)	978
Other income, net:	841	447	394
Total other expense, net	**(121,043)**	**(119,349)**	**(1,694)**
Loss before benefit for income taxes	**(83,132)**	**(458,811)**	**375,679**
Benefit for income taxes	(44,752)	(108,686)	63,934
Net loss	**$ (38,380)**	**$ (350,125)**	**$ 311,745**

Net sales. Net sales increased $151.3 million, or 14.3%, to $1,207.6 million during the year ended December 31, 2018, from $1,056.2 million during the year ended December 31, 2017. The increase in net sales during the year ended December 31, 2018, was primarily due to higher net sales in our orphan and rheumatology segment.

The following table presents a summary of total net sales attributed to geographic sources for the years ended December 31, 2018 and 2017 (in thousands, except percentages):

	Year Ended December 31, 2018		Year Ended December 31, 2017	
	Amount	% of Total Net Sales	Amount	% of Total Net Sales
United States	$ 1,186,519	98%	$ 1,026,527	97%
Rest of world	21,051	2%	29,704	3%
Total net sales	**$ 1,207,570**		**$ 1,056,231**	

The following table reflects the components of net sales for the years ended December 31, 2018 and 2017 (in thousands, except percentages):

	Year Ended December 31,		Change	Change
	2018	2017	$	%
KRYSTEXXA	$ 258,920	$ 156,483	$ 102,437	65%
RAVICTI	226,650	193,918	32,732	17%
PROCYSBI	154,895	137,740	17,155	12%
ACTIMMUNE	105,563	110,993	(5,430)	(5)%
RAYOS	61,067	52,125	8,942	17%
BUPHENYL	21,810	20,792	1,018	5%
LODOTRA	2,067	5,393	(3,326)	(62)%
QUINSAIR	504	3,442	(2,938)	(85)%
Orphan and Rheumatology segment net sales	**$ 831,476**	**$ 680,886**	**$ 150,590**	**22%**
PENNSAID 2%	$ 190,206	$ 191,050	$ (844)	(0)%
DUEXIS	114,672	121,161	(6,489)	(5)%
VIMOVO	67,646	57,666	9,980	17%
MIGERGOT	3,570	5,468	(1,898)	(35)%
Inflammation segment net sales	**$ 376,094**	**$ 375,345**	**$ 749**	**0%**
Total net sales	**$ 1,207,570**	**$ 1,056,231**	**$ 151,339**	**14%**

Orphan and Rheumatology

KRYSTEXXA. Net sales increased $102.4 million, or 65%, to $258.9 million during the year ended December 31, 2018, from $156.5 million during the year ended December 31, 2017. Net sales increased by approximately $108.5 million resulting from volume growth, partially offset by a decrease of approximately $6.1 million due to lower net pricing.

RAVICTI. Net sales increased $32.7 million, or 17%, to $226.6 million during the year ended December 31, 2018, from $193.9 million during the year ended December 31, 2017. Net sales in the United States increased by approximately $30.8 million, which was composed of an increase of $24.4 million due to higher net pricing and $6.4 million due to volume growth. Net sales outside the United States increased by approximately $1.9 million primarily due to higher sales volume. On December 28, 2018, we sold our rights to RAVICTI outside of North America and Japan to Immedica.

PROCYSBI. Net sales increased $17.2 million, or 12%, to $154.9 million during the year ended December 31, 2018, from $137.7 million during the year ended December 31, 2017. Net sales in the United States increased by approximately $22.7 million, which was composed of $15.6 million due to higher net pricing and $7.1 million resulting from volume growth. Net sales outside the United States decreased by approximately $5.5 million primarily as a result of the Chiesi divestiture in June 2017.

ACTIMMUNE. Net sales decreased $5.4 million, or 5%, to $105.6 million during the year ended December 31, 2018, from $111.0 million during the year ended December 31, 2017. Net sales decreased by approximately $11.2 million resulting from lower volume, partially offset by an increase of approximately $5.8 million due to higher net pricing.

RAYOS. Net sales increased $8.9 million, or 17%, to $61.0 million during the year ended December 31, 2018, from $52.1 million during the year ended December 31, 2017. Net sales increased by approximately $5.0 million resulting from volume growth and approximately $3.9 million due to higher net pricing.

BUPHENYL. Net sales increased $1.0 million, or 5%, to $21.8 million during the year ended December 31, 2018, from $20.8 million during the year ended December 31, 2017. Net sales increased by approximately $2.0 million due to volume growth, partially offset by a decrease of approximately $1.0 million resulting from lower net pricing. On December 28, 2018, we sold our rights to AMMONAPS outside of North America and Japan to Immedica.

LODOTRA. Net sales decreased $3.3 million, or 62%, to $2.1 million during the year ended December 31, 2018, from $5.4 million during the year ended December 31, 2017. The decrease was due to decreased shipments to our European distribution partner, Mundipharma International Corporation Limited, or Mundipharma. LODOTRA sales to Mundipharma occurred at the time we shipped, based on Mundipharma's estimated requirements. Accordingly, LODOTRA sales were not linear or directly tied to Mundipharma's in-market sales and could therefore fluctuate significantly from period to period. Effective January 1, 2019, we amended our license and supply agreements with Jagotec AG and Skyepharma AG, which are affiliates of Vectura. Under these amendments, we agreed to transfer all economic benefits of LODOTRA in Europe to Vectura during an initial transition period, with full rights transferring to Vectura when certain transfer activities have been completed. These transfer activities are ongoing. We ceased recording LODOTRA revenue from January 1, 2019. See "Manufacturing, Commercial, Supply and License Agreements" included in Item 1 of this Annual Report on Form 10-K for further details of the amendments.

QUINSAIR. Net sales decreased $2.9 million, or 85%, to $0.5 million during the year ended December 31, 2018, from $3.4 million during the year ended December 31, 2017, primarily due to lower volume following the Chiesi divestiture.

Inflammation

PENNSAID 2%. Net sales decreased $0.8 million to $190.2 million during the year ended December 31, 2018, from $191.0 million during the year ended December 31, 2017. Net sales decreased by approximately $12.1 million due to lower volume, partially offset by an increase of approximately $11.3 million due to higher net pricing.

DUEXIS. Net sales decreased $6.5 million, or 5%, to $114.7 million during the year ended December 31, 2018, from $121.2 million during the year ended December 31, 2017. Net sales decreased by approximately $6.4 million due to lower volume and approximately $0.1 million due to lower net pricing.

VIMOVO. Net sales increased $10.0 million, or 17%, to $67.6 million during the year ended December 31, 2018, from $57.6 million during the year ended December 31, 2017. Net sales increased by approximately $23.2 million due to higher net pricing, partially offset by a decrease of approximately $13.2 million resulting from lower volume.

MIGERGOT. Net sales decreased $1.9 million, or 35%, to $3.6 million during the year ended December 31, 2018, from $5.5 million during the year ended December 31, 2017. Net sales decreased by approximately $1.6 million due to lower volume and approximately $0.3 million due to lower net pricing. On June 28, 2019, we sold our rights to MIGEROT.

The table below reconciles our gross to net sales for the years ended December 31, 2018 and 2017 (in millions, except percentages):

	Year Ended December 31, 2018		Year Ended December 31, 2017	
	Amount	% of Gross Sales	Amount	% of Gross Sales
Gross sales	$ 4,264.5	100.0%	$ 4,057.8	100.0%
Adjustments to gross sales:				
Prompt pay discounts	(75.1)	(1.8)%	(80.2)	(2.0)%
Medicine returns	(25.1)	(0.6)%	(45.6)	(1.1)%
Co-pay and other patient assistance	(1,970.4)	(46.2)%	(1,907.6)	(47.0)%
Commercial rebates and wholesaler fees	(589.6)	(13.8)%	(641.5)	(15.8)%
Government rebates and chargebacks	(396.7)	(9.3)%	(326.7)	(8.1)%
Total adjustments	**(3,056.9)**	**(71.7)%**	**(3,001.6)**	**(74.0)%**
Net sales	**$ 1,207.6**	**28.3%**	**$ 1,056.2**	**26.0%**

During the year ended December 31, 2018, commercial rebates and wholesaler fees, as a percentage of gross sales, decreased to 13.8% from 15.8% during the year ended December 31, 2017, primarily as a result of a change in the mix of medicines sold and lower rates paid to distributors during 2018 compared to 2017.

During the year ended December 31, 2018, government rebates and chargebacks, as a percentage of gross sales, increased to 9.3% from 8.1% during the year ended December 31, 2017, primarily as a result of a change in the mix of medicines sold.

On a quarter-to-quarter basis, our net sales have traditionally been lower in first half of the year, particularly in the first quarter, with the second half of the year representing a greater share of overall net sales each year. This is due to annual managed care plan changes and the re-setting of patients' medical insurance deductibles at the beginning of each year, resulting in higher co-pay and other patient assistance costs as patients meet their annual medical insurance deductibles during the first and second quarters, and higher net sales in the second half of the year after patients meet their deductibles and healthcare plans reimburse a greater portion of the total cost of our medicines.

Additionally, on January 1, 2019, the 340B ceiling price rule became effective. With respect to KRYSTEXXA, the "additional rebate" scheme of the 340B pricing program, as applied to the historical pricing of KRYSTEXXA both before and after we acquired the medicine, have resulted in a 340B ceiling price of one penny. A material portion of KRYSTEXXA prescriptions (approximately 20 percent) are written by healthcare providers that are eligible for 340B drug pricing and therefore the reduction in 340B pricing to a penny has negatively impacted our net sales from KRYSTEXXA.

Cost of Goods Sold. Cost of goods sold decreased $102.1 million to $391.3 million during the year ended December 31, 2018, from $493.4 million during the year ended December 31, 2017. As a percentage of net sales, cost of goods sold was 32% during the year ended December 31, 2018, compared to 47% during the year ended December 31, 2017. The decrease in cost of goods sold was primarily attributable to a $101.8 million decrease in inventory step-up expense.

Because inventory step-up expense is acquisition-related, will not continue indefinitely and has a significant effect on our gross profit, gross margin percentage and net income (loss) for all affected periods, we disclose balance sheet and income statement amounts related to inventory step-up within the Notes to the Consolidated Financial Statements. The decrease in inventory step-up expense of $101.8 million recorded to cost of goods sold during the year ended December 31, 2018 compared to the prior year was primarily related to KRYSTEXXA, PROCYSBI and QUINSAIR inventory step-up expense. KRYSTEXXA inventory step-up expense recorded during the year ended December 31, 2018 was $17.0 million compared to $78.3 million recorded during the year ended December 31, 2017. PROCYSBI and QUINSAIR inventory step-up expense recorded during the year ended December 31, 2018 was $0.3 million compared to $40.8 million recorded during the year ended December 31, 2017.

Research and Development Expenses. Research and development expenses decreased $142.2 million to $82.8 million during the year ended December 31, 2018, from $225.0 million during the year ended December 31, 2017. The decrease was primarily attributable to $150.3 million related to the acquisition of River Vision during the year ended December 31, 2017. Pursuant to Accounting Standards Codification Topic 805, Business Combinations, or ASC 805, as amended by ASU No. 2017-01, we accounted for the River Vision acquisition as the purchase of an in-process research and development, or IPR&D, asset and, pursuant to ASC 730, Research and Development, or ASC 730, recorded the purchase as a research and development expense during the year ended December 31, 2017. Additionally, during the year ended December 31, 2017, we entered into an agreement to license HZN-003, a rheumatology pipeline program with the objective of enhancing our leadership position in the uncontrolled gout market, from MedImmune LLC, or MedImmune, and we paid MedImmune an upfront cash payment of $12.0 million which we recorded as a "research and development" expense in the consolidated statement of comprehensive income (loss) during the year ended December 31, 2017 and included in "accrued expenses" as of December 31, 2017. The upfront payment was subsequently paid in January 2018. Excluding the costs attributable to the acquisition of River Vision and HZN-003, research and development expenses increased by $20.1 million during the year ended December 31, 2018, compared to the year ended December 31, 2017, primarily due to the costs associated with the development of TEPEZZA.

Selling, General and Administrative Expenses. Selling, general and administrative expenses increased $37.4 million to $692.5 million during the year ended December 31, 2018, from $655.1 million during the year ended December 31, 2017. The increase was primarily attributable to the expansion of our KRYSTEXXA sales force that was initiated during the second half of 2017 and other activities to support the growth in sales of the medicine, and pre-launch costs for TEPEZZA.

Impairment of Long-Lived Assets. During the year ended December 31, 2018, we recorded an impairment of $33.6 million to fully write off the book value of developed technology related to PROCYSBI in Canada and Latin America due primarily to lower anticipated future net sales based on a Patented Medicine Prices Review Board, or PMPRB, review. We also recorded an impairment of $10.6 million during the year ended December 31, 2018, to fully write off the book value of developed technology related to LODOTRA as result of amendments to our license and supply agreements with Jagotec AG and Skyepharma AG, which are affiliates of Vectura. Under these amendments, effective January 1, 2019, we agreed to transfer all economic benefits of LODOTRA in Europe to Vectura during an initial transition period, with full rights transferring to Vectura when certain transfer activities have been completed. These transfer activities are ongoing. We ceased recording LODOTRA revenue from January 1, 2019. Impairment of long-lived assets of $22.3 million during the year ended December 31, 2017, represents the impairment of a non-current asset recorded following payment to Boehringer Ingelheim International for the acquisition of certain rights to interferon gamma-1b. This was previously included within "selling, general and administrative" expenses. On July 24, 2018, we completed the IMUKIN sale as further described in the next paragraph.

Gain on sale of assets. During the year ended December 31, 2018, we completed the sale of rights to RAVICTI and AMMONAPS outside of North America and Japan for cash proceeds of $35.0 million, and we recorded a gain of $30.7 million on the sale. Additionally, we completed the IMUKIN sale for cash proceeds of $9.5 million, with a potential additional contingent consideration payment and we recorded a gain of $12.3 million on the sale.

Interest Expense, Net. Interest expense, net, decreased $4.8 million to $121.7 million during the year ended December 31, 2018, from $126.5 million during the year ended December 31, 2017. The decrease in net interest expense was primarily due to an increase in interest income of $8.5 million primarily due to higher cash balances, partially offset by an increase of $3.7 million in interest expense.

Gain on divestiture. During the year ended December 31, 2017, we completed the Chiesi divestiture for an upfront payment of $72.5 million, which reflects $3.1 million of cash divested, with additional potential milestone payments based on sales thresholds, and we recorded a gain of $8.0 million on the divestiture.

Benefit for Income Taxes. During the year ended December 31, 2018, we recorded a benefit for income taxes of $44.8 million compared to $108.7 million during the year ended December 31, 2017. The reduction in benefit for income taxes of $63.9 million during the year ended December 31, 2018, compared to year ended December 31, 2017, was primarily due to a decrease in pre-tax losses and the tax rate at which some of these reduced losses were tax effected resulting in a tax provision of $57.9 million and income tax expense of $45.8 million generated on an intra-company transfer of assets other than inventory during the year ended December 31, 2018.

Additionally, during the year ended December 31, 2017, we recorded a provisional estimate of $84.0 million net benefit following the enactment in the United States of H.R. 1, “An Act to provide for reconciliation pursuant to titles II and V of the concurrent resolution on the budget for fiscal year 2018”, informally titled the Tax Cuts and Jobs Act, or the Tax Act, in December 2017, which net benefit included a $143.3 million tax benefit from the revaluation of our U.S. net deferred tax liability based on the revised U.S. federal tax rate of 21 percent, partially offset by the write-off of the $59.2 million deferred tax asset related to our U.S. interest expense carryforwards under Section 163(j) of the Internal Revenue Code of 1986, as amended, or the Code. On December 22, 2017, the SEC staff issued Staff Accounting Bulletin No. 118, or SAB 118, which provides guidance on accounting for the tax effects of the Tax Act. SAB 118 provided a measurement period that should not extend beyond one year from the date of enactment for companies to complete the accounting under ASC 740, Income Taxes. In accordance with SAB 118, we reflected the income tax effects of those aspects of the Tax Act for which the accounting under ASC 740 was complete. To the extent that our accounting for certain income tax effects of the Tax Act was incomplete but it was possible to determine a reasonable estimate, we recorded a provisional estimate in the consolidated financial statements as of December 31, 2017.

On April 2, 2018, the U.S. Treasury Department and the U.S. Internal Revenue Service issued Notice 2018-28, or the Notice, which provided guidance for computing the business interest expense limitation under the Tax Act and clarified the treatment of interest disallowed and carried forward under Section 163(j) of the Code prior to enactment of the Tax Act. In accordance with the measurement period provisions under SAB 118 and the guidance in the Notice we reinstated the deferred tax asset related to our U.S. interest expense carryforwards under Section 163(j) based on the revised U.S. federal tax rate of 21 percent. The impact of the deferred tax asset reinstatement in accordance with SAB 118 during the year ended December 31, 2018 was a $37.4 million increase to our benefit for income taxes and a corresponding decrease to the U.S. group net deferred tax liability position. We had no other material measurement period adjustments under SAB 118.

The remainder of the decrease in benefit for income taxes during the year ended December 31, 2018, compared to year ended December 31, 2017 resulted from a tax provision of $8.1 million attributable to the remeasurement of net U.S. deferred tax liabilities for the year ended December 31, 2018 due to an increase in U.S. state effective tax rates attributable to the enactment of certain U.S. state legislation during the year ended December 31, 2018. These decreases to the benefit for income taxes during the year ended December 31, 2018 were partially offset by an income tax expense of $51.1 million on non-deductible research and development costs which occurred during the year ended December 31, 2017 and did not re-occur for the year ended December 31, 2018, a tax benefit of $42.7 million U.S. federal tax and $7.9 million U.S. state tax benefit on the liquidation of a foreign partnership owned by us during the year ended December 31, 2018 and decreases to our current state income tax expense of $6.8 million resulting from current year pre-tax losses incurred in the U.S. group.

During the year ended December 31, 2017, the first of three tranches of our outstanding performance stock unit awards, or PSUs, issued in 2015 expired without payout as the minimum total compounded annual shareholder rate of return was not achieved. As a result, we wrote off to income tax expense $16.4 million of deferred tax assets related to previously recognized share-based compensation.

In relation to our outstanding PSUs at December 31, 2017, as our share price was lower than $32.70 for the twenty trading days ended March 22, 2018, and lower than $33.86 for the twenty trading days ended June 22, 2018, the second two tranches of PSU awards granted in 2015 expired without payment as the minimum total compounded annual shareholder rate of return was not achieved, and approximately $10.7 million and $12.6 million, respectively, of deferred tax assets at December 31, 2017, related to previously recognized share-based compensation expense was charged to income tax expense during the year ended December 31, 2018.

Information by Segment

See Note 11, *Segment and Other Information*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K for a reconciliation of our segment operating income to our total loss before benefit for income taxes for the years ended December 31, 2018 and 2017.

Orphan and Rheumatology

The following table reflects our orphan and rheumatology net sales and segment operating income for the years ended December 31, 2018 and 2017 (in thousands, except percentages).

	For the Year Ended December 31,			
	2018	2017	Change	% Change
Net sales	$ 831,476	$ 680,886	$ 150,590	22%
Segment operating income	290,014	241,135	48,879	20%

The increase in orphan and rheumatology net sales during the year ended December 31, 2018 is described in the *Consolidated Results* section above.

Segment operating income. Orphan and rheumatology segment operating income increased $48.9 million to $290.0 million during the year ended December 31, 2018, from $241.1 million during the year ended December 31, 2017. The increase was primarily attributable to an increase in net sales of $150.6 million as described above, partially offset by an increase in selling, general and administrative expenses of $68.2 million and an increase in research and development expenses of $17.6 million. The increase in selling, general and administrative expenses was mainly due to the expansion of our KRYSTEXXA sales force that was initiated during the second half of 2017 and other activities to support the growth in sales of the medicine, and pre-launch costs for TEPEZZA. The increase in research and development expenses was primarily due to costs associated with the development of TEPEZZA.

Inflammation

The following table reflects our inflammation net sales and segment operating income for the years ended December 31, 2018 and 2017 (in thousands, except percentages).

	For the Year Ended December 31,			
	2018	2017	Change	% Change
Net sales	$ 376,094	$ 375,345	$ 749	0%
Segment operating income	160,447	149,133	11,314	8%

The increase in inflammation net sales during the year ended December 31, 2018, is described in the *Consolidated Results* section above.

Segment operating income. Inflammation segment operating income increased $11.3 million to $160.4 million during the year ended December 31, 2018, from $149.1 million during the year ended December 31, 2017. The increase was primarily attributable to stability in net sales and a decrease in selling, general and administrative expenses of $10.7 million.

Non-GAAP Financial Measures

EBITDA, or earnings before interest, taxes, depreciation and amortization, adjusted EBITDA, non-GAAP net income and non-GAAP earnings per share are used and provided by us as non-GAAP financial measures. These non-GAAP financial measures are intended to provide additional information on our performance, operations and profitability. Adjustments to our GAAP figures as well as EBITDA exclude acquisition/divestiture-related costs, upfront, progress and milestone payments related to license and collaboration agreements, drug substance harmonization costs, fees related to refinancing activities, restructuring and realignment costs, litigation settlements and charges related to discontinuation of the Friedreich's ataxia program, or the FA discontinuation, loss (gain) on sale of assets, loss on debt extinguishments, the income tax effect on pre-tax non-GAAP adjustments and other non-GAAP income tax adjustments, as well as non-cash items such as share-based compensation, inventory step-up expense, depreciation and amortization, non-cash interest expense, long-lived assets impairment charges, and other non-cash adjustments. Certain other special items or substantive events may also be included in the non-GAAP adjustments periodically when their magnitude is significant within the periods incurred. We maintain an established non-GAAP cost policy that guides the determination of what costs will be excluded in non-GAAP measures. We believe that these non-GAAP financial measures, when considered together with the GAAP figures, can enhance an overall understanding of our financial and operating performance. The non-GAAP financial measures are included with the intent of providing investors with a more complete understanding of our historical financial results and trends and to facilitate comparisons between periods. In addition, these non-GAAP financial measures are among the indicators our management uses for planning and forecasting purposes and measuring our performance. For example, adjusted EBITDA is used by us as one measure of management performance under certain incentive compensation arrangements. These non-GAAP financial measures should be considered in addition to, and not as a substitute for, or superior to, financial measures calculated in accordance with GAAP. The non-GAAP financial measures used by us may be calculated differently from, and therefore may not be comparable to, non-GAAP financial measures used by other companies.

Reconciliations of reported GAAP net income (loss) to EBITDA, adjusted EBITDA and non-GAAP net income, and the related per share amounts, were as follows (in thousands, except share and per share amounts):

	For the Years Ended December 31,		
	2019	**2018**	**2017**
GAAP net income (loss)	**$ 573,020**	**$ (38,380)**	**$ (350,125)**
Depreciation [1]	6,733	6,126	6,631
Amortization and step-up:			
Intangible amortization expense [2]	230,424	243,634	249,456
Amortization of deferred revenue	—	—	(860)
Inventory step-up expense [3]	89	17,312	119,151
Interest expense, net (including amortization of debt discount and deferred financing costs)	87,089	121,692	126,523
Benefit for income taxes	(593,244)	(44,752)	(108,686)
EBITDA	**304,111**	**305,632**	**42,090**
Other non-GAAP adjustments:			
Share-based compensation [4]	91,215	114,860	121,553
Loss on debt extinguishment [5]	58,835	—	978
Loss (gain) on sale of assets [6]	10,963	(42,985)	—
Upfront, progress and milestone payments related to license and collaboration agreements [7]	9,073	(10)	12,186
Acquisition/divestiture-related costs [8]	3,556	4,396	177,631
Fees related to refinancing activities [9]	2,292	937	5,220
Charges relating to discontinuation of Friedreich's ataxia program [10]	1,076	(1,464)	239
Litigation settlements [11]	1,000	5,750	—
Drug substance harmonization costs [12]	457	2,855	10,651
Restructuring and realignment costs [13]	237	15,350	4,883
Impairment of long-lived assets [14]	—	46,096	22,270
Gain on divestiture [15]	—	—	(7,965)
Total of other non-GAAP adjustments	**178,704**	**145,785**	**347,646**
Adjusted EBITDA	**$ 482,815**	**$ 451,417**	**$ 389,736**

	For the Years Ended December 31,		
	2019	2018	2017
GAAP net income (loss)	**$ 573,020**	**$ (38,380)**	**$ (350,125)**
Non-GAAP adjustments:			
Depreciation (1)	6,733	6,126	6,631
Amortization and step-up:			
Intangible amortization expense (2)	230,424	243,634	249,456
Inventory step-up expense (3)	89	17,312	119,151
Amortization of debt discount and deferred financing costs (16)	22,602	22,752	21,619
Share-based compensation (4)	91,215	114,860	121,553
Loss on debt extinguishment (5)	58,835	—	978
Loss (gain) on sale of assets (6)	10,963	(42,985)	—
Upfront, progress and milestone payments related to license and collaboration agreements (7)	9,073	(10)	12,186
Acquisition/divestiture-related costs (8)	3,556	4,396	177,631
Fees related to refinancing activities (9)	2,292	937	5,220
Charges relating to discontinuation of Friedreich's ataxia program (10)	1,076	(1,464)	239
Litigation settlements (11)	1,000	5,750	—
Drug substance harmonization costs (12)	457	2,855	10,651
Restructuring and realignment costs (13)	237	15,350	4,883
Impairment of long-lived assets (14)	—	46,096	22,270
Gain on divestiture (15)	—	—	(7,965)
Total pre-tax non-GAAP adjustments	**438,552**	**435,609**	**744,503**
Income tax effect of pre-tax non-GAAP adjustments (17)	(66,568)	(45,186)	(115,569)
Other non-GAAP income tax adjustments (18)	(554,786)	(37,392)	(84,011)
Total non-GAAP adjustments	**(182,802)**	**353,031**	**544,923**
Non-GAAP Net Income	**$ 390,218**	**$ 314,651**	**$ 194,798**
Non-GAAP Earnings Per Share:			
Weighted average ordinary shares – Basic	**182,930,109**	**166,155,405**	**163,122,663**
Non-GAAP Earnings Per Share – Basic			
GAAP income (loss) per share - Basic	**$ 3.13**	**$ (0.23)**	**$ (2.15)**
Non-GAAP adjustments	(1.00)	2.12	3.34
Non-GAAP earnings per share – Basic	**$ 2.13**	**$ 1.89**	**$ 1.19**
Non-GAAP Net Income	**$ 390,218**	**$ 314,651**	**$ 194,798**
Effect of assumed conversion of Exchangeable Senior Notes, net of tax	7,500	—	—
Numerator - non-GAAP Net Income	**$ 397,718**	**$ 314,651**	**$ 194,798**
Weighted average ordinary shares – Diluted			
Weighted average ordinary shares – Basic	182,930,109	166,155,405	163,122,663
Ordinary share equivalents	22,294,112	5,393,514	2,582,576
Denominator - weighted average ordinary shares – Diluted	**205,224,221**	**171,548,919**	**165,705,239**
Non-GAAP Earnings Per Share – Diluted			
GAAP income (loss) per share – Diluted	**$ 2.90**	**$ (0.23)**	**$ (2.15)**
Non-GAAP adjustments	**(0.96)**	2.12	3.34
Diluted earnings per share effect of ordinary share equivalents	—	(0.06)	(0.01)
Non-GAAP earnings per share – Diluted	**$ 1.94**	**$ 1.83**	**$ 1.18**

(1) Represents depreciation expense related to our property, equipment, software and leasehold improvements.

(2) Intangible amortization expenses are associated with our intellectual property rights, developed technology and customer relationships related to KRYSTEXXA, RAVICTI, PROCYSBI, ACTIMMUNE, RAYOS, BUPHENYL, LODOTRA, PENNSAID 2%, VIMOVO and MIGERGOT.

(3) During the year ended December 31, 2018, we recognized in cost of goods sold $17.3 million for inventory step-up expense primarily related to KRYSTEXXA inventory sold.

During the year ended December 31, 2017, we recognized in cost of goods sold $78.3 million for inventory step-up expense related to KRYSTEXXA and MIGERGOT inventory sold and $40.8 million for inventory step-up expense related to PROCYSBI and QUINSAIR inventory sold.

(4) Represents share-based compensation expense associated with our stock option, restricted stock unit and performance stock unit grants to our employees and non-employee directors and our employee share purchase plan.

(5) During the year ended December 31, 2019, we recorded a loss on debt extinguishment of $58.8 million in the consolidated statements of comprehensive income (loss), which reflected the early redemption premiums and the write-off of the deferred financing fees and debt discount fees related to the prepayment of $775.0 million of our 2023 Senior Notes and 2024 Senior Notes and the write-off of the deferred financing fees and debt discount fees related to the $400.0 million of term loan repayments.

During the year ended December 31, 2017, we entered into two refinancing amendments for our term loans. We accounted for a portion of the repayments under these refinancing amendments as a debt extinguishment and recorded a loss on debt extinguishment of $1.0 million in the consolidated statements of comprehensive income (loss), which reflected the write-off of the unamortized portion of debt discount and deferred financing costs previously incurred and a 1 percent prepayment penalty fee.

(6) During the year ended December 31, 2019, we recorded a loss of $11.0 million on the sale of our rights to MIGERGOT.

During the year ended December 31, 2018, we completed the IMUKIN sale for cash proceeds of $9.5 million, with a potential additional contingent consideration payment and we recorded a gain of $12.3 million on the sale. The contingent consideration payment of €3.0 million ($3.3 million when converted using a Euro-to-Dollar exchange rate at the date of receipt of 1.0991) was received in September 2019. Additionally, during the year ended December 31, 2018, we sold our rights to RAVICTI and AMMONAPS outside of North America and Japan to Medical Need Europe AB, and we recorded a gain of $30.7 million.

(7) During the year ended December 31, 2019, we recorded an upfront, progress and milestone payments related to license and collaboration agreements of $9.1 million which was composed of a $3.0 million milestone payment to Roche relating to the TEPEZZA BLA submission to the FDA during the third quarter of 2019, and an upfront cash payment of $2.0 million and a progress payment of $4.0 million in relation to the collaboration agreement with HemoShear.

During the year ended December 31, 2017, we incurred $12.2 million of upfront and milestone payments related to license agreements, primarily related to our agreement to license HZN-003 (formerly MEDI4945), a rheumatology pipeline program with the objective of enhancing our leadership position in the uncontrolled gout market, from MedImmune for an upfront cash payment of $12.0 million.

(8) Represents expenses, including legal and consulting fees, incurred in connection with our acquisitions and divestitures. Costs recovered from subleases of acquired facilities and reimbursed expenses incurred under transition arrangements for divestitures are also reflected in this line-item.

(9) Represents arrangement and other fees relating to our refinancing activities.

(10) During the year ended December 31, 2019, we recorded charges related to the FA discontinuation of $1.1 million, primarily due to the remeasurement of an inventory purchase commitment liability.

During the year ended December 31, 2018, we recorded a reduction to previously incurred charges relating to the FA discontinuation of $1.5 million reflecting lower costs to discontinue the clinical trial than previously anticipated.

During the year ended December 31, 2017, we recorded charges relating to the FA discontinuation of $0.2 million.

(11) We recorded $1.0 million and $5.8 million of expense during the years ended December 31, 2019 and 2018, respectively, for litigation settlements.

(12) During the year ended December 31, 2016, we entered into a definitive agreement to acquire certain rights to interferon gamma-1b, marketed as IMUKIN in an estimated thirty countries primarily in Europe and the Middle East, or the IMUKIN purchase agreement. We already owned the rights to interferon gamma-1b marketed as ACTIMMUNE in the United States, Canada and Japan. In connection with the IMUKIN purchase agreement, we also committed to pay our contract manufacturer certain amounts related to the harmonization of the manufacturing processes for ACTIMMUNE and IMUKIN drug substance, or the harmonization program. At the time we entered into the IMUKIN purchase agreement and the harmonization program commitment was made, we had anticipated achieving certain benefits should the Phase 3 clinical trial evaluating ACTIMMUNE for the treatment of FA be successful. If the study had been successful and if U.S. marketing approval had subsequently been obtained, we had forecasted significant increases in demand for the medicine and the harmonization program would have resulted in significant benefits for us. Following our discontinuation of the FA program, we determined that certain assets, including an upfront payment related to the IMUKIN purchase agreement, were impaired, and the costs under the harmonization program would no longer have benefit to us and should be expensed as incurred.

(13) Represents expenses, including severance costs and consulting fees, related to restructuring and realignment activities.

(14) Impairment of long-lived assets during the year ended December 31, 2018, primarily relates to the write-off of the book value of developed technology related to PROCYSBI in Canada and Latin America and LODOTRA.

Impairment of long-lived assets during the year ended December 31, 2017 of $22.3 million relates to an impairment recorded following payment to Boehringer Ingelheim International for the acquisition of certain rights to interferon gamma-1b. This was presented in the “charges relating to the discontinuation of the Friedreich’s ataxia program” line item in the reconciliation of GAAP to non-GAAP measures during the year ended December 31, 2017.

(15) During the year ended December 31, 2017, we completed the divestiture of a European subsidiary that owns the marketing rights to PROCYSBI and QUINSAIR in EMEA to Chiesi and in connection with this divestiture we recorded a gain of $8.0 million.

(16) Represents amortization of debt discount and deferred financing costs associated with our debt.

(17) Income tax adjustments on pre-tax non-GAAP adjustments represent the estimated income tax impact of each pre-tax non-GAAP adjustment based on the statutory income tax rate of the applicable jurisdictions for each non-GAAP adjustment.

(18) Other non-GAAP income tax adjustments during the year ended December 31, 2019, primarily reflect a tax benefit of $553.3 million resulting from an intra-company transfer of intellectual property assets to an Irish subsidiary.

Other non-GAAP income tax adjustments during the year ended December 31, 2018, reflect the impact of the deferred tax asset reinstatement in accordance with SAB 118, which was a $37.4 million increase to our benefit for income taxes and a corresponding decrease to the U.S. group net deferred tax liability position. Following Notice 2018-28 that was issued by the U.S. Treasury Department and the U.S. Internal Revenue Service during the year ended December 31, 2018 and in accordance with the measurement period provisions under SAB 118, we reinstated the deferred tax asset related to our U.S. interest expense carry forwards under Section 163(j) of the Code based on the revised U.S. federal tax rate of 21 percent.

Other non-GAAP income tax adjustments during the year ended December 31, 2017, reflect the provisional $84.0 million net benefit recorded following the enactment of the Tax Act, which net benefit included a $143.3 million tax benefit from the revaluation of our U.S. net deferred tax liability based on the revised U.S. federal tax rate of 21 percent, partially offset by the write-off of the $59.2 million deferred tax asset related to our U.S. interest expense carryforwards under Section 163(j) of the Code.

Liquidity, Financial Position and Capital Resources

We have incurred losses in most fiscal years since our inception in June 2005 and, as of December 31, 2019, we had an accumulated deficit of $605.7 million. We expect that our sales and marketing expenses will continue to increase as a result of the commercialization of our medicines, including as a result of the commercial launch of TEPEZZA, but we believe these cost increases will be more than offset by higher net sales and gross profits. Additionally, we expect that our research and development costs will increase as we acquire or develop more development-stage medicine candidates and advance our candidates through the clinical development and regulatory approval processes.

In February 2020, we purchased a three-building campus in Deerfield, Illinois, for total cash consideration of $115.0 million. The Deerfield campus totals 70 acres and consists of more than 650,000 square feet of office space. We expect to move to the Deerfield campus in the second half of 2020 and market our Lake Forest office for sub-lease. We expect to make significant capital expenditures during 2020 in order to prepare the Deerfield campus for occupancy.

As a result of the FDA approval of TEPEZZA in January 2020, we will make a milestone payment of $100.0 million under the agreement for the acquisition of River Vision during the first quarter of 2020.

We have financed our operations to date through equity financings, debt financings and the issuance of convertible notes, along with cash flows from operations during the last several years. During 2019, we reduced the principal amount of our total debt outstanding by $575.0 million. As of December 31, 2019, we had $1,080.0 million in cash and cash equivalents and total debt with a book value of $1,352.8 million and principal amount of $1,418.0 million. We believe our existing cash and cash equivalents and our expected cash flows from operations will be sufficient to fund our business needs for at least the next twelve months from the issuance of the financial statements in this Annual Report on Form 10-K. Part of our strategy is to expand and leverage our commercial capabilities and to develop a pipeline of rare disease medicine candidates by researching, developing and commercializing innovative medicines that address unmet treatment needs for rare and rheumatic diseases. To the extent we enter into transactions to acquire medicines or businesses in the future, we may need to finance a significant portion of those acquisitions through additional debt, equity or convertible debt financings, or through the use of cash on hand.

Equity Issuances

On March 11, 2019, we closed an underwritten public equity offering of 14.1 million ordinary shares at a price to the public of $24.50 per share, resulting in net proceeds of approximately $326.8 million after deducting underwriting discounts and other estimated offering expenses payable by us. This included the exercise in full by the underwriters of their option to purchase up to 1.8 million additional ordinary shares.

During the year ended December 31, 2019, we issued an aggregate of 5.1 million of our ordinary shares in connection with stock option exercises, the vesting of restricted stock units and performance stock units, and employee share purchase plan purchases. We received a total of $36.2 million in proceeds in connection with such issuances.

Amendments to Credit Agreement, Debt Repayments and 2027 Senior Notes

On March 11, 2019, Horizon Therapeutics USA, Inc. (formerly known as Horizon Pharma USA, Inc.), our wholly owned subsidiary, or HTUSA, received $200.0 million aggregate principal amount of revolving commitments, or the Incremental Revolving Commitments, pursuant to an amendment to our credit agreement, dated as of May 7, 2015, with Citibank, N.A., as amended, or the Credit Agreement. The Incremental Revolving Commitments were established pursuant to an incremental facility, or the Revolving Credit Facility, and will provide HTUSA with $200.0 million of additional borrowing capacity, which includes a $50.0 million letter of credit sub-facility. The Incremental Revolving Commitments will terminate in March 2024. Borrowings under the Revolving Credit Facility are available for general corporate purposes. As of December 31, 2019, the Revolving Credit Facility was undrawn.

On March 18, 2019, HTUSA completed the repayment of $300.0 million of the outstanding principal amount of term loans under our Credit Agreement.

On April 1, 2019, we delivered a notice of partial optional redemption of $250.0 million of the 2023 Senior Notes to the trustee under the indenture governing the 2023 Senior Notes and the holders of the 2023 Senior Notes, which were redeemed on May 1, 2019. In connection with this early redemption, we paid a premium of $8.3 million on May 1, 2019.

On May 22, 2019, HTUSA borrowed approximately $518.0 million aggregate principal amount of loans, or the May 2019 Refinancing Loans, pursuant to an amendment to our Credit Agreement. HTUSA used the proceeds of the May 2019 Refinancing Loans to repay the outstanding amounts under our prior term loans, which totaled approximately $518.0 million.

On July 16, 2019, HTUSA completed a private placement of $600.0 million aggregate principal amount of 5.5% Senior Notes due 2027, or the 2027 Senior Notes, to several investment banks acting as initial purchasers, in reliance on the exemption from registration provided by Section 4(a)(2) of the Securities Act, who subsequently resold the 2027 Senior Notes to persons reasonably believed to be qualified institutional buyers in reliance on the exemption from registration provided by Rule 144A under the Securities Act and in offshore transactions to certain non-U.S. persons in reliance on Regulation S under the Securities Act.

We used the net proceeds from the offering of the 2027 Senior Notes, together with approximately $65.0 million in cash on hand, to redeem or prepay $625.0 million of our outstanding debt, consisting of (i) the outstanding $225.0 million principal amount of our 2023 Senior Notes, (ii) the outstanding $300.0 million principal amount of our 2024 Senior Notes and (iii) $100.0 million of the outstanding principal amount of senior secured term loans under the Credit Agreement, as well as to pay the related premiums and fees and expenses, excluding accrued interest, associated with such redemption and prepayment.

On December 18, 2019, HTUSA borrowed approximately $418.0 million aggregate principal amount of loans, or the December 2019 Refinancing Loans, pursuant to an amendment to our Credit Agreement. HTUSA used the proceeds of the December 2019 Refinancing Loans to repay the outstanding amounts under our prior term loans, which totaled approximately $418.0 million.

Following these transactions, our total aggregate outstanding principal amount of indebtedness was $1,418.0 million, a decrease of $575.0 million from $1,993.0 million at December 31, 2018.

For a more detailed description of our debt agreements, see Note 13, *Debt Agreements*, of the Notes to Consolidated Financial Statements, included in Item 1 of this Annual Report on Form 10-K.

We have a significant amount of debt outstanding on a consolidated basis. This substantial level of debt could have important consequences to our business, including, but not limited to: making it more difficult for us to satisfy our obligations; requiring a substantial portion of our cash flows from operations to be dedicated to the payment of principal and interest on our indebtedness, therefore reducing our ability to use our cash flows to fund acquisitions, capital expenditures, and future business opportunities; limiting our ability to obtain additional financing, including borrowing additional funds; increasing our vulnerability to, and reducing our flexibility to respond to, general adverse economic and industry conditions; limiting our flexibility in planning for, or reacting to, changes in our business and the industry in which we operate; and placing us at a disadvantage as compared to our competitors, to the extent that they are not as highly leveraged. We may not be able to generate sufficient cash to service all of our indebtedness and may be forced to take other actions to satisfy our obligations under our indebtedness.

In addition, the indenture governing our 2027 Senior Notes and our Credit Agreement impose various covenants that limit our ability and/or our restricted subsidiaries' ability to, among other things, pay dividends or distributions, repurchase equity, prepay junior debt and make certain investments, incur additional debt and issue certain preferred stock, incur liens on assets, engage in certain asset sales or merger transactions, enter into transactions with affiliates, designate subsidiaries as unrestricted subsidiaries; and allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to us.

Sources and Uses of Cash

The following table provides a summary of our cash position and cash flows for the years ended December 31, 2019, 2018 and 2017 (in thousands):

	For the Years Ended December 31,		
	2019	2018	2017
Cash, cash equivalents and restricted cash	$ 1,080,039	$ 962,117	$ 757,897
Cash provided by (used in):			
Operating activities	426,332	194,543	284,340
Investing activities	(17,857)	27,653	(102,185)
Financing activities	(290,446)	(16,596)	54,276

Operating Cash Flows

During the years ended December 31, 2019, 2018 and 2017, net cash provided by operating activities was $426.3 million, $194.5 million and $284.3 million, respectively.

Net cash provided by operating activities during the year ended December 31, 2019 was primarily attributable to cash collections from gross sales, partially offset by payments made related to patient assistance programs and commercial rebates for our inflammation segment medicines, and payments related to selling, general and administrative expenses and research and development expenses. Operating cash flow was also used to fund interest on outstanding debt of $78.0 million.

Net cash provided by operating activities during the year ended December 31, 2018 was primarily attributable to cash collections from net sales, net of operating expenses. Operating cash flow was also used to fund interest on outstanding debt of $112.5 million and income taxes of $53.1 million.

Net cash provided by operating activities during the year ended December 31, 2017 was primarily attributable to cash collections from net sales. Cash provided by operating activities was negatively impacted during the year ended December 31, 2017 by cash payments of $113.8 million for interest, $32.5 million outlay for the remaining 50 percent of the litigation settlement amount with Express Scripts, cash payments of $54.0 million for acquisition/divestiture-related costs, cash payments relating to term loan refinancing of $9.1 million, cash payments related to the discontinuation of the FA program of $7.2 million, cash payments relating to our drug substance harmonization program of $5.2 million and cash payments related to our restructuring and realignment activities of $4.7 million.

Investing Cash Flows

During the years ended December 31, 2019 and 2017, net cash used in investing activities was $17.9 million and $102.2 million, respectively. During the year ended December 31, 2018, net cash provided by investing activities was $27.7 million.

Net cash used in investing activities during the year ended December 31, 2019, was primarily attributable to the purchases of property and equipment of $17.9 million and an escrow deposit payment of $6.0 million related to the purchase of the Deerfield campus, partially offset by proceeds from the MIGERGOT transaction of $6.0 million.

Net cash provided by investing activities during the year ended December 31, 2018, was primarily attributable to proceeds from the sale of assets during the year, including cash proceeds of $35.0 million following the sale of rights to RAVICTI and AMMONAPS outside of North America and Japan to Immedica and cash proceeds of $9.5 million following the IMUKIN sale. This was partially offset by $12.0 million we paid to MedImmune to license HZN-003 (formerly MEDI4945).

Net cash used in investing activities during the year ended December 31, 2017, was primarily associated with $144.9 million of payments for the acquisition of River Vision, net of cash acquired, and associated transaction costs, and $22.3 million relating to the payment for certain rights for interferon gamma-1b. This was partially offset by $69.4 million of proceeds received from the Chiesi divestiture, net of cash divested.

Financing Cash Flows

During the years ended December 31, 2019 and 2018, net cash used in financing activities was $290.5 million and $16.6 million, respectively. During the year ended December 31, 2017, net cash provided by financing activities was $54.3 million.

Net cash used in financing activities during the year ended December 31, 2019, was primarily attributable to the net repayment of $400.0 million of the outstanding principal amount of term loans under our Credit Agreement, the repayment of the outstanding principal amount of our 2023 Senior Notes and 2024 Senior Notes of $775.0 million and related early redemption premiums of $39.5 million, partially offset by net proceeds from the issuance of our 2027 Senior Notes of $590.1 million and net proceeds from the issuance of ordinary shares of $326.8 million.

Net cash used in financing activities during the year ended December 31, 2018, was primarily attributable to the repayment of term loans of $845.7 million, partially offset by $818.0 million in net proceeds from term loans. In June 2018, we made a mandatory prepayment of $23.5 million under our term loan facility. In October 2018, we refinanced our term loans without changing the principal amount outstanding.

Net cash provided by financing activities during the year ended December 31, 2017, was primarily attributable to the net proceeds of $1,693.5 million from term loans, offset in part by repayment of term loans of $1,622.8 million. We refinanced our term loans during March 2017 and October 2017. The March 2017 refinancing loans replaced the $394.0 million 2015 term loan facility and the $375.0 million 2016 incremental loan facility and the October 2017 refinancing loans replaced the October 2017 refinanced loans. The March 2017 amendment to the Credit Agreement resulted in an increase of $81.0 million of principal amount of our outstanding debt and the October 2017 refinancing loans did not result in any changes to the principal amount outstanding. Additionally, during the year ended December 31, 2017, we paid $20.0 million relating to milestones in connection with a contingent consideration liability assumed in our acquisition of Raptor.

Financial Condition as of December 31, 2019 compared to December 31, 2018

Accounts receivable, net. Accounts receivable, net, decreased $56.0 million, from $464.7 million as of December 31, 2018 to $408.7 million as of December 31, 2019. The decrease was due to lower gross sales of our medicines during the fourth quarter of 2019 when compared to the fourth quarter of 2018.

Prepaid expenses and other current assets. Prepaid expenses and other current assets increased $75.4 million, from $68.2 million as of December 31, 2018 to $143.6 million as of December 31, 2019. The increase was primarily due to an increase in advance payments for inventory of $29.8 million, an increase in deferred charge for taxes on intra-company profits of $24.7 million and an increase in prepaid income taxes of $6.7 million.

Developed technology, net. Developed technology, net, decreased $246.8 million, from $1,945.6 million as of December 31, 2018 to $1,698.8 million as of December 31, 2019. The decrease was due to the amortization of developed technology of $230.4 million during the year ended December 31, 2019 and the recording of a reduction in the net book value of $17.0 million related to the MIGERGOT transaction.

Deferred Tax Assets, net. Deferred tax assets, net, increased $552.0 million from $3.1 million as of December 31, 2018 to $555.2 million as of December 31, 2019. This was primarily attributable to the recognition of a $553.3 million deferred tax asset resulting from an intra-company transfer of intellectual property assets to an Irish subsidiary.

Other assets. Other assets increased $39.3 million, from $9.0 million as of December 31, 2018 to $48.3 million as of December 31, 2019. Upon adoption of Accounting Standards Update No. 2016-02, Leases (Topic 842), or ASU No. 2016-02, on January 1, 2019, we established $38.0 million of liabilities and corresponding lease assets of $36.0 million on the consolidated balance sheet for leases, primarily related to operating leases on rented office properties, that existed as of the January 1, 2019, adoption date.

Accrued expenses. Accrued expenses increased $19.5 million, from $215.7 million as of December 31, 2018 to $235.2 million as of December 31, 2019. This was primarily due to an increase in allowance for returns of $6.0 million, payroll-related expenses of $6.0 million and accrued interest of $5.5 million.

Accrued trade discounts and rebates. Accrued trade discounts and rebates increased $8.6 million, from $457.8 million as of December 31, 2018 to $466.4 million as of December 31, 2019. This was primarily due to an increase of $39.3 million in accrued government rebates and chargebacks offset by a $15.8 million decrease in co-pay and other patient assistance costs and a $14.8 million decrease in accrued commercial rebates and wholesaler fees.

Long-term debt, net of current. Long-term debt, net of current decreased $563.2 million from $1,564.5 million as of December 31, 2018 to $1,001.3 million as of December 31, 2019. The decrease was primarily related to the repayment of $400.0 million of the outstanding principal amount of our term loans and the repayment of our 2023 Senior Notes and 2024 Senior Notes. See Note 13, *Debt Agreements*, of the Notes to Consolidated Financial Statements, included in Item 1 of this Annual Report on Form 10-K for further detail.

Deferred tax liabilities, net. Deferred tax liabilities, net, decreased $13.6 million, from $107.8 million as of December 31, 2018 to $94.2 million as of December 31, 2019. The decrease was primarily due to the U.S. federal and state tax credits generated during 2019 of $10.5 million and the decrease in state effective tax rate on the U.S. group net deferred tax liabilities of $1.5 million.

Other long-term liabilities. Other long-term liabilities increased $41.6 million, from $38.7 million as of December 31, 2018 to $80.3 million as of December 31, 2019. This was primarily due to $46.5 million related to long-term lease liabilities as of December 31, 2019. Upon adoption of ASU No. 2016-02 on January 1, 2019, we established $38.0 million of liabilities and corresponding lease assets of $36.0 million on the consolidated balance sheet for leases, primarily related to operating leases on rented office properties, that existed as of the January 1, 2019, adoption date.

Contractual Obligations

As of December 31, 2019, minimum future cash payments due under contractual obligations, including, among others, our debt agreements, purchase agreements with third-party manufacturers and non-cancelable operating lease agreements, were as follows (in thousands):

	2020	2021	2022	2023	2024	2025 & Thereafter	Total
Debt agreements – principal [1]	$ —	$ —	$ 400,000	$ —	$ —	$ 1,018,026	$ 1,418,026
Debt agreements - interest [1]	61,697	60,832	55,832	49,253	50,880	124,062	402,556
Purchase commitments [2]	88,754	40,298	10,169	10,266	7,155	10,000	166,642
Operating lease obligations [3]	7,804	7,116	5,940	5,867	6,485	39,607	72,819
Total contractual cash obligations	**$ 158,255**	**$ 108,246**	**$ 471,941**	**$ 65,386**	**$ 64,520**	**$ 1,191,695**	**$ 2,060,043**

(1) Represents the minimum contractual obligation due under the following debt agreements:

- $418.0 million under the December 2019 Refinancing Loans, which includes estimated monthly interest payments based on the applicable interest rate at December 31, 2019 of 3.94% and repayment of the remaining principal in May 2026. In June 2018, we repaid $23.5 million under the mandatory prepayment provisions of the Credit Agreement. In March 2019, we completed the repayment of $300.0 million of our outstanding principal amount of term loans under the Credit Agreement following the closing of our underwritten public equity offering. In July 2019, we repaid an additional $100.0 million of our term loans under the Credit Agreement. Following these repayments, our outstanding principal balance of term loans under the Credit Agreement was $418.0 million and we are not required to pay any further quarterly installments.
- $600.0 million 2027 Senior Notes, which includes bi-annual interest payments and repayment of the principal in August 2027.
- $400.0 million Exchangeable Senior Notes, which includes bi-annual interest payments and repayment of the principal in March 2022.

(2) These amounts reflect the following purchase commitments with our third-party manufacturers:

- Purchase commitment for TEPEZZA drugs substance with AGC Biologics A/S to be delivered through the second half of 2021. Purchase commitments with Catalent Indiana, LLC for TEPEZZA drug product to be delivered through December 2020.
- Purchase commitment for PROCYSBI through March 2020.
- Minimum annual order quantities required to be placed with Boehringer Ingelheim for final packaged ACTIMMUNE through July 2024 and additional units we also committed to purchase which were intended to cover anticipated demand if the results of the FA program of ACTIMMUNE for the treatment of FA had been successful. As of December 31, 2019, the minimum binding purchase commitment to Boehringer Ingelheim Biopharmaceuticals GmbH, or Boehringer Ingelheim Biopharmaceuticals, was $15.6 million (converted using a Dollar-to-Euro exchange rate of 1.1215) through July 2024.
- A commitment to spend $0.7 million with Boehringer Ingelheim related to the harmonization of the manufacturing process for ACTIMMUNE drug substance.
- Minimum purchase commitment for KRYSTEXXA through 2026.
- Minimum purchase commitment for RAYOS tablets from Jagotec AG through December 2023.

- At December 31, 2019, the minimum purchase commitment based on tablet pricing in effect under the agreement was $2.0 million through March 2020. Purchase commitment for final packaged PENNSAID 2% from Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.) through March 2020.
- Purchase commitment for final packaged DUEXIS tablets from Sanofi-Aventis U.S. through June 2020.
- Purchase commitment for RAVICTI, BUPHENYL and QUINSAIR outstanding at December 31, 2019.

(3) These amounts reflect payments due under our operating leases, which are principally for our facilities. For further details regarding these properties, see Item 2 of Part I, *Properties*, of this Annual Report on Form 10-K.

The above table does not include details of an agreement to lease entered into on October 14, 2019, relating to approximately 63,000 square feet of office space under construction in Dublin, Ireland. Lease commencement will begin when construction of the offices are completed by the lessor and we have access to begin the construction of leasehold improvements. We expect to incur leasehold improvement costs during 2020 and 2021 in order to prepare the building for occupancy.

As of December 31, 2019, our contingent liability for uncertain tax positions amounted to $27.4 million (excluding interest and penalties). Due to the nature and timing of the ultimate outcome of these uncertain tax positions, we cannot make a reasonably reliable estimate of the amount and period of related future payments, if any. Therefore, our contingent liability has been excluded from the above contractual obligations table. We do not expect a significant tax payment related to these obligations within the next year.

In addition to the obligations set out in the above table, we have assumed material obligations to make royalty and milestone payments to certain third parties on net sales of certain of our medicines. See Note 15 of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K, for details of these material obligations.

In February 2020, we purchased a three-building campus in Deerfield, Illinois, for total cash consideration of $115.0 million. The Deerfield campus totals 70 acres and consists of more than 650,000 square feet of office space. We expect to move to the Deerfield campus in the second half of 2020 and market our Lake Forest office for sub-lease. We expect to make significant capital expenditures during 2020 in order to prepare the Deerfield campus for occupancy.

OFF-BALANCE SHEET ARRANGEMENTS

Since our inception, we have not engaged in any off-balance sheet arrangements, including the use of structured finance, special purpose entities or variable interest entities, other than the indemnification agreements discussed in Note 15, *Commitments and Contingencies*, of the Notes to Consolidated Financial Statements, included in Item 1 of this Annual Report on Form 10-K.

CRITICAL ACCOUNTING POLICIES

The methods, estimates and judgments that we use in applying our critical accounting policies have a significant impact on the results that we report in our financial statements. Some of our accounting policies require us to make difficult and subjective judgments, often as a result of the need to make estimates regarding matters that are inherently uncertain.

We have identified the accounting policies and estimates listed below as those that we believe require management's most subjective and complex judgments in estimating the effect of inherent uncertainties. This section should also be read in conjunction with Note 2 in the Notes to our Consolidated Financial Statements included in this report, which includes a discussion of these and other significant accounting policies.

Revenue Recognition

In the United States, we sell our medicines primarily to wholesale distributors, specialty distributors and specialty pharmacy providers. In other countries, we sell our medicines primarily to wholesale distributors and other third-party distribution partners. These customers subsequently resell our medicines to health care providers and patients. In addition, we enter into arrangements with health care providers and payers that provide for government-mandated or privately negotiated discounts and allowances related to our medicines. Revenue is recognized when performance obligations under the terms of a contract with a customer are satisfied. The majority of our contracts have a single performance obligation to transfer medicines. Accordingly, revenues from medicine sales are recognized when the customer obtains control of our medicines, which occurs at a point in time, typically upon delivery to the customer. Revenue is measured as the amount of consideration we expect to receive in exchange for transferring medicines and is generally based upon a list or fixed price less allowances for medicine returns, rebates and discounts. We sell our medicines to wholesale pharmaceutical distributors and pharmacies under agreements with payment terms typically less than 90 days. Our process for estimating reserves established for these variable consideration components does not differ materially from our historical practices.

Medicine Sales Discounts and Allowances

The nature of our contracts gives rise to variable consideration because of allowances for medicine returns, rebates and discounts. Allowances for medicine returns, rebates and discounts are recorded at the time of sale to wholesale pharmaceutical distributors and pharmacies. We apply significant judgments and estimates in determining some of these allowances. If actual results differ from our estimates, we will be required to make adjustments to these allowances in the future. Our adjustments to gross sales are discussed further below.

Commercial Rebates

We participate in certain commercial rebate programs. Under these rebate programs, we pay a rebate to the commercial entity or third-party administrator of the program. We calculate accrued commercial rebate estimates using the expected value method. We accrue estimated rebates based on contract prices, estimated percentages of medicine that will be prescribed to qualified patients and estimated levels of inventory in the distribution channel and record the rebate as a reduction of revenue. Accrued commercial rebates are included in “accrued trade discounts and rebates” on the consolidated balance sheet.

Co-pay and Other Patient Assistance Programs

We offer discount card and other programs such as our HorizonCares program to patients under which the patient receives a discount on his or her prescription. In certain circumstances when a patient’s prescription is rejected by a managed care vendor, we will pay for the full cost of the prescription. We reimburse pharmacies for this discount through third-party vendors. We reduce gross sales by the amount of actual co-pay and other patient assistance in the period based on invoices received. We also record an accrual to reduce gross sales for estimated co-pay and other patient assistance on units sold to distributors that have not yet been prescribed/dispensed to a patient. We calculate accrued co-pay and other patient assistance costs using the expected value method. The estimate is based on contract prices, estimated percentages of medicine that will be prescribed to qualified patients, average assistance paid based on reporting from the third-party vendors and estimated levels of inventory in the distribution channel. Accrued co-pay and other patient assistance costs are included in “accrued trade discounts and rebates” on the consolidated balance sheet.

Sales Returns

Consistent with industry practice, we maintain a return policy that allows customers to return certain medicines within a specified period prior to and subsequent to the medicine expiration date. Generally, medicines may be returned for a period beginning six months prior to its expiration date and up to one year after its expiration date. The right of return expires on the earlier of one year after the medicine expiration date or the time that the medicine is dispensed to the patient. The majority of medicine returns result from medicine dating, which falls within the range set by our policy, and are settled through the issuance of a credit to the customer. We calculate sales returns using the expected value method. The estimate of the provision for returns is based upon our historical experience with actual returns. The return period is known to us based on the shelf life of medicines at the time of shipment. We record sales returns in “accrued expenses” and as a reduction of revenue.

Government Rebates

We participate in certain government rebate programs such as Medicare Coverage Gap and Medicaid. We calculate accrued government rebate estimates using the expected value method. We accrue estimated rebates based on percentages of medicine prescribed to qualified patients, estimated rebate percentages and estimated levels of inventory in the distribution channel that will be prescribed to qualified patients and record the rebates as a reduction of revenue. Accrued government rebates are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Chargebacks

We provide discounts to government qualified entities with whom we have contracted. These entities purchase medicines from the wholesale pharmaceutical distributors at a discounted price and the wholesale pharmaceutical distributors then charge back to us the difference between the current retail price and the contracted price that the entities paid for the medicines. We calculate accrued chargeback estimates using the expected value method. We accrue estimated chargebacks based on contract prices, sell-through sales data obtained from third-party information and estimated levels of inventory in the distribution channel and record the chargeback as a reduction of revenue. Accrued chargebacks are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Intangible Assets

Definite-lived intangible assets are amortized over their estimated useful lives. We review our intangible assets when events or circumstances may indicate that the carrying value of these assets is not recoverable and exceeds their fair value. We measure fair value based on the estimated future discounted cash flows associated with our assets in addition to other assumptions and projections that we deem to be reasonable and supportable. The estimated useful lives, from the date of acquisition, for all identified intangible assets that are subject to amortization are between five and thirteen years.

Goodwill

Goodwill represents the excess of the purchase price of acquired businesses over the estimated fair value of the identifiable net assets acquired. Goodwill is not amortized but is tested for impairment at least annually at the reporting unit level or more frequently if events or changes in circumstances indicate that the asset might be impaired. Impairment loss, if any, is recognized based on a comparison of the fair value of the asset to its carrying value, without consideration of any recoverability. We test goodwill for impairment annually during the fourth quarter and whenever indicators of impairment exist by first assessing qualitative factors to determine whether it is more likely than not that the fair value is less than its carrying amount. If we conclude it is more likely than not that the fair value of a reporting unit is less than its carrying amount, a quantitative impairment test is performed. If we conclude that goodwill is impaired, we will record an impairment charge in our consolidated statement of comprehensive income (loss).

Provision for Income Taxes

We account for income taxes based upon an asset and liability approach. Deferred tax assets and liabilities represent the future tax consequences of the differences between the financial statement carrying amounts of assets and liabilities versus the tax basis of assets and liabilities. Under this method, deferred tax assets are recognized for deductible temporary differences, and operating loss and tax credit carryforwards. Deferred tax liabilities are recognized for taxable temporary differences. Deferred tax assets are reduced by a valuation allowance when, in the opinion of management, it is more likely than not that some portion or all of the deferred tax assets will not be realized. Significant judgment is required in determining whether it is probable that sufficient future taxable income will be available against which a deferred tax asset can be utilized. In determining future taxable income, we are required to make assumptions including the amount of taxable income in the various jurisdictions in which we operate. These assumptions require significant judgment about forecasts of future taxable income. Actual operating results in future years could render our current assumption of recoverability of deferred tax assets inaccurate. The impact of tax rate changes on deferred tax assets and liabilities is recognized in the period that the change is enacted. From time to time, we execute intra-company transactions in response to changes in operations, regulations, tax laws, funding needs and other circumstances. These transactions require the interpretation and application of tax laws in the applicable jurisdiction to support the tax treatment taken. The valuations which support the tax treatment of the transactions require significant estimates and assumptions within discounted cash flow models. We also account for the uncertainty in income taxes by utilizing a comprehensive model for the recognition, measurement, presentation and disclosure in financial statements of any uncertain tax positions that have been taken or are expected to be taken on an income tax return. Deferred tax assets and deferred tax liabilities are netted by each tax-paying entity within each jurisdiction in our consolidated balance sheets.

Share-Based Compensation

We account for employee share-based compensation by measuring and recognizing compensation expense for all share-based payments based on estimated grant date fair values. We use the straight-line method to allocate compensation cost to reporting periods over each awardee's requisite service period, which is generally the vesting period. If an award includes both a service condition and a market or performance condition, the graded vesting method is used to allocate compensation cost to reporting periods. We adopted ASU No. 2016-09 on January 1, 2017 and elected to retain a forfeiture rate after adoption.

New Accounting Pronouncements Impacting Critical Accounting Policies

Refer to Note 2 in the Notes to our Consolidated Financial Statements included in this report, which includes a discussion of the new accounting pronouncements impacting critical accounting policies.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

We are exposed to various market risks, which include potential losses arising from adverse changes in market rates and prices, such as interest rates and foreign exchange fluctuations. We do not enter into derivatives or other financial instruments for trading or speculative purposes.

Interest Rate Risk. We are subject to interest rate fluctuation exposure through our borrowings under the Credit Agreement and our investment in money market accounts which bear a variable interest rate. Term loans under the Credit Agreement bear interest, at our option, at a rate equal to the London Inter-Bank Offered Rate, or LIBOR, plus 2.25% per annum (subject to a 0.00% LIBOR floor), or the adjusted base rate plus 1.25% per annum with a step-down to LIBOR plus 2.00% per annum or the adjusted base rate plus 1.00% per annum at the time our leverage ratio is less than or equal to 2.00 to 1.00. The adjusted base rate is defined as the greatest of (a) LIBOR (using one-month interest period) plus 1.00%, (b) the prime rate, (c) the federal funds rate plus 0.50%, and (d) 1.00%. The loans under the Revolving Credit Facility bear interest, at our option, at a rate equal to either LIBOR plus an applicable margin of 2.25% per annum (subject to a LIBOR floor of 0.00%), or the adjusted base rate plus 1.25% per annum with a step-down to LIBOR plus 2.00% per annum or the adjusted base rate plus 1.00% per annum at the time our leverage ratio is less than or equal to 2.00 to 1.00. Our approximately $418.0 million of senior secured term loans under the Credit Agreement is based on LIBOR. As of December 31, 2019, the Revolving Credit Facility was undrawn. The one-month LIBOR rate as of February 6, 2020, which was the most recent date the interest rate on the term loan was fixed, was 1.69%, and as a result, the interest rate on our borrowings is currently 3.94% per annum. Because the United Kingdom Financial Conduct Authority, which regulates LIBOR, intends to phase out the use of LIBOR by the end of 2021, future borrowings under our Credit Agreement could be subject to reference rates other than LIBOR.

An increase in the LIBOR of 100 basis points above the current LIBOR rate would increase our interest expense related to the Credit Agreement by $4.2 million per year.

The goals of our investment policy are to preserve capital, fulfill liquidity needs and maintain fiduciary control of cash. To achieve our goal of maximizing income without assuming significant market risk, we maintain our excess cash and cash equivalents in money market funds. Because of the short-term maturities of our cash equivalents, we do not believe that a decrease in interest rates would have any material negative impact on the fair value of our cash equivalents.

Foreign Currency Risk. Our purchase costs of TEPEZZA drug substance and ACTIMMUNE inventory are principally denominated in Euros and are subject to foreign currency risk. We have contracts relating to RAVICTI, QUINSAIR and PROCYSBI for sales in Canada which sales are subject to foreign currency risk. We also incur certain operating expenses in currencies other than the U.S. dollar in relation to our Irish operations and foreign subsidiaries. Therefore, we are subject to volatility in cash flows due to fluctuations in foreign currency exchange rates, particularly changes in the Euro and the Canadian dollar.

Inflation Risk. We do not believe that inflation has had a material impact on our business or results of operations during the periods for which the consolidated financial statements are presented in this report.

Credit Risk. Historically, our accounts receivable balances have been highly concentrated with a select number of customers, consisting primarily of large wholesale pharmaceutical distributors who, in turn, sell the medicines to pharmacies, hospitals and other customers. As of December 31, 2019 and 2018, our top four customers accounted for approximately 84% and 85%, respectively, of our total outstanding accounts receivable balances.

Item 8. Financial Statements and Supplementary Data

The financial information required by Item 8 is contained in Part IV, Item 15 of this Annual Report on Form 10-K.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our Chief Executive Officer and Chief Financial Officer, after evaluating the effectiveness of our “disclosure controls and procedures” (as defined in Rule 13a-15(e) promulgated under the Securities Exchange Act of 1934, as amended, or the Exchange Act), have concluded that, as of December 31, 2019, our disclosure controls and procedures were effective to provide reasonable assurance that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the Securities and Exchange Commission’s rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by an issuer in the reports that it files or submits under the Exchange Act is accumulated and communicated to the issuer’s management, including its principal executive officer or officers and principal financial officer or officers, or persons performing similar functions, as appropriate to allow timely decisions regarding required disclosure.

Management’s Report on Internal Control over Financial Reporting

Our management, under the supervision of our chief executive officer and our chief financial officer, is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined under Rule 13a-15(f) of the Exchange Act. Internal control over financial reporting is designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate. Therefore, even those systems determined to be effective can provide only reasonable assurance with respect to financial statement preparation and presentation.

Our management has assessed the effectiveness of our internal control over financial reporting as of December 31, 2019. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in *Internal Control – Integrated Framework (2013)*. Management's assessment included an evaluation of the design of our internal control over financial reporting and testing of the operational effectiveness of our internal control over financial reporting. Based on management's assessment, management has concluded that, as of December 31, 2019, our internal control over financial reporting was effective based on those criteria.

The effectiveness of our internal control over financial reporting as of December 31, 2019, has been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm, as stated in their report which appears herein.

Changes in Internal Control Over Financial Reporting

There have been no material changes to our internal control over financial reporting, as defined in Exchange Act Rules 13a-15(f) and 15d-15(f), during the three months ended December 31, 2019, that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The information required by this item is incorporated herein by reference to our definitive Proxy Statement to be filed in connection with our 2020 Annual General Meeting of Shareholders, or our 2020 Proxy Statement, which will be filed with the Securities and Exchange Commission within 120 days after December 31, 2019.

We have adopted a written Code of Business Conduct and Ethics, or Ethics Code, that applies to all officers, directors and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. The Ethics Code is available on our website at www.horizontherapeutics.com. If we make any substantive amendments to the Ethics Code or grant any waiver from a provision of the Ethics Code to any executive officer or director, we will promptly disclose the nature of the amendment or waiver on our website or in a Current Report on Form 8-K.

Item 11. Executive Compensation

The information required by this item is incorporated herein by reference to our 2020 Proxy Statement.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this item is incorporated herein by reference to our 2020 Proxy Statement.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this item is incorporated herein by reference to our 2020 Proxy Statement.

Item 14. Principal Accounting Fees and Services

The information required by this item is incorporated herein by reference to our 2020 Proxy Statement.

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a) Documents filed as part of this report.

1. Financial Statements

The financial statements listed on the Index to Consolidated Financial Statements F-1 to F-60 are filed as part of this Annual Report on Form 10-K.

2. Financial Statement Schedules

Schedule II – Valuation and Qualifying Accounts and Reserves for each of the three fiscal years ended December 31, 2019, 2018 and 2017 appearing on page F-61. Other financial statement schedules have been omitted because the required information is included in the consolidated financial statements or notes thereto or because they are not applicable or not required.

3. Exhibits

INDEX TO EXHIBITS

Exhibit Number	Description of Document
3.1	Memorandum and Articles of Association of Horizon Therapeutics Public Limited Company, as amended (incorporated by reference to Exhibit 3.1 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on May 8, 2019).
4.1	Indenture, dated March 13, 2015, by and among Horizon Therapeutics Public Limited Company, Horizon Therapeutics Investment Limited and U.S. Bank National Association (incorporated by reference to Exhibit 4.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on March 13, 2015).
4.2	Form of 2.50% Exchangeable Senior Note due 2022 (incorporated by reference to Exhibit 4.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on March 13, 2015).
4.3	Rights Agreement, dated as of February 28, 2019, by and between Horizon Therapeutics Public Limited Company and Computershare Trust Company, N.A. (incorporated by reference to Exhibit 4.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on February 28, 2019).
4.4	Indenture dated as of July 16, 2019 by and between Horizon Therapeutics USA, Inc., the guarantors party thereto and U.S. Bank National Association, as trustee (incorporated by reference to Exhibit 4.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on July 16, 2019).
4.5	Form of 5.500% Senior Note due 2027 (incorporated by reference to Exhibit 4.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on July 16, 2019).
4.6	Description of securities registered under Section 12 of the Exchange Act of 1934.
10.1+	Form of Indemnification Agreement entered into by and between Horizon Therapeutics Public Limited Company and certain of its directors, officers and employees (incorporated by reference to Exhibit 10.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on September 19, 2014).
10.2+	Form of Indemnification Agreement entered into by and between Horizon Therapeutics USA, Inc. and certain directors, officers and employees of Horizon Therapeutics Public Limited Company (incorporated by reference to Exhibit 10.2 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on September 19, 2014).
10.3+	Horizon Therapeutics Public Limited Company Non-Employee Director Compensation Policy, as amended (incorporated by reference to Exhibit 10.5 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2019).
10.4+**	Horizon Therapeutics USA, Inc. 2005 Stock Plan and Form of Stock Option Agreement thereunder (incorporated by reference to Exhibit 10.2 to Horizon Therapeutics, Inc.'s Registration Statement on Form S-1 (No. 333-168504), as amended).
10.5+**	Horizon Therapeutics USA, Inc. 2011 Equity Incentive Plan, as amended, and Form of Option Agreement and Form of Stock Option Grant Notice thereunder (incorporated by reference to Exhibit 99.1 to Horizon Therapeutics, Inc.'s Current Report on Form 8-K, filed on July 2, 2014).
10.6+	Horizon Therapeutics Public Limited Company Amended and Restated 2014 Equity Incentive Plan and Form of Option Agreement, Form of Stock Option Grant Notice, Forms of Restricted Stock Unit Agreement and Forms of Restricted Stock Unit Grant Notice thereunder (incorporated by reference to Exhibit 10.7 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on May 8, 2019).

10.7+	Horizon Therapeutics Public Limited Company 2014 Non-Employee Equity Plan, as amended, and Form of Option Agreement, Form of Stock Option Grant Notice, Forms of Restricted Stock Unit Agreement and Forms of Restricted Stock Unit Grant Notice thereunder (incorporated by reference to Exhibit 10.8 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on May 8, 2019).
10.8+	Horizon Therapeutics Public Limited Company 2014 Employee Share Purchase Plan, as amended (incorporated by reference to Exhibit 99.2 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on May 4, 2016).
10.9+	Form of Employee Proprietary Information and Inventions Agreement (incorporated by reference to Exhibit 10.15 to Horizon Pharma, Inc.'s Registration Statement on Form S-1 (No. 333-168504), as amended).
10.10+	Amended and Restated Executive Employment Agreement, dated July 27, 2010, by and between Horizon Therapeutics USA, Inc. and Timothy Walbert (incorporated by reference to Exhibit 10.22 to Horizon Pharma, Inc.'s Registration Statement on Form S-1 (No. 333-168504), as amended).
10.11*	Manufacturing and Supply Agreement, dated May 25, 2011, by and between Horizon Therapeutics USA, Inc. and Sanofi-Aventis U.S. LLC (incorporated by reference to Exhibit 10.35 to Horizon Pharma, Inc.'s Registration Statement on Form S-1 (No. 333-168504), as amended).
10.12*	Amendment to Manufacturing and Supply Agreement, effective as of September 25, 2013, by and between Horizon Therapeutics USA, Inc. and Sanofi-Aventis U.S. LLC (incorporated by reference to Exhibit 10.3 to Horizon Pharma, Inc.'s Quarterly Report on Form 10-Q, filed on November 8, 2013).
10.13+	First Amendment to Amended and Restated Executive Employment Agreement, dated January 16, 2014, by and between Horizon Therapeutics USA, Inc. and Timothy Walbert (incorporated by reference to Exhibit 99.1 to Horizon Pharma, Inc.'s Current Report on Form 8-K, filed on January 16, 2014).
10.14+	Executive Employment Agreement, effective as of June 23, 2014, by and between Horizon Therapeutics USA, Inc. and Paul W. Hoelscher (incorporated by reference to Exhibit 99.4 to Horizon Pharma, Inc.'s Current Report on Form 8-K, filed on June 18, 2014).
10.15*	Supply Agreement, dated October 17, 2014, by and between Horizon Therapeutics Ireland DAC and Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.) (incorporated by reference to Exhibit 10.57 to Horizon Therapeutics Public Limited Company's Amendment No. 2 to Annual Report on Form 10-K, filed on April 10, 2015).
10.16*	License Agreement for Interferon Gamma, dated May 5, 1998, by and between Genentech, Inc. and Horizon Therapeutics Ireland DAC (as successor in interest to Connetics Corporation) (incorporated by reference to Exhibit 10.62 to Horizon Therapeutics Public Limited Company's Amendment No. 3 to Annual Report on Form 10-K, filed on May 26, 2017).
10.17	Amendment No. 1 to License Agreement for Interferon Gamma, dated December 28, 1998, by and between Genentech, Inc. and Horizon Therapeutics Ireland DAC (as successor in interest to Connetics Corporation) (incorporated by reference to Exhibit 10.63 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).
10.18*	Amendment No. 2 to License Agreement for Interferon Gamma, dated January 15, 1999, by and between Genentech, Inc. and Horizon Therapeutics Ireland DAC (as successor in interest to Connetics Corporation) (incorporated by reference to Exhibit 10.64 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).
10.19*	Amendment No. 3 to License Agreement for Interferon Gamma, dated April 27, 1999, by and between Genentech, Inc. and Horizon Therapeutics Ireland DAC (as successor in interest to Connetics Corporation) (incorporated by reference to Exhibit 10.65 to Horizon Therapeutics Public Limited Company's Amendment No. 3 to Annual Report on Form 10-K, filed on May 26, 2017).
10.20	Consent to Assignment Agreement, dated June 23, 2000 (Amendment No. 4), by and among Genentech, Inc., Connetics Corporation and Horizon Therapeutics Ireland DAC (as successor in interest to InterMune Pharmaceuticals, Inc.) (incorporated by reference to Exhibit 10.66 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).

10.21	Amendment No. 5 to License Agreement for Interferon Gamma, dated January 25, 2001, by and between Genentech, Inc. and Horizon Therapeutics Ireland DAC (as successor in interest to InterMune Pharmaceuticals, Inc.) (incorporated by reference to Exhibit 10.67 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).
10.22*	Amendment No. 6 to License Agreement for Interferon Gamma, dated February 27, 2006, by and between Genentech, Inc. and Horizon Therapeutics Ireland DAC (as successor in interest to InterMune, Inc.) (incorporated by reference to Exhibit 10.68 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).
10.23*	Amendment No. 7 to License Agreement for Interferon Gamma, dated December 17, 2013, by and between Genentech, Inc. and Horizon Therapeutics Ireland DAC (as successor in interest to Vidara Therapeutics International Public Limited Company) (incorporated by reference to Exhibit 10.69 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).
10.24+	Executive Employment Agreement, effective as of September 18, 2014, by and between Horizon Therapeutics USA, Inc. and Barry Moze (incorporated by reference to Exhibit 10.74 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2015).
10.25+	Horizon Therapeutics USA, Inc. Deferred Compensation Plan (incorporated by reference to Exhibit 10.30 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 28, 2018).
10.26+	Horizon Therapeutics Public Limited Company Equity Long-Term Incentive Program (incorporated by reference to Exhibit 10.2 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on May 8, 2015).
10.27+	Executive Employment Agreement, dated May 7, 2015, by and between Horizon Therapeutics USA, Inc. and Brian Beeler (incorporated by reference to Exhibit 10.4 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on May 8, 2015).
10.28	Credit Agreement, dated May 7, 2015, by and among Horizon Therapeutics USA, Inc., as borrower, Horizon Therapeutics Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 10.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on May 11, 2015).
10.29*	License Agreement, dated April 16, 1999, by and among Saul Brusilow, M.D., Brusilow Enterprises, Inc. and Horizon Therapeutics, LLC (as successor in interest to Medicis Pharmaceutical Corporation) (incorporated by reference to Exhibit 10.8 to Horizon Therapeutics Public Limited Company's Amendment No. 2 to Quarterly Report on Form 10-Q, filed on May 26, 2017).
10.30*	Settlement Agreement and First Amendment to License Agreement, dated August 21, 2007, by and among Saul Brusilow, M.D., Brusilow Enterprises, Inc., and Horizon Therapeutics, LLC (as successor in interest to Medicis Pharmaceutical Corporation and Ucyclyd Pharma, Inc.) (incorporated by reference to Exhibit 10.22 to Hyperion Therapeutics, Inc.'s Amendment No. 1 to the Registration Statement on Form S-1, filed on May 24, 2012).
10.31+	Horizon Therapeutics Public Limited Company Share Clog Program Trust Deed, as amended, and Form of Clog Letter (incorporated by reference to Exhibit 10.6 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on August 8, 2016).
10.32*	License Agreement, dated August 12, 1998, by and among Mountain View Pharmaceuticals, Inc., Duke University and Horizon Therapeutics Ireland DAC (as successor in interest to Bio-Technology General Corporation), as amended November 12, 2001, August 30, 2010, March 12, 2014 and July 16, 2015 (incorporated by reference to Exhibit 10.61 to Horizon Therapeutics Public Limited Company's Amendment No. 1 to Annual Report on Form 10-K, filed on May 26, 2017).

10.33*	Commercial Supply Agreement, dated March 20, 2007, by and between Horizon Therapeutics Ireland DAC (as successor in interest to Savient Pharmaceuticals, Inc.) and Bio-Technology General (Israel) Ltd., as amended September 24, 2007, January 24, 2009, July 1, 2010 and March 21, 2012 (incorporated by reference to Exhibit 10.62 to Horizon Therapeutics Public Limited Company's Amendment No. 1 to Annual Report on Form 10-K, filed on May 26, 2017).
10.34*	Supply Agreement, dated August 3, 2015, by and between NOF Corporation and Horizon Therapeutics Ireland DAC (as successor in interest to Crealta Pharmaceuticals LLC) (incorporated by reference to Exhibit 10.63 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 29, 2016).
10.35*	Asset Purchase Agreement, dated March 22, 2012, by and between Horizon Therapeutics, LLC (as successor in interest to Hyperion Therapeutics, Inc.) and Bausch Health Companies Inc. (formerly Ucyclyd Pharma, Inc.) (incorporated by reference to Exhibit 2.1 to Hyperion Therapeutics, Inc.'s Amendment No. 1 to the Registration Statement on Form S-1, filed on May 24, 2012).
10.36*	Amendment No. 1 to Supply Agreement, dated February 4, 2016, by and between Horizon Therapeutics Ireland DAC and Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.) (incorporated by reference to Exhibit 10.66 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 29, 2016).
10.37*	Commercial Supply Agreement, dated October 16, 2008, by and between Exelead, Inc. (formerly known as Sigma-Tau PharmaSource, Inc. (as successor in interest to Enzon Pharmaceuticals, Inc.)) and Horizon Therapeutics Ireland DAC (as successor in interest to Savient Pharmaceuticals, Inc.), as amended October 5, 2009, October 22, 2009 and July 29, 2014 (incorporated by reference to Exhibit 10.68 to Horizon Therapeutics Public Limited Company's Amendment No. 1 to Annual Report on Form 10-K, filed on May 26, 2017).
10.38*	Fifth Amendment to Commercial Supply Agreement, effective as of August 31, 2016, by and between Horizon Therapeutics Ireland DAC and Bio-Technology General (Israel) Ltd. (incorporated by reference to Exhibit 10.1 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on November 7, 2016).
10.39	Amendment No. 1, dated October 25, 2016, to Credit Agreement, dated May 7, 2015, by and among Horizon Therapeutics USA, Inc., as borrower, Horizon Therapeutics Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 99.1 to Horizon Therapeutics Public Limited Company's Amendment No. 1 to Current Report on Form 8-K, filed on October 25, 2016).
10.40*	API Supply Agreement, dated November 3, 2010, by and between Cambrex Profarmaco Milano and Horizon Therapeutics Ireland DAC (as successor in interest to Raptor Therapeutics Inc. and Raptor Pharmaceuticals Europe B.V.), as amended April 9, 2013 (incorporated by reference to Exhibit 10.4 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on November 7, 2016).
10.41*	Manufacturing Services Agreement, dated November 15, 2010, by and among Patheon Pharmaceuticals Inc., Horizon Orphan LLC (as successor in interest to Raptor Therapeutics Inc.) and Horizon Pharma Europe B.V. (as successor in interest to Raptor Pharmaceuticals Europe B.V.), as amended April 5, 2012 and June 21, 2013 (incorporated by reference to Exhibit 10.5 to Horizon Therapeutics Public Limited Company's Amendment No. 1 to Quarterly Report on Form 10-Q, filed on May 26, 2017).
10.42+	Horizon Therapeutics Public Limited Company Equity Long-Term Incentive Program (incorporated by reference to Exhibit 99.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on January 11, 2018).
10.43+	Horizon Therapeutics Public Limited Company Cash Incentive Program (incorporated by reference to Exhibit 99.2 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on January 11, 2018).

10.44+	Horizon Therapeutics Public Limited Company Incentive Compensation Recoupment Policy (incorporated by reference to Exhibit 99.4 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on January 11, 2018).
10.45+	Separation Agreement, dated January 23, 2020, by and between Horizon Therapeutics USA, Inc. and Shao-Lee Lin, M.D., Ph.D.
10.46+	Executive Employment Agreement, effective as of September 11, 2017, by and between Horizon Therapeutics USA, Inc. and Irina Konstantinovsky (incorporated by reference to Exhibit 10.2 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on November 6, 2017).
10.47	Amendment No. 2, dated March 29, 2017, to Credit Agreement, dated May 7, 2015, by and among Horizon Therapeutics USA, Inc., as Borrower, Horizon Therapeutics Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 99.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on March 30, 2017).
10.48	Amendment No. 3, dated October 23, 2017, to Credit Agreement, dated May 7, 2015, by and among Horizon Therapeutics USA, Inc., as Borrower, Horizon Therapeutics Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 99.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on October 23, 2017).
10.49*	Global Supply Agreement, dated June 30, 2017, by and between Horizon Therapeutics Ireland DAC and Boehringer Ingelheim Biopharmaceuticals GmbH (incorporated by reference to Exhibit 10.3 to Horizon Therapeutics Public Limited Company's Amendment No. 1 to Quarterly Report on Form 10-Q, filed on September 28, 2017).
10.50*	Amended and Restated License Agreement, dated May 31, 2017, by and between Horizon Orphan LLC and The Regents of the University of California (incorporated by reference to Exhibit 10.4 to Horizon Therapeutics Public Limited Company's Amendment No. 1 to Quarterly Report on Form 10-Q, filed on September 28, 2017).
10.51+	Amended and Restated Executive Employment Agreement, effective as of March 1, 2018, by and between Horizon Therapeutics USA, Inc. and Vikram Karnani (incorporated by reference to Exhibit 10.10 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on May 9, 2018).
10.52+	First Amendment to Executive Employment Agreement, dated May 4, 2017, by and between Horizon Therapeutics USA, Inc. and Paul W. Hoelscher (incorporated by reference to Exhibit 10.7 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2017).
10.53+	First Amendment to Executive Employment Agreement, dated May 4, 2017, by and between Horizon Therapeutics USA, Inc. and Barry Moze (incorporated by reference to Exhibit 10.8 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2017).
10.54+	First Amendment to Executive Employment Agreement, dated May 4, 2017, by and between Horizon Therapeutics USA, Inc. and Brian Beeler (incorporated by reference to Exhibit 10.9 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2017).
10.55+	Second Amendment to Amended and Restated Executive Employment Agreement, dated May 4, 2017, by and between Horizon Therapeutics USA, Inc. and Timothy Walbert (incorporated by reference to Exhibit 10.13 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2017).
10.56+	Executive Employment Agreement, effective as of February 16, 2017, by and between Horizon Therapeutics USA, Inc. and Michael DesJardin (incorporated by reference to Exhibit 10.68 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 28, 2018).

10.57+	First Amendment to Executive Employment Agreement, dated May 4, 2017, by and between Horizon Therapeutics USA, Inc. and Michael DesJardin (incorporated by reference to Exhibit 10.69 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 28, 2018).
10.58*	Second Amendment to Supply Agreement, dated January 1, 2017, by and between Horizon Therapeutics Ireland DAC and Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.) (incorporated by reference to Exhibit 10.71 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 28, 2018).
10.59*	Third Amendment to Supply Agreement, dated February 16, 2018, by and between Horizon Therapeutics Ireland DAC and Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.) (incorporated by reference to Exhibit 10.72 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 28, 2018).
10.60*	Confidential Settlement and License Agreement, effective as of June 27, 2018, by and among Horizon Therapeutics, LLC, Lupin Ltd. and Lupin Pharmaceuticals, Inc. (incorporated by reference to Exhibit 10.1 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on August 8, 2018).
10.61*	Letter Agreement, dated May 1, 2018, by and between Horizon Therapeutics USA, Inc. and Sanofi US Services, Inc. (incorporated by reference to Exhibit 10.2 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on August 8, 2018).
10.62*	Confidential Settlement and License Agreement, effective as of September 17, 2018, by and between Horizon Therapeutics, LLC and Par Pharmaceutical, Inc. (incorporated by reference to Exhibit 10.1 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on November 7, 2018).
10.63	Amendment No. 4, dated October 19, 2018, to Credit Agreement, dated May 7, 2015 (as amended by Amendment No. 1, dated October 25, 2016, Amendment No. 2, dated March 29, 2017 and Amendment No. 3, dated October 23, 2017), by and among Horizon Therapeutics USA, Inc., as Borrower, Horizon Therapeutics Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 99.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on October 19, 2018).
10.64*	Amendment No. 1 to Amended and Restated License Agreement, dated September 11, 2018, by and between Horizon Orphan LLC and The Regents of the University of California (incorporated by reference to Exhibit 10.3 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on November 7, 2018).
10.65+	Amended and Restated Executive Employment Agreement, effective as of August 1, 2018, by and between Horizon Therapeutics USA, Inc. and Geoffrey M. Curtis (incorporated by reference to Exhibit 10.69 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 27, 2019).
10.66	Amendment No. 5, dated March 11, 2019, to Credit Agreement, dated May 7, 2015 (as amended by Amendment No. 1, dated October 25, 2016, Amendment No. 2, dated March 29, 2017, Amendment No. 3, dated October 23, 2017, and Amendment No. 4, dated October 19, 2018), by and among Horizon Therapeutics USA, Inc., as Borrower, Horizon Therapeutics Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 99.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on March 11, 2019).
10.67+	Executive Employment Agreement, effective as of May 1, 2019, by and between Horizon Therapeutics USA, Inc. and Jeffery Kent, M.D., FACP, FACG (incorporated by reference to Exhibit 10.2 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on May 8, 2019).
10.68***	Commercial Supply Agreement, effective as of February 14, 2018, by and between CMC Biologics A/S, dba AGC Biologics and Horizon Therapeutics Ireland DAC (incorporated by reference to Exhibit 10.3 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on May 8, 2019).

10.69***	Commercial Supply Agreement, effective as of December 18, 2018, by and between Catalent Indiana, LLC and Horizon Therapeutics Ireland DAC (incorporated by reference to Exhibit 10.4 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on May 8, 2019).
10.70***	License Agreement, effective as of June 15, 2011, by and among F. Hoffmann-La Roche Ltd, Hoffman-La Roche Inc. and Horizon Therapeutics Ireland DAC (as successor in interest to River Vision Development Corp), as amended through Amendment No. 9 to the License Agreement, effective as of October 21, 2016.
10.71***	Exclusive License Agreement, dated December 5, 2012, by and between Lundquist Institute (formerly known as Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center) and Horizon Therapeutics Ireland DAC (as successor in interest to River Vision Development Corp) (incorporated by reference to Exhibit 10.6 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on May 8, 2019).
10.72	Amendment No. 6, dated May 22, 2019, to Credit Agreement, dated May 7, 2015 (as amended by Amendment No. 1, dated October 25, 2016, Amendment No. 2, dated March 29, 2017, Amendment No. 3, dated October 23, 2017, Amendment No. 4, dated October 19, 2018 and Amendment No. 5, dated March 11, 2019), by and among Horizon Therapeutics USA, Inc., as Borrower, Horizon Therapeutics Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 99.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on May 22, 2019).
10.73***	Amendment No. 1 to Commercial Supply Agreement, dated May 15, 2019, by and between AGC Biologics A/S (formerly known as CMC Biologics A/S) and Horizon Therapeutics Ireland DAC (incorporated by reference to Exhibit 10.6 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2019).
10.74***	Mutual Settlement, Release and Media License Agreement, effective as of December 21, 2016, by and between Horizon Therapeutics Ireland DAC (as successor in interest to River Vision Development Corp). and Boehringer Ingelheim Biopharmaceuticals GmbH (incorporated by reference to Exhibit 10.1 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on November 6, 2019).
10.75+	Release and Waiver of Claims of Robert F. Carey, dated as of September 18, 2019 (incorporated by reference to Exhibit 10.2 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on November 6, 2019).
10.76+	Executive Employment Agreement, effective as of November 1, 2019, by and among Horizon Therapeutics Public Limited Company, Horizon Therapeutics USA, Inc. and Andy Pasternak (incorporated by reference to Exhibit 10.3 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on November 6, 2019).
10.77	Amendment No. 7, dated December 18, 2019, to Credit Agreement, dated May 7, 2015 (as amended by Amendment No. 1, dated October 25, 2016, Amendment No. 2, dated March 29, 2017, Amendment No. 3, dated October 23, 2017, Amendment No. 4, dated October 19, 2018, Amendment No. 5, dated March 11, 2019 and Amendment No. 6, dated May 22, 2019), by and among Horizon Therapeutics USA, Inc., as Borrower, Horizon Therapeutics Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 99.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on December 18, 2019).
10.78***	Amendment No. 2 to Commercial Supply Agreement, dated December 18, 2019, by and between AGC Biologics A/S (formerly known as CMC Biologics A/S) and Horizon Therapeutics Ireland DAC.
10.79	Amendment No. 2 to API Supply Agreement, effective as of January 17, 2018, by and between Cambrex Profarmaco Milano and Horizon Therapeutics Ireland DAC.
10.80***	Amendment to Supply Agreement, effective as of November 30, 2018, by and between NOF Corporation and Horizon Therapeutics Ireland DAC.

21.1	Subsidiaries of Horizon Therapeutics Public Limited Company.
23.1	Consent of PricewaterhouseCoopers LLP, independent registered public accounting firm.
24.1	Power of Attorney. Reference is made to the signature page hereto.
31.1	Certification of Principal Executive Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Exchange Act.
31.2	Certification of Principal Financial Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Exchange Act.
32.1	Certification of Principal Executive Officer pursuant to Rule 13a-14(b) or 15d-14(b) of the Exchange Act and 18 U.S.C. Section 1350.
32.2	Certification of Principal Financial Officer pursuant to Rule 13a-14(b) or 15d-14(b) of the Exchange Act and 18 U.S.C. Section 1350.
101.INS	Inline XBRL Instance Document – the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document
101.SCH	Inline XBRL Taxonomy Extension Schema Document
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104	Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101)

+ Indicates management contract or compensatory plan.

* Confidential treatment has been granted with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.

** Indicates an instrument, agreement or compensatory arrangement or plan assumed by Horizon Therapeutics Public Limited Company in the merger with Vidara and no longer binding on Horizon Therapeutics USA, Inc.

*** Certain portions of this exhibit (indicated by "[***]") have been omitted as the Registrant has determined (i) the omitted information is not material and (ii) the omitted information would likely cause harm to the Registrant if publicly disclosed.

Item 16. Form 10-K Summary

None.

HORIZON THERAPEUTICS PLC

Index to Consolidated Financial Statements

Report of Independent Registered Public Accounting Firm

To the Board of Directors and Shareholders of Horizon Therapeutics plc

Opinions on the Financial Statements and Internal Control over Financial Reporting

We have audited the accompanying consolidated balance sheets of Horizon Therapeutics plc and its subsidiaries (the "Company") as of December 31, 2019 and 2018, and the related consolidated statements of comprehensive income (loss), of shareholders' equity, and of cash flows for each of the three years in the period ended December 31, 2019, including the related notes and financial statement schedule listed in the index appearing under Item 15(a)(2) (collectively referred to as the "consolidated financial statements"). We also have audited the Company's internal control over financial reporting as of December 31, 2019, based on criteria established in *Internal Control - Integrated Framework* (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO).

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of the Company as of December 31, 2019 and 2018, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2019 in conformity with accounting principles generally accepted in the United States of America. Also in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2019, based on criteria established in *Internal Control - Integrated Framework* (2013) issued by the COSO.

Change in Accounting Principles

As discussed in Notes 1 and 2 to the consolidated financial statements, the Company changed the manner in which it accounts for business combinations and the manner in which it accounts for leases in 2019.

Basis for Opinions

The Company's management is responsible for these consolidated financial statements, for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting, included in Management's Report on Internal Control over Financial Reporting appearing under Item 9A. Our responsibility is to express opinions on the Company's consolidated financial statements and on the Company's internal control over financial reporting based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud, and whether effective internal control over financial reporting was maintained in all material respects.

Our audits of the consolidated financial statements included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audits also included performing such other procedures as we considered necessary in the circumstances. We believe that our audits provide a reasonable basis for our opinions.

Definition and Limitations of Internal Control over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Critical Audit Matters

The critical audit matters communicated below are matters arising from the current period audit of the consolidated financial statements that were communicated or required to be communicated to the audit committee and that (i) relate to accounts or disclosures that are material to the consolidated financial statements and (ii) involved our especially challenging, subjective, or complex judgments. The communication of critical audit matters does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matters below, providing separate opinions on the critical audit matters or on the accounts or disclosures to which they relate.

Accrued Medicaid Rebates and Accrued Co-Pay and Other Patient Assistance

As described in Notes 2 and 10 to the consolidated financial statements, the Company has accrued government rebates and chargebacks of $164.5 million as of December 31, 2019. A significant portion of these accruals relates to the Company's Medicaid rebates. The Company also has accrued co-pay and other patient assistance of $163.6 million as of December 31, 2019. Collectively these are referred to as "the allowances". Management calculates the allowances using the expected value method. Management applied significant judgment in estimating the allowances at the time of sale to wholesale pharmaceutical distributors and pharmacies based on estimated rebate percentages, estimated percentages of medicine that will be prescribed to qualified patients, average assistance paid based on reporting from the third-party vendors, and estimated levels of inventory in the distribution channel.

The principal considerations for our determination that performing procedures relating to accrued Medicaid rebates and accrued co-pay and other patient assistance is a critical audit matter is that there was significant judgment by management when estimating the allowances. This in turn led to a high degree of auditor judgment, subjectivity and effort in applying procedures to evaluate management's estimate and significant assumptions, including estimated rebate percentages, average assistance paid based on reporting from third-party vendors, estimated percentages of medicine prescribed to qualified patients and estimated levels of inventory in the distribution channel.

Addressing the matter involved performing procedures and evaluating audit evidence in connection with forming our overall opinion on the consolidated financial statements. These procedures included testing the effectiveness of controls relating to the valuation of the accrued Medicaid rebates and accrued co-pay and other patient assistance, including controls over the assumptions used to estimate the allowances. These procedures also included, among others, i) developing an independent estimate of the accrued Medicaid rebates by utilizing third-party prescription data, the terms of the specific rebate programs, and the historical trend of actual rebate claims paid, ii) comparing the independent estimate to management's estimate to evaluate the reasonableness of the estimate, iii) testing rebate claims processed by the Company, including evaluating those claims for consistency with the terms of the specific rebate programs, iv) testing management's process for developing the co-pay and other patient assistance allowances and evaluating the appropriateness of the methodology used by management, v) testing co-pay and other patient assistance payments, including evaluating the consistency with third-party invoices, vi) testing the completeness, accuracy and relevance of underlying data used by management, and vii) evaluating the significant assumptions used by management including estimated rebate percentages, average assistance paid based on reporting from third-party vendors, estimated percentages of medicine prescribed to qualified patients and estimated levels of inventory in the distribution channel. Evaluating management's assumptions involved evaluating whether the assumptions used by management were reasonable by (i) evaluating the consistency of the assumptions with historical trends, (ii) comparing assumptions and inputs to government prices, invoices, current payment trends, and other third party data on a test basis where relevant, (iii) considering whether relevant company and industry specific considerations have been incorporated into the assumptions appropriately, and (iv) evaluating evidence identified that was considered contrary to management's assumptions and evaluating its impact on management's estimate.

Income Tax Impacts of Intra-company Transfer of Intellectual Property Assets

As described in Notes 2 and 19 to the consolidated financial statements, the Company executed an intra-company transfer of intellectual property assets to an Irish subsidiary. During the year ended December 31, 2019, the Company recognized a deferred tax asset and related income tax benefit of $553.3 million, which represents the difference between the book and tax basis of the transferred assets multiplied by the Irish statutory income tax rate. The transaction required the interpretation and application of tax laws in the applicable jurisdiction to support the tax treatment taken. The valuation of the step-up tax basis of intellectual property assets, which supports the tax treatment of the transaction, required significant estimates and assumptions within discounted cash flow models.

The principal considerations for our determination that performing procedures relating to income tax impacts of intra-company transfer of intellectual property assets is a critical audit matter are that there was significant judgment by management when interpreting and applying the tax laws in the applicable jurisdiction, and in estimating the valuation of the step-up tax basis of intellectual property assets. This in turn led to a high degree of auditor judgment, subjectivity and effort to evaluate management's interpretation of the tax laws in the relevant jurisdiction and to evaluate management's estimate of the valuation of the intellectual property assets. In addition, the audit effort involved the use of professionals with specialized skill and knowledge to assist in performing these procedures and evaluating the audit evidence obtained.

Addressing the matter involved performing procedures and evaluating audit evidence in connection with forming our overall opinion on the consolidated financial statements. These procedures included testing the effectiveness of controls relating to the income tax impacts of the intra-company transfer of intellectual property assets, including controls over the tax treatment and application of tax laws, and the valuation of the step-up tax basis of intellectual property assets. These procedures also included, among others, (i) testing the information used in the determination of the tax impacts of the transaction, including examining intercompany agreements and management's interpretation and application of tax law; (ii) testing the calculation of the deferred tax asset and related income tax benefit for the intra-company transfer for intellectual property assets; (iii) testing the valuation of intellectual property assets; and (iv) testing the completeness and accuracy of data provided by management. Professionals with specialized skill and knowledge were used (i) to assist in the evaluation of the reasonableness of management's assessment of the income tax impact of intra-company transfer of intellectual property assets based on relevant tax laws in the applicable jurisdiction and (ii) to assist in evaluating the valuation of intellectual property assets.

/s/ PricewaterhouseCoopers LLP
Chicago, Illinois
February 26, 2020

We have served as the Company's auditor since 2009.

HORIZON THERAPEUTICS PLC

CONSOLIDATED BALANCE SHEETS
(In thousands, except share data)

	As of December 31, 2019	As of December 31, 2018
ASSETS		
CURRENT ASSETS:		
Cash and cash equivalents	$ 1,076,287	$ 958,712
Restricted cash	3,752	3,405
Accounts receivable, net	408,685	464,730
Inventories, net	53,802	50,751
Prepaid expenses and other current assets	143,577	68,218
Total current assets	**1,686,103**	**1,545,816**
Property and equipment, net	30,159	20,101
Developed technology, net	1,698,808	1,945,639
Other intangible assets, net	3,820	4,630
Goodwill	413,669	413,669
Deferred tax assets, net	555,165	3,148
Other assets	48,310	8,959
Total assets	**$ 4,436,034**	**$ 3,941,962**
LIABILITIES AND SHAREHOLDERS' EQUITY		
CURRENT LIABILITIES:		
Accounts payable	$ 21,514	$ 30,284
Accrued expenses	235,234	215,739
Accrued trade discounts and rebates	466,421	457,763
Deferred revenues, current portion	—	4,901
Total current liabilities	**723,169**	**708,687**
LONG-TERM LIABILITIES:		
Exchangeable notes, net	351,533	332,199
Long-term debt, net of current	1,001,308	1,564,485
Deferred tax liabilities, net	94,247	107,768
Other long-term liabilities	80,328	38,717
Total long-term liabilities	**1,527,416**	**2,043,169**
COMMITMENTS AND CONTINGENCIES		
SHAREHOLDERS' EQUITY:		
Ordinary shares, $0.0001 nominal value; 600,000,000 and 300,000,000 shares authorized at December 31, 2019 and December 31, 2018, respectively; 188,402,040 and 169,244,520 shares issued at December 31, 2019 and December 31, 2018, respectively, and 188,017,674 and 168,860,154 shares outstanding at December 31, 2019 and December 31, 2018, respectively	19	17
Treasury stock, 384,366 ordinary shares at December 31, 2019 and December 31, 2018	(4,585)	(4,585)
Additional paid-in capital	2,797,602	2,374,966
Accumulated other comprehensive loss	(1,905)	(1,523)
Accumulated deficit	(605,682)	(1,178,769)
Total shareholders' equity	**2,185,449**	**1,190,106**
Total liabilities and shareholders' equity	**$ 4,436,034**	**$ 3,941,962**

The accompanying notes are an integral part of these consolidated financial statements.

HORIZON THERAPEUTICS PLC

CONSOLIDATED STATEMENTS OF COMPREHENSIVE INCOME (LOSS)
(In thousands, except share and per share data)

	For the Years Ended December 31,		
	2019	**2018**	**2017**
Net sales	$ 1,300,029	$ 1,207,570	$ 1,056,231
Cost of goods sold	362,175	391,301	493,368
Gross profit	**937,854**	**816,269**	**562,863**
OPERATING EXPENSES:			
Research and development	103,169	82,762	224,962
Selling, general and administrative	697,111	692,485	655,093
Loss (gain) on sale of assets	10,963	(42,985)	—
Impairment of long-lived assets	—	46,096	22,270
Total operating expenses	**811,243**	**778,358**	**902,325**
Operating income (loss)	**126,611**	**37,911**	**(339,462)**
OTHER EXPENSE, NET:			
Interest expense, net	(87,089)	(121,692)	(126,523)
Loss on debt extinguishment	(58,835)	—	(978)
Gain on divestiture	—	—	7,965
Foreign exchange gain (loss)	33	(192)	(260)
Other (expense) income, net	(944)	841	447
Total other expense, net	**(146,835)**	**(121,043)**	**(119,349)**
Loss before benefit for income taxes	**(20,224)**	**(83,132)**	**(458,811)**
Benefit for income taxes	(593,244)	(44,752)	(108,686)
Net income (loss)	**$ 573,020**	**$ (38,380)**	**$ (350,125)**
Net income (loss) per ordinary share—basic	$ 3.13	$ (0.23)	$ (2.15)
Weighted average ordinary shares outstanding—basic	182,930,109	166,155,405	163,122,663
Net income (loss) per ordinary share—diluted	$ 2.90	$ (0.23)	$ (2.15)
Weighted average ordinary shares outstanding—diluted	205,224,221	166,155,405	163,122,663
OTHER COMPREHENSIVE (LOSS) INCOME, NET OF TAX			
Foreign currency translation adjustments	$ (382)	$ (826)	$ 2,067
Pension remeasurements	—	286	36
Other comprehensive (loss) income	(382)	(540)	2,103
Comprehensive income (loss)	**$ 572,638**	**$ (38,920)**	**$ (348,022)**

The accompanying notes are an integral part of these consolidated financial statements.

HORIZON THERAPEUTICS PLC

CONSOLIDATED STATEMENTS OF SHAREHOLDERS' EQUITY
(In thousands, except share data)

	Ordinary Shares		Treasury Stock		Additional Paid-in	Accumulated Other Comprehensive	Accumulated	Total Shareholders'
	Shares	Amount	Shares	Amount	Capital	Loss	Deficit	Equity
Balances at December 31, 2016	**162,004,956**	**$ 16**	**384,366**	**$ (4,585)**	**$ 2,119,455**	**$ (3,086)**	**$ (798,068)**	**$ 1,313,732**
Cumulative effect adjustment from adoption of ASU 2016-09	—	—	—	—	—	—	7,210	7,210
Issuance of ordinary shares in conjunction with vesting of restricted stock units and stock option exercises	1,117,876	—	—	—	2,167	—		2,167
Ordinary shares withheld for payment of employees' withholding tax liability	—	—	—	—	(6,533)	—	—	(6,533)
Issuance of ordinary shares in conjunction with ESPP program	822,231	—	—	—	7,082	—	—	7,082
Issuance of ordinary shares in conjunction with PSU vesting	25,000	—	—	—	—	—	—	—
Share-based compensation	—	—	—	—	125,019	—	—	125,019
Issuance of ordinary shares in conjunction with warrant exercises	915,020	—	—	—	1,789	—	—	1,789
Shares repurchased	(100,000)	—	—	—	—	—	(992)	(992)
Currency translation adjustment	—	—	—	—	—	2,067	—	2,067
Pension remeasurements	—	—	—	—	—	36	—	36
Net loss	—	—	—	—	—	—	(350,125)	(350,125)
Balances at December 31, 2017	**164,785,083**	**$ 16**	**384,366**	**$ (4,585)**	**$ 2,248,979**	**$ (983)**	**$ (1,141,975)**	**$ 1,101,452**
Cumulative effect adjustment from adoption of ASUs 2014-09 and 2016-16	—	—	—	—	—	—	1,586	1,586
Issuance of ordinary shares in conjunction with vesting of restricted stock units and stock option exercises	3,541,933	1	—	—	16,972	—	—	16,973
Ordinary shares withheld for payment of employees' withholding tax liability	—	—	—	—	(14,455)	—	—	(14,455)
Issuance of ordinary shares in conjunction with ESPP program	917,504	—	—	—	8,610	—	—	8,610
Share-based compensation	—	—	—	—	114,860	—	—	114,860
Currency translation adjustment	—	—	—	—	—	(826)	—	(826)
Pension remeasurements	—	—	—	—	—	286	—	286
Net loss	—	—	—	—	—	—	(38,380)	(38,380)
Balances at December 31, 2018	**169,244,520**	**$ 17**	**384,366**	**$ (4,585)**	**$ 2,374,966**	**$ (1,523)**	**$ (1,178,769)**	**$ 1,190,106**
Cumulative effect adjustments from adoption of ASUs 2016-02	—	—	—	—	—	—	67	67
Issuance of ordinary shares - public offering	14,081,632	2	—	—	326,792	—	—	326,794
Issuance of ordinary shares in conjunction with vesting of restricted stock units, performance stock units and stock option exercises	4,227,998	—	—	—	24,881	—	—	24,881
Ordinary shares withheld for payment of employees' withholding tax liability	—	—	—	—	(31,569)	—	—	(31,569)
Issuance of ordinary shares in conjunction with ESPP program	847,890	—	—	—	11,317	—	—	11,317
Share-based compensation	—	—	—	—	91,215	—	—	91,215
Currency translation adjustment	—	—	—	—	—	(382)	—	(382)
Net income	—	—	—	—	—	—	573,020	573,020
Balances at December 31, 2019	**188,402,040**	**$ 19**	**384,366**	**$ (4,585)**	**$ 2,797,602**	**$ (1,905)**	**$ (605,682)**	**$ 2,185,449**

The accompanying notes are an integral part of these consolidated financial statements.

HORIZON THERAPEUTICS PLC

CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	For the Years Ended December 31,		
	2019	**2018**	**2017**
CASH FLOWS FROM OPERATING ACTIVITIES:			
Net income (loss)	$ 573,020	$ (38,380)	$ (350,125)
Adjustments to reconcile net income (loss) to net cash provided by operating activities:			
Depreciation and amortization expense	237,157	249,759	256,087
Equity-settled share-based compensation	91,215	114,860	125,019
Loss on debt extinguishment	58,835	—	978
Amortization of debt discount and deferred financing costs	22,602	22,751	21,619
Loss (gain) on sale of assets	10,963	(42,985)	—
Deferred income taxes	(565,537)	(64,491)	(132,231)
Impairment of long-lived assets	—	46,096	22,270
Gain on divestiture	—	—	(1,236)
Acquired in-process research and development expense	—	—	159,171
Foreign exchange and other adjustments	574	332	(1,466)
Changes in operating assets and liabilities:			
Accounts receivable	56,166	(59,697)	(84,444)
Inventories	(3,268)	10,280	108,371
Prepaid expenses and other current assets	(72,763)	(25,313)	5,110
Accounts payable	(8,723)	(4,593)	(16,521)
Accrued trade discounts and rebates	8,591	(44,028)	205,487
Accrued expenses	19,788	40,787	(43,937)
Deferred revenues	(4,901)	(395)	4,468
Other non-current assets and liabilities	2,613	(10,440)	5,720
Net cash provided by operating activities	**426,332**	**194,543**	**284,340**
CASH FLOWS FROM INVESTING ACTIVITIES:			
Proceeds from sale of assets	6,000	44,424	—
Purchases of property and equipment	(17,857)	(4,771)	(4,336)
Change in escrow deposit for property purchase	(6,000)	—	—
Payment related to license agreement	—	(12,000)	—
Payments for acquisitions, net of cash acquired	—	—	(167,220)
Proceeds from divestiture, net of cash divested	—	—	69,371
Net cash (used in) provided by investing activities	**(17,857)**	**27,653**	**(102,185)**
CASH FLOWS FROM FINANCING ACTIVITIES:			
Net proceeds from the issuance of senior notes	590,057	—	—
Net proceeds from the issuance of ordinary shares	326,793	—	—
Repayment of senior notes	(814,420)	—	—
Net proceeds from term loans	935,404	818,026	1,693,512
Repayment of term loans	(1,336,207)	(845,749)	(1,622,749)
Contingent consideration proceeds from divestiture	3,297	—	—
Payment of contingent consideration	—	—	(20,000)
Repurchase of ordinary shares	—	—	(992)
Proceeds from the issuance of ordinary shares in connection with warrant exercises	—	—	1,789
Proceeds from the issuance of ordinary shares in conjunction with ESPP program	11,317	8,610	7,082
Proceeds from the issuance of ordinary shares in connection with stock option exercises	24,882	16,972	2,167
Payment of employee withholding taxes relating to share-based awards	(31,569)	(14,455)	(6,533)
Net cash (used in) provided by financing activities	**(290,446)**	**(16,596)**	**54,276**
Effect of foreign exchange rate changes on cash, cash equivalents and restricted cash	(107)	(1,380)	5,316
Net increase in cash, cash equivalents and restricted cash	117,922	204,220	241,747
Cash, cash equivalents and restricted cash, beginning of the year	962,117	757,897	516,150
Cash, cash equivalents and restricted cash, end of the year	**$ 1,080,039**	**$ 962,117**	**$ 757,897**

HORIZON THERAPEUTICS PLC

CONSOLIDATED STATEMENTS OF CASH FLOWS (CONTINUED)
(In thousands)

	For the Years Ended December 31,		
	2019	**2018**	**2017**
Supplemental cash flow information:			
Cash paid for interest	$ 78,044	$ 112,468	$ 113,790
Cash paid for income taxes	9,925	53,058	2,548
Cash paid for amounts included in the measurement of lease liabilities, net of lease incentive payments	6,484	—	—
Supplemental non-cash flow information:			
Purchases of property and equipment included in accounts payable and accrued expenses	117	1,101	—
Lease liabilities arising from obtaining right-of-use assets	11,444	—	—
Purchases of acquired in-process research and development included in accounts payable and accrued expenses	—	—	12,000

The accompanying notes are an integral part of these consolidated financial statements.

NOTE 1 – BASIS OF PRESENTATION AND BUSINESS OVERVIEW

Unless otherwise indicated or the context otherwise requires, references to "Horizon", the "Company", "we", "us" and "our" refer to Horizon Therapeutics plc (formerly known as Horizon Pharma plc) and its consolidated subsidiaries.

On May 2, 2019, the shareholders of the Company approved changing the name of the Company from "Horizon Pharma Public Limited Company" to "Horizon Therapeutics Public Limited Company" to better reflect the Company's long-term strategy to develop and commercialize innovative new medicines to address rare diseases with very few effective options.

Business Overview

Horizon is focused on researching, developing and commercializing medicines that address critical needs for people impacted by rare and rheumatic diseases. The Company's pipeline is purposeful: it applies scientific expertise and courage to bring clinically meaningful therapies to patients. Horizon believes science and compassion must work together to transform lives. The Company has two reportable segments, the orphan and rheumatology segment and the inflammation segment (previously named the primary care segment), and currently markets eleven medicines in the areas of orphan diseases, rheumatology and inflammation.

On January 21, 2020, the U.S. Food and Drug Administration ("FDA") approved TEPEZZA™ (teprotumumab-trbw) for the treatment of thyroid eye disease.

As of December 31, 2019, the Company's marketed medicines consisted of the following:

Orphan and Rheumatology
KRYSTEXXA® (pegloticase injection), for intravenous infusion
RAVICTI® (glycerol phenylbutyrate) oral liquid
PROCYSBI® (cysteamine bitartrate) delayed-release capsules, for oral use
ACTIMMUNE® (interferon gamma-1b) injection, for subcutaneous use
RAYOS® (prednisone) delayed-release tablets
BUPHENYL® (sodium phenylbutyrate) tablets and powder
QUINSAIR™ (levofloxacin) solution for inhalation
Inflammation
PENNSAID® (diclofenac sodium topical solution) 2% w/w ("PENNSAID 2%"), for topical use
DUEXIS® (ibuprofen/famotidine) tablets, for oral use
VIMOVO® (naproxen/esomeprazole magnesium) delayed-release tablets, for oral use

Change in Accounting Method

When accounting for business combinations under ASC Topic 805, Business Combinations, the Company previously separately identified and recorded at fair value intangible assets acquired and their related third-party contingent royalties at the date of acquisition. Third-party contingent royalties are royalties payable to parties other than sellers of the businesses. Effective January 1, 2019, the Company retrospectively changed its accounting for business combinations and now records acquired intangible assets and their related third-party contingent royalties on a net basis ("New Method"). The Company changed its accounting principle on the basis that the use of the New Method is preferable primarily due to improved comparability with the Company's peers. The Company has adjusted the accompanying consolidated balance sheet as at December 31, 2018, consolidated statement of comprehensive income (loss) for the years ended December 31, 2018 and 2017 and the consolidated statements of cash flows for the years ended December 31, 2018 and 2017 to reflect this change in accounting. Total shareholders' equity at December 31, 2018 was adjusted by $135.9 million to reflect the cumulative impact of the change to the earliest year presented. The impact on the consolidated statement of cash flows consisted of adjustments to reconcile net income (loss) to net cash provided by operating activities and changes in operating assets and liabilities for all periods presented. There was no impact on total operating, investing or financing cash flows for any prior period. The following are selected line items from the Company's consolidated financial statements illustrating the effect of the change in accounting method (in thousands, except per share data):

	Consolidated Balance Sheet as of December 31, 2018		
	As Previously Reported	Impact of Accounting Change (1)	As Adjusted
Prepaid expenses and other current assets	$ 70,828	$ (2,610)	$ 68,218
Total current assets	1,548,426	(2,610)	1,545,816
Developed technology, net	2,120,596	(174,957)	1,945,639
Goodwill	426,441	(12,772)	413,669
Other assets	23,029	(14,070)	8,959
Total assets	4,146,371	(204,409)	3,941,962
Accrued expenses	205,593	10,146	215,739
Accrued royalties - current portion	63,363	(63,363)	—
Total current liabilities	761,904	(53,217)	708,687
Accrued royalties - net of current	285,374	(285,374)	—
Deferred tax liabilities, net	93,630	14,138	107,768
Other long-term liabilities	54,622	(15,905)	38,717
Total long-term liabilities	2,330,310	(287,141)	2,043,169
Accumulated deficit	(1,314,718)	135,949	(1,178,769)
Total shareholders' equity	1,054,157	135,949	1,190,106
Total liabilities and shareholders' equity	4,146,371	(204,409)	3,941,962

(1) The change in accounting principle resulted in the Company re-performing its purchase price allocations as of the respective acquisition dates for prior business combinations. The adjustments to the purchase price allocations primarily resulted in a decrease in developed technology intangible assets and the elimination of liabilities for accrued contingent royalties due to recording these items on a net basis. The re-performance of purchase price allocations also impacted goodwill and deferred tax liabilities. In addition, the change in accounting principle resulted in the elimination of royalty reimbursement assets and accrued contingent royalty liabilities that were recorded in connection with divestitures, impacting prepaid expenses and other current assets, other assets, accrued expenses and other long-term liabilities captions as shown in the table above. In addition, under the New Method of accounting, the Company is presenting accrued royalties based on each periods' net sales as part of the accrued expenses line item on its consolidated balance sheets.

	Consolidated Statement of Comprehensive Loss For the Year Ended December 31, 2018		
	As Previously Reported	Impact of Accounting Change (1)	As Adjusted
Cost of goods sold	$ 422,317	$ (31,016)	$ 391,301
Gross profit	785,253	31,016	816,269
Impairment of long-lived assets	50,302	(4,206)	46,096
Gain on sale of assets	(42,688)	(297)	(42,985)
Total operating expenses	782,861	(4,503)	778,358
Operating income	2,392	35,519	37,911
Other income, net	346	495	841
Total other expenses, net	(121,538)	495	(121,043)
Loss before benefit for income taxes	(119,146)	36,014	(83,132)
Benefit for income taxes	(44,959)	207	(44,752)
Net loss	(74,187)	35,807	(38,380)
Net loss per ordinary share - basic and diluted	(0.45)	0.22	(0.23)
Comprehensive loss	(74,727)	35,807	(38,920)

	Consolidated Statement of Comprehensive Loss For the Year Ended December 31, 2017		
	As Previously Reported	Impact of Accounting Change (1)	As Adjusted
Cost of goods sold	$ 537,334	$ (43,966)	$ 493,368
Gross profit	518,897	43,966	562,863
Operating loss	(383,428)	43,966	(339,462)
Gain on divestiture	6,267	1,698	7,965
Other income, net	588	(141)	447
Total other expenses, net	(120,906)	1,557	(119,349)
Loss before benefit for income taxes	(504,334)	45,523	(458,811)
Benefit for income taxes	(102,749)	(5,937)	(108,686)
Net loss	(401,585)	51,460	(350,125)
Net loss per ordinary share - basic and diluted	(2.46)	0.31	(2.15)
Comprehensive loss	(399,482)	51,460	(348,022)

(1) The change in accounting principle resulted in the Company re-performing its purchase price allocations as of the respective acquisition dates for prior business combinations. The adjustments to the purchase price allocations primarily resulted in a net decrease in cost of goods sold reflecting lower intangible asset amortization and the elimination of royalty accretion and remeasurement expenses, partially offset by the royalty expense based on the periods' net sales. The re-performance of purchase price allocations also directly impacted impairments of long-lived assets and benefit/expense for income taxes, as shown in the tables above. In addition, the elimination of royalty reimbursement assets and accrued contingent royalty liabilities that were recorded in connection with divestitures resulted in adjustments to other income, net.

NOTE 2 – SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Basis of Presentation

The accompanying consolidated financial statements have been prepared in accordance with the accounting principles generally accepted in the United States of America ("GAAP").

Principles of Consolidation

The consolidated financial statements include the Company's accounts and those of its wholly owned subsidiaries. All intercompany accounts and transactions have been eliminated.

Segment Information

The Company's reportable segments, which are the orphan and rheumatology segment and the inflammation segment, are reported in a manner consistent with the internal reporting provided to the Company's chief operating decision maker ("CODM"). The Company's CODM has been identified as its chief executive officer. The Company has no transactions between reportable segments.

Use of Estimates

The preparation of the accompanying consolidated financial statements in conformity with GAAP requires management to make certain estimates and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent liabilities at the date of the financial statements and reported amounts of revenues and expenses during the reporting period. Actual results could differ from those estimates.

Foreign Currency Translation and Transactions

The reporting currency of the Company and its subsidiaries is the U.S. dollar.

The U.S. dollar is the functional currency for the Company's Ireland and United States-based businesses and the majority of its subsidiaries. The Company has foreign subsidiaries that have the Euro and the Canadian Dollar as their functional currency. Foreign currency-denominated assets and liabilities of these subsidiaries are translated into U.S. dollars based on exchange rates prevailing at the end of the period, revenues and expenses are translated at average exchange rates prevailing during the corresponding period, and shareholders' equity accounts are translated at historical exchange rates as of the date of any equity transaction. The effects of foreign exchange gains and losses arising from the translation of assets and liabilities of those entities where the functional currency is not the U.S. dollar are included as a component of accumulated other comprehensive (loss) income.

Gains and losses resulting from foreign currency transactions are reflected within the Company's results of operations.

Revenue Recognition

On January 1, 2018, the Company adopted ASU 2014-09, Revenue from Contracts with Customers, and subsequent amendments (ASC 606 or new guidance), using the modified retrospective method. The Company applied the new guidance to all contracts with customers within the scope of the standard that were in effect on January 1, 2018 and recognized the cumulative effect of initially applying the new guidance as an adjustment to the opening balance of retained earnings. Comparative information for prior periods has not been restated and continues to be reported under the accounting standards in effect for those periods. In the United States, the Company sells its medicines primarily to wholesale distributors and specialty pharmacy providers. In other countries, the Company sells its medicines primarily to wholesale distributors and other third-party distribution partners. These customers subsequently resell the Company's medicines to health care providers and patients. In addition, the Company enters into arrangements with health care providers and payers that provide for government-mandated or privately negotiated discounts and allowances related to the Company's medicines. Revenue is recognized when performance obligations under the terms of a contract with a customer are satisfied. The majority of the Company's contracts have a single performance obligation to transfer medicines. Accordingly, revenues from medicine sales are recognized when the customer obtains control of the Company's medicines, which occurs at a point in time, typically upon delivery to the customer. Revenue is measured as the amount of consideration the Company expects to receive in exchange for transferring medicines and is generally based upon a list or fixed price less allowances for medicine returns, rebates and discounts. The Company sells its medicines to wholesale pharmaceutical distributors and pharmacies under agreements with payment terms typically less than 90 days. The Company's process for estimating reserves established for these variable consideration components does not differ materially from the Company's historical practices.

Medicine Sales Discounts and Allowances

The nature of the Company's contracts gives rise to variable consideration because of allowances for medicine returns, rebates and discounts. Allowances for medicine returns, rebates and discounts are recorded at the time of sale to wholesale pharmaceutical distributors and pharmacies. The Company applies significant judgments and estimates in determining some of these allowances. If actual results differ from its estimates, the Company will be required to make adjustments to these allowances in the future. The Company's adjustments to gross sales are discussed further below.

Commercial Rebates

The Company participates in certain commercial rebate programs. Under these rebate programs, the Company pays a rebate to the commercial entity or third-party administrator of the program. The Company calculates accrued commercial rebate estimates using the expected value method. The Company accrues estimated rebates based on contract prices, estimated percentages of medicine that will be prescribed to qualified patients and estimated levels of inventory in the distribution channel and records the rebate as a reduction of revenue. Accrued commercial rebates are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Distribution Service Fees

The Company includes distribution service fees paid to its wholesalers for distribution and inventory management services as a reduction to revenue. The Company calculates accrued distribution service fee estimates using the most likely amount method. The Company accrues estimated distribution fees based on contractually determined amounts, typically as a percentage of revenue. Accrued distribution service fees are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Co-pay and Other Patient Assistance Programs

The Company offers discount card and other programs such as its HorizonCares program to patients under which the patient receives a discount on his or her prescription. In certain circumstances when a patient's prescription is rejected by a managed care vendor, the Company will pay for the full cost of the prescription. The Company reimburses pharmacies for this discount through third-party vendors. The Company reduces gross sales by the amount of actual co-pay and other patient assistance in the period based on invoices received. The Company also records an accrual to reduce gross sales for estimated co-pay and other patient assistance on units sold to distributors that have not yet been prescribed/dispensed to a patient. The Company calculates accrued co-pay and other patient assistance costs using the expected value method. The estimate is based on contract prices, estimated percentages of medicine that will be prescribed to qualified patients, average assistance paid based on reporting from the third-party vendors and estimated levels of inventory in the distribution channel. Accrued co-pay and other patient assistance costs are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Sales Returns

Consistent with industry practice, the Company maintains a return policy that allows customers to return certain medicines within a specified period prior to and subsequent to the medicine expiration date. Generally, medicines may be returned for a period beginning six months prior to its expiration date and up to one year after its expiration date. The right of return expires on the earlier of one year after the medicine expiration date or the time that the medicine is dispensed to the patient. The majority of medicine returns result from medicine dating, which falls within the range set by the Company's policy, and are settled through the issuance of a credit to the customer. The Company calculates sales returns using the expected value method. The estimate of the provision for returns is based upon the Company's historical experience with actual returns. The return period is known to the Company based on the shelf life of medicines at the time of shipment. The Company records sales returns in "accrued expenses" and as a reduction of revenue.

Prompt Pay Discounts

As an incentive for prompt payment, the Company offers a 2% cash discount to most customers. The Company calculates accrued prompt pay discounts using the most likely amount method. The Company expects that all eligible customers will comply with the contractual terms to earn the discount. The Company records the discount as an allowance against "accounts receivable, net" and a reduction of revenue.

Government Rebates

The Company participates in certain government rebate programs such as Medicare Coverage Gap and Medicaid. The Company calculates accrued government rebate estimates using the expected value method. The Company accrues estimated rebates based on percentages of medicine prescribed to qualified patients, estimated rebate percentages and estimated levels of inventory in the distribution channel that will be prescribed to qualified patients and records the rebates as a reduction of revenue. Accrued government rebates are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Chargebacks

The Company provides discounts to government qualified entities with whom the Company has contracted. These entities purchase medicines from the wholesale pharmaceutical distributors at a discounted price and the wholesale pharmaceutical distributors then charge back to the Company the difference between the current retail price and the contracted price that the entities paid for the medicines. The Company calculates accrued chargeback estimates using the expected value method. The Company accrues estimated chargebacks based on contract prices, sell-through sales data obtained from third-party information and estimated levels of inventory in the distribution channel and records the chargeback as a reduction of revenue. Accrued chargebacks are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Bad Debt Expense

The Company's medicines are sold to wholesale pharmaceutical distributors and pharmacies. The Company monitors its accounts receivable balances to determine the impact, if any, of such factors as changes in customer concentration, credit risk and the realizability of its accounts receivable, and records a bad debt reserve when applicable.

Inventories

Inventories are stated at the lower of cost or net realizable value, using the first-in, first-out convention. Inventories consist of raw materials, work-in-process and finished goods. The Company has entered into manufacturing and supply agreements for the manufacture or purchase of raw materials and production supplies. The Company's inventories include the direct purchase cost of materials and supplies and manufacturing overhead costs. The Company reviews its inventory balance and purchase obligations to assess if it has obsolete or excess inventory and records a charge to "cost of goods sold" when applicable.

Inventories acquired in business combinations are recorded at their estimated fair values. "Step-up" represents the write-up of inventory from the lower of cost or net realizable value (the historical book value as previously recorded on the acquired company's balance sheet) to fair market value at the acquisition date. Inventory step-up expense is recorded in the consolidated statement of comprehensive income (loss) based on actual sales, or usage, using the first-in, first-out convention.

Inventories exclude medicine sample inventory, which is included in other current assets and is expensed as a component of "selling, general and administrative" expense when shipped to sales representatives.

Pre-launch Inventories

The Company capitalizes inventory costs associated with its medicine candidates prior to regulatory approval when, based on management judgment, future commercialization is considered probable and future economic benefit is expected to be realized. A number of factors are taken into consideration by management, including the current status of the regulatory approval process and any potential impediments to the approval process such as safety or efficacy. If future commercialization and future economic benefit is no longer considered probable, the capitalized pre-launch inventory would be expensed.

Cost of Goods Sold

The Company recognizes cost of goods sold in connection with its sales of each of its distributed medicines. Cost of goods sold includes all costs directly related to the acquisition of the Company's medicines from its third-party manufacturers, including freight charges and other direct expenses such as insurance and supply chain costs. Cost of goods sold also includes amortization of intellectual property as described in the intangible assets accounting policy below, inventory step-up expense, drug substance harmonization costs, share-based compensation, charges relating to discontinuation of clinical trials, royalty payments to third parties and loss on inventory purchase commitments.

Pre-clinical Studies and Clinical Trial Accruals

The Company's pre-clinical studies and clinical trials have historically been conducted by third-party contract research organizations and other vendors. Pre-clinical study and clinical trial expenses are based on the services received from these contract research organizations and vendors. Payments depend on factors such as the milestones accomplished, successful enrollment of certain numbers of patients and site initiation. In accruing service fees, the Company estimates the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from the estimate, the Company adjusts the accrual accordingly.

Net Income (Loss) Per Share

Basic net income (loss) per share is computed by dividing net income (loss) by the weighted-average number of ordinary shares outstanding during the period. Diluted earnings per share ("EPS") reflects the potential dilution beyond shares for basic EPS that could occur if securities or other contracts to issue ordinary shares were exercised, converted into ordinary shares, or resulted in the issuance of ordinary shares that would have shared in the Company's earnings.

Cash and Cash Equivalents

The Company considers all highly liquid investments, readily convertible to cash, that mature within three months or less from date of purchase to be cash equivalents. Cash and cash equivalents primarily consist of cash balances and money market funds. The Company generally invests excess cash in money market funds and other financial instruments with short-term durations, based upon operating requirements.

Restricted Cash

Restricted cash consists primarily of balances in interest-bearing money market accounts required by a vendor for the Company's sponsored employee business credit card program and collateral for a letter of credit.

Fair Value of Financial Instruments

The carrying amounts of the Company's financial instruments, including cash and cash equivalents, restricted cash, accounts receivable, accounts payable and accrued expenses, approximate their fair values due to their short maturities.

Concentration of Credit Risk and Other Risks and Uncertainties

Financial instruments that potentially subject the Company to concentrations of credit risk consist of cash, cash equivalents and investments. The Company's investment policy permits investments in U.S. federal government and federal agency securities, corporate bonds or commercial paper, money market instruments, certain qualifying money market mutual funds, certain repurchase agreements, and tax-exempt obligations of municipalities and places restrictions on credit ratings, maturities, and concentration by type and issuer. The Company is exposed to credit risk in the event of a default by the financial institutions holding the Company's cash, cash equivalents and investments to the extent recorded on the balance sheet.

The purchase cost of TEPEZZA drug substance and ACTIMMUNE inventory are principally denominated in Euros and are subject to foreign currency risk. The Company has contracts relating to RAVICTI, QUINSAIR and PROCYSBI for sales in Canada which are subject to foreign currency risk. The Company also incurs certain operating expenses in currencies other than the U.S. dollar in relation to its Irish operations and foreign subsidiaries. Therefore, the Company is subject to volatility in cash flows due to fluctuations in foreign currency exchange rates, particularly changes in the Euro and the Canadian dollar.

Historically, the Company's accounts receivable balances have been highly concentrated with a select number of customers consisting primarily of large wholesale pharmaceutical distributors who, in turn, sell the medicines to pharmacies, hospitals and other customers. As of December 31, 2019 and 2018, the Company's top four customers accounted for approximately 84% and 85%, respectively, of the Company's total outstanding accounts receivable balances.

The Company depends on single-source suppliers and manufacturers for certain of its medicines, medicine candidates and their active pharmaceutical ingredients.

Business Combinations

The Company accounts for business combinations in accordance with the guidance in Accounting Standards Codification Topic 805, *Business Combinations* ("ASC 805") under which acquired assets and liabilities are measured at their respective estimated fair values as of the acquisition date. The Company may be required, as in the case of intangible assets, to determine the fair value associated with these amounts by estimating the fair value using an income approach under the discounted cash flow method, which may include revenue projections and other assumptions made by the Company to determine the fair value.

Provision for Income Taxes

The Company accounts for income taxes based upon an asset and liability approach. Deferred tax assets and liabilities represent the future tax consequences of the differences between the financial statement carrying amounts of assets and liabilities versus the tax basis of assets and liabilities. Under this method, deferred tax assets are recognized for deductible temporary differences, and operating loss and tax credit carryforwards. Deferred tax liabilities are recognized for taxable temporary differences. Deferred tax assets are reduced by a valuation allowance when, in the opinion of management, it is more likely than not that some portion or all of the deferred tax assets will not be realized. Significant judgment is required in determining whether it is probable that sufficient future taxable income will be available against which a deferred tax asset can be utilized. In determining future taxable income, the Company is required to make assumptions including the amount of taxable income in the various jurisdictions in which the Company operates. These assumptions require significant judgment about forecasts of future taxable income. Actual operating results in future years could render our current assumption of recoverability of deferred tax assets inaccurate. The impact of tax rate changes on deferred tax assets and liabilities is recognized in the period that the change is enacted. From time to time, the Company executes intra-company transactions in response to changes in operations, regulations, tax laws, funding needs and other circumstances. These transactions require the interpretation and application of tax laws in the applicable jurisdiction to support the tax treatment taken. The valuations which support the tax treatment of the transactions require significant estimates and assumptions within discounted cash flow models. The Company also accounts for the uncertainty in income taxes by utilizing a comprehensive model for the recognition, measurement, presentation and disclosure in financial statements of any uncertain tax positions that have been taken or are expected to be taken on an income tax return. Deferred tax assets and deferred tax liabilities are netted by each tax-paying entity within each jurisdiction on the Company’s consolidated balance sheets.

Property and Equipment, Net

Property and equipment are stated at cost less accumulated depreciation. Depreciation is recognized using the straight-line method over the estimated useful lives of the related assets for financial reporting purposes and an accelerated method for income tax reporting purposes. Upon retirement or sale of an asset, the cost and related accumulated depreciation and amortization are removed from the balance sheet and the resulting gain or loss is reflected in operations. Repair and maintenance costs are charged to expenses as incurred and improvements are capitalized.

Leasehold improvements are amortized on a straight-line basis over the term of the applicable lease, or the useful life of the assets, whichever is shorter.

Depreciation and amortization periods for the Company’s property and equipment are as follows:

Machinery and equipment	5 to 7 years
Furniture and fixtures	3 to 5 years
Computer equipment	3 years
Software	3 years
Trade show equipment	3 years

The Company capitalizes software development costs associated with internal use software, including external direct costs of materials and services and payroll costs for employees devoting time to a software project. Costs incurred during the preliminary project stage, as well as costs for maintenance and training, are expensed as incurred.

Software includes internal-use software acquired and modified to meet the Company’s internal requirements. Amortization commences when the software is ready for its intended use.

Intangible Assets

Definite-lived intangible assets are amortized over their estimated useful lives. The Company reviews its intangible assets when events or circumstances may indicate that the carrying value of these assets is not recoverable and exceeds their fair value. The Company measures fair value based on the estimated future discounted cash flows associated with these assets in addition to other assumptions and projections that the Company deems to be reasonable and supportable. The estimated useful lives, from the date of acquisition, for all identified intangible assets that are subject to amortization are between five and thirteen years.

Goodwill

Goodwill represents the excess of the purchase price of acquired businesses over the estimated fair value of the identifiable net assets acquired. Goodwill is not amortized but is tested for impairment at least annually at the reporting unit level or more frequently if events or changes in circumstances indicate that the asset might be impaired. Impairment loss, if any, is recognized based on a comparison of the fair value of the asset to its carrying value, without consideration of any recoverability. The Company tests goodwill for impairment annually during the fourth quarter and whenever indicators of impairment exist by first assessing qualitative factors to determine whether it is more likely than not that the fair value is less than its carrying amount. If the Company concludes it is more likely than not that the fair value of a reporting unit is less than its carrying amount, a quantitative impairment test is performed. If the Company concludes that goodwill is impaired, it will record an impairment charge in its consolidated statement of comprehensive income (loss).

Research and Development Expenses

Research and development expenses include, but are not limited to, payroll and other personnel expenses, consultant expenses, expenses incurred under agreements with contract research organizations to conduct clinical trials, expenses incurred to manufacture clinical trial materials and acquired in-process research and development ("IPR&D") assets. Research and development expenses were $103.2 million, $82.8 million and $225.0 million for the years ended December 31, 2019, 2018 and 2017, respectively.

Advertising Expenses

We expense the costs of advertising as incurred. Advertising expenses were $35.8 million, $21.6 million and $19.2 million for the years ended December 31, 2019, 2018 and 2017, respectively.

Deferred Financing Costs

Costs incurred in connection with debt financings have been capitalized to "Long-term debt, net of current" and "Exchangeable notes, net" in the Company's consolidated balance sheets as deferred financing costs, and are charged to interest expense using the effective interest method over the terms of the related debt agreements. These costs include document preparation costs, commissions, fees and expenses of investment bankers and underwriters, and accounting and legal fees.

Comprehensive Income (Loss)

Comprehensive income (loss) is composed of net income (loss) and other comprehensive income (loss) ("OCI"). OCI includes certain changes in shareholders' equity that are excluded from net income (loss), which consist of foreign currency translation adjustments and pension remeasurements. The Company reports the effect of significant reclassifications out of accumulated OCI on the respective line items in net income (loss) if the amount being reclassified is required under GAAP to be reclassified in its entirety to net income (loss). For other amounts that are not required under GAAP to be reclassified in their entirety to net income (loss) in the same reporting period, the Company cross-references other disclosures required under GAAP that provide additional detail about those amounts.

Share-Based Compensation

The Company accounts for employee share-based compensation by measuring and recognizing compensation expense for all share-based payments based on estimated grant date fair values. The Company uses the straight-line method to allocate compensation cost to reporting periods over each awardee's requisite service period, which is generally the vesting period. The Company adopted ASU No. 2016-09, *Improvements to Employee Share-Based Payment Accounting* ("ASU No. 2016-09") on January 1, 2017 and has elected to retain a forfeiture rate after adoption.

Royalties

The Company records royalty expense based on each periods' net sales as part of cost of goods sold.

Leases

The Company's leases primarily relate to operating leases of rented office properties. For contracts entered into on or after January 1, 2019, at the inception of a contract the Company assesses whether the contract is, or contains, a lease. The Company's assessment is based on: (1) whether the contract involves the use of a distinct identified asset, (2) whether the Company obtains the right to substantially all the economic benefit from the use of the asset throughout the period, and (3) whether the Company has the right to direct the use of the asset. At inception of a lease, the Company allocates the consideration in the contract to each lease component based on its relative stand-alone price to determine the lease payments.

For leases with terms greater than 12 months, the Company records the related asset and obligation at the present value of lease payments over the term. The right-of-use lease asset represents the right to use the leased asset for the lease term. The lease liability represents the present value of the lease payments under the lease.

The right-of-use lease asset is initially measured at cost, which primarily comprises the initial amount of the lease liability, plus any initial direct costs incurred. All right-of-use lease assets are reviewed for impairment. The lease liability is initially measured at the present value of the lease payments, discounted using the interest rate implicit in the lease or, if that rate cannot be readily determined, the Company's secured incremental borrowing rate for the same term as the underlying lease.

The Company identified and assessed the following significant assumptions in recognizing the right-of-use lease assets and corresponding liabilities.

Expected lease term – The expected lease term includes both contractual lease periods and, when applicable, cancelable option periods. When determining the lease term, the Company includes options to extend or terminate the lease when it is reasonably certain that the Company will exercise that option.

Incremental borrowing rate – As the Company's leases do not provide an implicit rate, the Company obtained the incremental borrowing rate ("IBR") based on the remaining term of each lease. The IBR is the rate of interest that a lessee would have to pay to borrow on a collateralized basis over a similar term an amount equal to the lease payments in a similar economic environment.

The Company has elected not to recognize right-of-use lease assets and lease liabilities for short-term leases that have a term of 12 months or less.

The Company reports right-of-use lease assets within non-current "Other assets" in its consolidated balance sheet. The Company reports the current portion of lease liabilities within "Accrued expenses" and long-term lease liabilities within "Other long-term liabilities" in its consolidated balance sheet.

Contingencies

From time to time, the Company may become involved in claims and other legal matters arising in the ordinary course of business. The Company records accruals for loss contingencies to the extent that it concludes that it is probable that a liability has been incurred and the amount of the related loss can be reasonably estimated. Legal fees and other expenses related to litigation are expensed as incurred and included in "selling, general and administrative" expenses.

Recent Accounting Pronouncements

From time to time, the Company adopts new accounting pronouncements issued by the Financial Accounting Standards Board ("FASB") or other standard-setting bodies.

Effective January 1, 2019, the Company adopted Accounting Standards Updated ("ASU") No. 2016-02, *Leases (Topic 842)* ("ASU No. 2016-02"). Under ASU No. 2016-02, an entity is required to recognize right-of-use lease assets and lease liabilities on its balance sheet and disclose key information about leasing arrangements. The Company adopted this standard on January 1, 2019, using a modified retrospective approach at the adoption date through a cumulative-effect adjustment to retained earnings. The Company elected the package of transition provisions available for expired or existing contracts, which allowed the Company to carry forward its historical assessments of (i) whether contracts are or contain leases, (ii) lease classification and (iii) initial direct costs. In addition, the Company elected the hindsight practical expedient to determine the lease term for existing leases. The Company applied the new guidance to all operating leases within the scope of the standard that were in effect on January 1, 2019, or entered into after, the adoption date. Comparative information for prior periods has not been restated and continues to be reported under the accounting standards in effect for those periods. The adoption did not have a material impact on the Company's consolidated statement of comprehensive income (loss). However, the new standard established $38.0 million of liabilities and corresponding right-of-use assets of $36.0 million on the Company's consolidated balance sheet for leases, primarily related to operating leases on rented office properties, that existed as of the January 1, 2019, adoption date.

Effective January 1, 2019, the Company adopted ASU No. 2018-07, *Compensation—Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting* ("ASU No. 2018-07"). ASU No. 2018-07 largely aligns the accounting for share-based payment awards issued to employees and non-employees. The adoption of ASU No. 2018-07 did not have a material impact on the Company's consolidated financial statements and related disclosures.

Effective January 1, 2019, the Company adopted ASU No. 2018-08, *Clarifying the Scope and the Accounting Guidance for Contributions Received and Contributions Made* ("ASU No. 2018-08"), using prospective application to any new agreements entered into after the effective date. The new guidance applies to all entities that receive or make contributions, including business entities. The adoption of ASU No. 2018-08 did not have a material impact on the Company's consolidated financial statements and related disclosures.

In June 2016, the FASB issued Accounting Standards Update No. 2016-13, *Financial Instruments – Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments* ("ASU 2016-13"), which modifies the measurement of expected credit losses on certain financial instruments and is effective for the Company as of January 1, 2020. The Company does not expect the adoption of ASU 2016-13 to have a material impact to the Company's consolidated financial statements and related disclosures.

In December 2019, the FASB issued Accounting Standards Update No. 2019-12, *Income Taxes (Topic 740): Simplification and reduce the cost of accounting for income taxes* ("ASU 2019-12") and is effective for the Company January 1, 2021. The Company is currently evaluating the impact of ASU 2019-12.

Other recent authoritative guidance issued by the FASB (including technical corrections to the Accounting Standards Codification), the American Institute of Certified Public Accountants, and the Securities and Exchange Commission ("SEC") did not, or are not expected to, have a material impact on the Company's consolidated financial statements and related disclosures.

NOTE 3 – NET INCOME (LOSS) PER SHARE

The following table presents basic and diluted net income (loss) per share for the years ended December 31, 2019, 2018 and 2017 (in thousands, except share and per share data):

	For the Years Ended December 31,		
	2019	2018	2017
Basic net income (loss) per share calculation:			
Numerator - net income (loss)	$ 573,020	$ (38,380)	$ (350,125)
Denominator - weighted average of ordinary shares outstanding	182,930,109	166,155,405	163,122,663
Basic net income (loss) per share	**$ 3.13**	**$ (0.23)**	**$ (2.15)**

	For the Years Ended December 31,		
	2019	2018	2017
Diluted net income (loss) per share calculation:			
Net income (loss)	$ 573,020	$ (38,380)	$ (350,125)
Effect of assumed conversion of Exchangeable Senior Notes, net of tax	22,440	—	—
Numerator - net income (loss)	$ 595,460	$ (38,380)	$ (350,125)
Denominator - weighted average of ordinary shares outstanding	205,224,221	166,155,405	163,122,663
Diluted net income (loss) per share	**$ 2.90**	**$ (0.23)**	**$ (2.15)**

Basic net income (loss) per share is computed by dividing net income (loss) by the weighted-average number of ordinary shares outstanding during the period. Diluted net income (loss) per share reflects the potential dilution that could occur if securities or other contracts to issue ordinary shares were exercised, converted into ordinary shares, or resulted in the issuance of ordinary shares that would have shared in the Company's earnings.

Beginning in the fourth quarter of 2019, with the ordinary share price significantly above the $28.66 exchange price, the Company decided that it no longer had the intent to settle the notes for cash. Accordingly, during the year ended December 31, 2019, the Company prospectively applied the if-converted method to its 2.50% Exchangeable Senior Notes due 2022 (the "Exchangeable Senior Notes") when determining the diluted net income (loss) per share.

The outstanding securities listed in the table below were excluded from the computation of diluted net income (loss) per ordinary share for the years ended December 31, 2019, 2018 and 2017 due to being anti-dilutive:

	For the Years Ended December 31,		
	2019	2018	2017
Stock options	233,260	6,406,914	12,887,595
Restricted stock units	1,840	2,299,254	1,095,768
Performance stock units	586,868	1,248,632	2,742,301
Employee stock purchase plan shares	2,207	265,886	63,445
Warrants	—	—	388,841
	824,175	**10,220,686**	**17,177,950**

During the years ended December 31, 2018 and 2017, the potentially dilutive impact of the Exchangeable Senior Notes was determined using a method similar to the treasury stock method. Under this method, no numerator or denominator adjustments arose from the principal and interest components of the Exchangeable Senior Notes because the Company had the intent and ability to settle the Exchangeable Senior Notes' principal and interest in cash. Instead, the Company was required to increase the diluted net income (loss) per share denominator by the variable number of shares that would be issued upon conversion if it settled the conversion spread obligation with shares. For diluted net income (loss) per share purposes, the conversion spread obligation was calculated based on whether the average market price of the Company's ordinary shares over the reporting period was in excess of the exchange price of the Exchangeable Senior Notes. There was no calculated spread added to the denominator for the years ended December 31, 2018 and 2017.

NOTE 4 –ACQUISITIONS, DIVESTITURES AND OTHER ARRANGEMENTS

Sale of MIGERGOT rights

On June 28, 2019, the Company sold its rights to MIGERGOT to Cosette Pharmaceuticals, Inc., for $6.0 million and total potential contingent consideration payments of $4.0 million (the "MIGERGOT transaction").

Pursuant to ASC 805 (as amended by ASU No. 2017-01, Business *Combinations (Topic 805): Clarifying the Definition of a Business* ("ASU No. 2017-01")), the Company accounted for the MIGERGOT transaction as a sale of assets, specifically a sale of intellectual property rights, and a sale of inventory.

The loss on sale of assets recorded to the consolidated statement of comprehensive income (loss) during the year ended December 31, 2019, was determined as follows (in thousands):

Cash proceeds	$	6,000
Less net assets sold:		
Developed technology		(16,999)
Inventory		(236)
Release of contingent consideration liability		272
Loss on sale of assets	**$**	**(10,963)**

Sale of RAVICTI and AMMONAPS Rights outside of North America and Japan

On December 28, 2018, the Company sold its rights to RAVICTI and AMMONAPS (known as BUPHENYL in the United States) outside of North America and Japan to Medical Need Europe AB, part of the Immedica Group, for $35.0 million (the "Immedica transaction"). The Company previously distributed RAVICTI and AMMONAPS through a commercial partner in Europe and other non-U.S. markets. The Company has retained the rights to RAVICTI and BUPHENYL in North America and Japan.

Pursuant to ASU No. 2017-01, the Company accounted for the Immedica transaction as a sale of assets, specifically a sale of intellectual property rights.

The gain on sale of assets recorded to the consolidated statement of comprehensive income (loss) during the year ended December 31, 2018, was determined as follows (in thousands):

Cash proceeds	$	35,000
Less net assets sold:		
Developed technology		(4,146)
Transaction costs		(197)
Gain on sale of assets	**$**	**30,657**

Acquisition and Subsequent Sale of Additional Rights to Interferon Gamma-1b

On June 30, 2017, the Company completed its acquisition of certain rights to interferon gamma-1b from Boehringer Ingelheim International GmbH ("Boehringer Ingelheim International") in all territories outside of the United States, Canada and Japan and in connection therewith, paid Boehringer Ingelheim International €19.5 million ($22.3 million when converted using a Euro-to-Dollar exchange rate at date of payment of 1.1406). Boehringer Ingelheim International commercialized interferon gamma-1b as IMUKIN in an estimated thirty countries, primarily in Europe and the Middle East. Upon closing, during the year ended December 31, 2017, the Company accounted for the payment as the acquisition of an asset which was immediately impaired as projections for future net sales of IMUKIN in these territories did not exceed the related costs, and included the payment in the "impairment of long-lived assets" line item in its consolidated statement of comprehensive income (loss).

On July 24, 2018, the Company sold its rights to interferon gamma-1b in all territories outside the United States, Canada and Japan to Clinigen Group plc ("Clinigen") for an upfront payment of €7.5 million ($8.8 million when converted using a Euro-to-Dollar exchange rate at date of payment of 1.1683) and a potential additional contingent consideration payment of €3.0 million ($3.5 million when converted using a Euro-to-Dollar exchange rate of 1.1673) (the "IMUKIN sale"). The contingent consideration payment of €3.0 million ($3.3 million when converted using a Euro-to-Dollar exchange rate at the date of receipt of 1.0991) was received in September 2019. The Company continues to market interferon gamma-1b as ACTIMMUNE in the United States.

Pursuant to ASU No. 2017-01, the Company accounted for the IMUKIN sale as a sale of assets, specifically a sale of intellectual property rights and a sale of inventory.

The gain on sale of assets recorded to the consolidated statement of comprehensive income (loss) during the year ended December 31, 2018, was determined as follows (in thousands):

Cash proceeds including $715 for inventory	$	9,477
Contingent consideration receivable		3,502
Less net assets sold:		
Inventory		(623)
Transaction costs		(28)
Gain on sale of assets	**$**	**12,328**

Acquisition of River Vision

On May 8, 2017, the Company acquired 100% of the equity interests in River Vision Development Corp. ("River Vision") for upfront cash payments totaling approximately $150.3 million, including cash acquired of $6.3 million, with additional potential future milestone and royalty payments contingent on the satisfaction of certain regulatory milestones and sales thresholds. Pursuant to ASU No. 2017-01, the Company accounted for the River Vision acquisition as the purchase of an IPR&D asset and, pursuant to ASC Topic 730, *Research and Development*, recorded the purchase price as research and development expense during the year ended December 31, 2017. Further, the Company recognized approximately $32.4 million of federal net operating losses, $2.2 million of state net operating losses and $9.5 million of federal tax credits. The acquired tax attributes were set up as deferred tax assets which were further netted within the net deferred tax liabilities of the U.S. group, offset by a deferred credit recorded in long-term liabilities.

Under the agreement for the acquisition of River Vision, the Company is required to pay up to $325.0 million upon the attainment of various milestones, composed of $100.0 million related to FDA approval and $225.0 million related to net sales thresholds for TEPEZZA. The agreement also includes a royalty payment of 3 percent of the portion of annual worldwide net sales exceeding $300.0 million (if any). The Company will make a milestone payment of $100.0 million related to FDA approval during the first quarter of 2020 and is expected to be capitalized as a finite-lived intangible asset representing the developed technology for TEPEZZA. Refer to Note 15 for further detail on TEPEZZA milestone payments.

Divestiture of PROCYSBI and QUINSAIR rights in EMEA Regions

On June 23, 2017, the Company completed the sale of its European subsidiary that owned the marketing rights to PROCYSBI and QUINSAIR in Europe, the Middle East and Africa ("EMEA") regions (the "Chiesi divestiture") to Chiesi Farmaceutici S.p.A. ("Chiesi") for an upfront payment of $72.5 million, which reflects $3.1 million of cash divested, with additional potential milestone payments based on sales thresholds.

Pursuant to ASU No. 2017-01, the Company accounted for the Chiesi divestiture as a sale of a business. The Company determined that the sale of the business and its assets in connection with the Chiesi divestiture did not constitute a strategic shift and that it did not and will not have a major effect on its operations and financial results. Accordingly, the operations associated with the Chiesi divestiture are not reported in discontinued operations.

The gain on divestiture recorded during the year ended December 31, 2017 was determined as follows (in thousands):

Cash proceeds	$	72,462
Add reimbursement of royalties		5,074
Less net assets sold:		
Developed technology		(42,627)
Goodwill		(15,692)
Other		(5,984)
Transaction and other costs		(5,268)
Gain on divestiture	**$**	**7,965**

Under the terms of its agreement with Chiesi, the Company will continue to pay third parties for the royalties on sales of PROCYSBI and QUINSAIR in the EMEA regions, and Chiesi will reimburse the Company for those royalties. At the date of divestiture, the Company recorded an asset of $5.1 million to "other assets", which represented the estimated amounts that are expected to be reimbursed from Chiesi for the PROCYSBI and QUINSAIR royalties. These estimated royalties are accrued in "accrued expenses" and "other long-term liabilities".

Transaction and other costs primarily relate to professional and license fees attributable to the divestiture.

Licensing Agreement

On December 12, 2017, the Company entered into an agreement to license HZN-003 (formerly MEDI4945), a potential next-generation biologic for uncontrolled gout, from MedImmune LLC ("MedImmune"), the global biologics research and development arm of the AstraZeneca Group. HZN-003 is a pre-clinical, genetically engineered uricase derivative with optimized uricase and optimized PEGylation technology that has the potential to improve the response rate to the biologic as well as the potential for subcutaneous dosing. Under the terms of the agreement, the Company agreed to pay MedImmune an upfront cash payment of $12.0 million with additional potential future milestone payments of up to $153.5 million contingent on the satisfaction of certain development and sales thresholds. The $12.0 million upfront payment was accounted for as the acquisition of an asset and was recorded as "research and development" expenses in the consolidated statement of comprehensive income (loss) during the year ended December 31, 2017 and included in "accrued expenses" as of December 31, 2017. The upfront payment was subsequently paid in January 2018.

Other Arrangements

On January 3, 2019, the Company entered into a collaboration agreement with HemoShear Therapeutics, LLC ("HemoShear"), a biotechnology company, to discover novel therapeutic targets for gout. The collaboration provides the Company with an opportunity to address unmet treatment needs for people with gout by evaluating new targets for the control of serum uric acid levels as well as new targets to address the inflammation associated with acute flares of gout. Under the terms of the agreement, the Company paid HemoShear an upfront cash payment of $2.0 million with additional potential future milestone payments upon commencement of new stages of development, contingent on the Company's approval at each stage. In June 2019, the Company incurred a $4.0 million progress payment, which was subsequently paid in July 2019.

NOTE 5 – INVENTORIES

The components of inventories as of December 31, 2019 and 2018 consisted of the following (in thousands):

	As of December 31,	
	2019	2018
Raw materials	$ 6,750	$ 5,092
Work-in-process	22,465	27,068
Finished goods	24,587	18,591
Inventories, net	**$ 53,802**	**$ 50,751**

At December 31, 2019, the Company had approximately $3.2 million of raw materials and $3.9 million of work-in-process inventory related to TEPEZZA.

NOTE 6 – PREPAID EXPENSES AND OTHER CURRENT ASSETS

Prepaid expenses and other current assets as of December 31, 2019 and 2018 consisted of the following (in thousands):

	As of December 31,	
	2019	2018
Deferred charge for taxes on intra-company profit	$ 46,388	$ 21,734
Advance payments for inventory	31,203	1,449
Rabbi trust assets	12,704	8,203
Prepaid income taxes	12,583	5,899
Other prepaid expenses and other current assets	40,699	30,933
Prepaid expenses and other current assets	**$ 143,577**	**$ 68,218**

Advance payments for inventory as of December 31, 2019, represents payments made to the manufacturer of TEPEZZA drug substance.

NOTE 7 – PROPERTY AND EQUIPMENT

Property and equipment as of December 31, 2019 and 2018 consisted of the following (in thousands):

	As of December 31,	
	2019	2018
Leasehold improvements	$ 25,985	$ 9,982
Software	14,890	14,843
Machinery and equipment	5,217	4,800
Computer equipment	3,316	2,485
Other	6,334	2,501
	55,742	**34,611**
Less accumulated depreciation	(25,848)	(19,197)
Construction in process	265	4,687
Property and equipment, net	**$ 30,159**	**$ 20,101**

Depreciation expense for the years ended December 31, 2019, 2018 and 2017 was $6.7 million, $6.1 million and $6.6 million, respectively.

In February 2020, the Company purchased a three-building campus in Deerfield, Illinois for total cash consideration of $115.0 million. The Deerfield campus totals 70 acres and consists of more than 650,000 square feet of office space. The Company expects to move to the Deerfield campus in the second half of 2020 and market its Lake Forest office for sub-lease.

NOTE 8 – GOODWILL AND INTANGIBLE ASSETS

Effective January 1, 2019, the Company retrospectively changed its accounting for business combinations, which impacted the carrying amounts of its goodwill and intangible assets. Refer to Note 1 for further detail.

Goodwill

The gross carrying amount of goodwill as of December 31, 2019 and 2018 was $413.7 million.

The table below presents goodwill for the Company's reportable segments as of December 31, 2019 (in thousands):

	Orphan and Rheumatology	Inflammation	Total
Goodwill	$ 360,745	$ 52,924	**$ 413,669**

As of December 31, 2019, there were no accumulated goodwill impairment losses.

Intangible Assets

As of December 31, 2019, the Company's finite-lived intangible assets consisted of developed technology related to ACTIMMUNE, BUPHENYL, KRYSTEXXA, PENNSAID 2%, PROCYSBI, RAVICTI and RAYOS, as well as customer relationships for ACTIMMUNE. The intangible asset related to VIMOVO developed technology was fully amortized as of December 31, 2019.

During the year ended December 31, 2019, in connection with the MIGERGOT transaction, the Company wrote off the remaining net book value of developed technology related to MIGERGOT of $17.0 million. See Note 4 for further details.

During the year ended December 31, 2018, in connection with the Immedica transaction, the Company recorded a reduction in the net book value of developed technology related to RAVICTI and AMMONAPS of $4.1 million. See Note 4 for further details.

The Company tests its intangible assets for impairment when events or circumstances may indicate that the carrying value of these assets exceeds their fair value. During the year ended December 31, 2018, the Company recorded an impairment of $33.6 million to fully write off the book value of developed technology related to PROCYSBI in Canada and Latin America due primarily to lower anticipated future net sales based on a Patented Medicine Prices Review Board review. The fair value of developed technology was determined using an income approach.

The Company also recorded an impairment of $10.6 million during the year ended December 31, 2018, to fully write off the book value of developed technology related to LODOTRA as result of amendments to its license and supply agreements with Jagotec AG ("Jagotec") and Skyepharma AG, which are affiliates of Vectura Group plc ("Vectura"). Under these amendments, effective January 1, 2019, the Company agreed to transfer all economic benefits of LODOTRA in Europe to Vectura during an initial transition period, with full rights transferring to Vectura when certain transfer activities have been completed. These transfer activities are ongoing. The Company ceased recording LODOTRA net sales beginning January 1, 2019. The fair value of developed technology was determined using an income approach.

Intangible assets as of December 31, 2019 and December 31, 2018 consisted of the following (in thousands):

	As of December 31,						
	2019			2018			
	Cost Basis	Accumulated Amortization	Net Book Value	Cost Basis	Impairment	Accumulated Amortization	Net Book Value
Developed technology	$ 2,758,403	$(1,059,595)	$ 1,698,808	$ 2,828,648	$ (44,245)	$ (838,764)	$ 1,945,639
Customer relationships	8,100	(4,280)	3,820	8,100	—	(3,470)	4,630
Total intangible assets	**$ 2,766,503**	**$(1,063,875)**	**$ 1,702,628**	**$ 2,836,748**	**$ (44,245)**	**$ (842,234)**	**$ 1,950,269**

Amortization expense for the years ended December 31, 2019, 2018 and 2017 was $230.4 million, $243.6 million and $249.5 million, respectively. As of December 31, 2019, estimated future amortization expense was as follows (in thousands):

2020	$ 228,728
2021	221,244
2022	220,071
2023	219,454
2024	218,022
Thereafter	595,109
Total	**$ 1,702,628**

NOTE 9 – ACCRUED EXPENSES

Accrued expenses as of December 31, 2019 and 2018 consisted of the following (in thousands):

	As of December 31,	
	2019	2018
Payroll-related expenses	$ 84,516	$ 78,555
Allowances for returns	45,082	39,041
Consulting and professional services	32,423	35,799
Accrued royalties	19,985	15,746
Accrued interest	18,709	13,196
Pricing review liability	9,831	9,091
Accrued other	24,688	24,311
Accrued expenses	**$ 235,234**	**$ 215,739**

NOTE 10 – ACCRUED TRADE DISCOUNTS AND REBATES

Accrued trade discounts and rebates as of December 31, 2019 and 2018 consisted of the following (in thousands):

	As of December 31,	
	2019	2018
Accrued commercial rebates and wholesaler fees	$ 138,272	$ 153,083
Accrued co-pay and other patient assistance	163,641	179,463
Accrued government rebates and chargebacks	164,508	125,217
Accrued trade discounts and rebates	**$ 466,421**	**$ 457,763**
Invoiced commercial rebates and wholesaler fees, co-pay and other patient assistance, and government rebates and chargebacks in accounts payable	489	3,666
Total customer-related accruals and allowances	**$ 466,910**	**$ 461,429**

The following table summarizes changes in the Company's customer-related accruals and allowances during the years ended December 31, 2019 and 2018 (in thousands):

	Wholesaler Fees and Commercial Rebates	Co-Pay and Other Patient Assistance	Government Rebates and Chargebacks	Total
Balance at December 31, 2017	**$ 190,485**	**$ 232,325**	**$ 93,985**	**$ 516,795**
Current provisions relating to sales during the year ended December 31, 2018	590,316	1,970,714	411,449	**2,972,479**
Adjustments relating to prior-year sales	(667)	(374)	(14,787)	**(15,828)**
Payments relating to sales during the year ended December 31, 2018	(436,871)	(1,791,252)	(283,124)	**(2,511,247)**
Payments relating to prior-year sales	(189,818)	(231,951)	(79,001)	**(500,770)**
Balance at December 31, 2018	**$ 153,445**	**$ 179,462**	**$ 128,522**	**$ 461,429**
Current provisions relating to sales during the year ended December 31, 2019	484,843	1,519,712	503,652	**2,508,207**
Adjustments relating to prior-year sales	(5,296)	—	11,121	**5,825**
Payments relating to sales during the year ended December 31, 2019	(346,082)	(1,356,071)	(339,603)	**(2,041,756)**
Payments relating to prior-year sales	(148,149)	(179,462)	(139,184)	**(466,795)**
Balance at December 31, 2019	**$ 138,761**	**$ 163,641**	**$ 164,508**	**$ 466,910**

NOTE 11 – SEGMENT AND OTHER INFORMATION

The Company has two reportable segments, the orphan and rheumatology segment and the inflammation segment, and the Company reports net sales and segment operating income for each segment.

The orphan and rheumatology segment includes the marketed medicines KRYSTEXXA, RAVICTI, PROCYSBI, ACTIMMUNE, RAYOS, BUPHENYL and QUINSAIR. The inflammation segment includes the marketed medicines PENNSAID 2%, DUEXIS and VIMOVO and previously included MIGERGOT prior to the MIGERGOT transaction.

The Company's CODM evaluates the financial performance of the Company's segments based upon segment operating income. Segment operating income is defined as loss before benefit for income taxes adjusted for the items set forth in the reconciliation below. Items below income from operations are not reported by segment, since they are excluded from the measure of segment profitability reviewed by the Company's CODM. Additionally, certain expenses are not allocated to a segment. The Company does not report balance sheet information by segment as no balance sheet by segment is reviewed by the Company's CODM.

The following table reflects net sales by medicine for the Company's reportable segments (in thousands):

	Year Ended December 31,		
	2019	2018	2017
KRYSTEXXA	$ 342,379	$ 258,920	$ 156,483
RAVICTI	228,755	226,650	193,918
PROCYSBI	161,941	154,895	137,740
ACTIMMUNE	107,302	105,563	110,993
RAYOS	78,595	61,067	52,125
BUPHENYL	9,806	21,810	20,792
QUINSAIR	817	504	3,442
LODOTRA	—	2,067	5,393
Orphan and Rheumatology segment net sales	**$ 929,595**	**$ 831,476**	**$ 680,886**
PENNSAID 2%	200,756	190,206	191,050
DUEXIS	115,750	114,672	121,161
VIMOVO	52,106	67,646	57,666
MIGERGOT	1,822	3,570	5,468
Inflammation segment net sales	**$ 370,434**	**$ 376,094**	**$ 375,345**
Total net sales	**$ 1,300,029**	**$ 1,207,570**	**$ 1,056,231**

The table below provides reconciliations of the Company's segment operating income to the Company's total loss before benefit for income taxes (in thousands):

	Year Ended December 31,		
	2019	2018	2017
Segment operating income:			
Orphan and Rheumatology	$ 306,333	$ 290,014	$ 241,135
Inflammation	174,869	160,447	149,133
Reconciling items:			
Amortization and step-up:			
Intangible amortization expense	(230,424)	(243,634)	(249,456)
Inventory step-up expense	(89)	(17,312)	(119,151)
Interest expense, net	(87,089)	(121,692)	(126,523)
Share-based compensation	(91,215)	(114,860)	(121,553)
Impairment of long-lived assets	—	(46,096)	(22,270)
Restructuring and realignment costs	(237)	(15,350)	(4,883)
Acquisition/divestiture-related costs	(1,032)	(3,989)	(177,490)
Depreciation	(6,733)	(6,126)	(6,631)
Litigation settlements	(1,000)	(5,750)	—
Drug substance harmonization costs	(457)	(2,855)	(10,651)
Fees relating to term loan refinancing	(2,292)	(937)	(5,220)
Foreign exchange gain (loss)	33	(192)	(260)
Upfront and milestone payments related to license agreements	(9,073)	(90)	(12,186)
Gain on divestiture	—	—	7,965
Loss on debt extinguishment	(58,835)	—	(978)
Other (expense) income, net	(944)	841	447
Charges relating to discontinuation of Friedreich's ataxia program	(1,076)	1,464	(239)
(Loss) gain on sale of assets	(10,963)	42,985	—
Loss before benefit for income taxes	**$ (20,224)**	**$ (83,132)**	**$ (458,811)**

As a result of the change in accounting method described in Note 1, certain adjustments in the above table have been changed from the amounts presented in the reconciliation of the Company's segment operating income to its total loss before benefit for income taxes as previously reported. The Company's segment operating income was not impacted by the change in accounting method.

The following table presents the amount and percentage of gross sales to customers that represented more than 10% of the Company's gross sales included in its two reportable segments, and all other customers as a group (in thousands, except percentages):

	Year ended December 31,					
	2019		2018		2017	
	Amount	% of Gross Sales	Amount	% of Gross Sales	Amount	% of Gross Sales
Customer A	$ 1,414,617	36%	$ 1,553,333	36%	$ 1,165,591	29%
Customer B	757,138	19%	526,398	12%	567,583	14%
Customer C	664,454	17%	1,011,996	24%	1,205,268	30%
Customer D	391,628	10%	458,074	11%	16,304	0%
Other Customers	683,987	18%	714,652	17%	1,103,093	27%
Gross Sales	**$ 3,911,824**	**100%**	**$ 4,264,453**	**100%**	**$ 4,057,839**	**100%**

Geographic revenues are determined based on the country in which the Company's customers are located. The following table presents a summary of net sales attributed to geographic sources (in thousands, except percentages):

	Year Ended December 31, 2019		Year Ended December 31, 2018		Year Ended December 31, 2017	
	Amount	% of Total Net Sales	Amount	% of Total Net Sales	Amount	% of Total Net Sales
United States	$ 1,292,419	99%	$ 1,186,519	98%	$ 1,026,527	97%
Rest of world	7,610	1%	21,051	2%	29,704	3%
Total net sales	**$ 1,300,029**		**$ 1,207,570**		**$ 1,056,231**	

The following table presents total tangible long-lived assets by location (in thousands):

	As of December 31,	
	2019	2018
United States	$ 27,497	$ 17,107
Other	2,662	2,994
Total long-lived assets (1)	**$ 30,159**	**$ 20,101**

(1) Long-lived assets consist of property and equipment.

NOTE 12 – FAIR VALUE MEASUREMENTS

The following tables and paragraphs set forth the Company's financial instruments that are measured at fair value on a recurring basis within the fair value hierarchy. Assets and liabilities measured at fair value are classified in their entirety based on the lowest level of input that is significant to the fair value measurement. The Company's assessment of the significance of a particular input to the fair value measurement in its entirety requires management to make judgments and consider factors specific to the asset or liability. The following describes three levels of inputs that may be used to measure fair value:

Level 1—Observable inputs such as quoted prices in active markets for identical assets or liabilities;

Level 2—Observable inputs other than Level 1 prices such as quoted prices for similar assets or liabilities, quoted prices in markets that are not active, or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities; and

Level 3—Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

The Company utilizes the market approach to measure fair value for its money market funds. The market approach uses prices and other relevant information generated by market transactions involving identical or comparable assets or liabilities.

As of December 31, 2018, the Company's cash and cash equivalents included bank time deposits which were measured at fair value using Level 2 inputs and their carrying values were approximately equal to their fair values. Level 2 inputs, obtained from various third-party data providers, represent quoted prices for similar assets in active markets, or these inputs were derived from observable market data, or if not directly observable, were derived from or corroborated by other observable market data.

Other current assets and other long-term liabilities recorded at fair value on a recurring basis are composed of investments held in a rabbi trust and the related deferred liability for deferred compensation arrangements. Quoted prices for this investment, primarily in mutual funds, are available in active markets. Thus, the Company's investments related to deferred compensation arrangements and the related long-term liability are classified as Level 1 measurements in the fair value hierarchy.

Assets and liabilities measured at fair value on a recurring basis

The following tables set forth the Company's financial assets and liabilities at fair value on a recurring basis as of December 31, 2019 and 2018 (in thousands):

	December 31, 2019			
	Level 1	Level 2	Level 3	Total
Assets:				
Money market funds	1,029,725	—	—	1,029,725
Other current assets	12,704	—	—	12,704
Total assets at fair value	**$ 1,042,429**	**$ —**	**$ —**	**$ 1,042,429**
Liabilities:				
Other long-term liabilities	(12,704)	—	—	(12,704)
Total liabilities at fair value	**$ (12,704)**	**$ —**	**$ —**	**$ (12,704)**

	December 31, 2018			
	Level 1	Level 2	Level 3	Total
Assets:				
Bank time deposits	$ —	$ 6,500	$ —	$ 6,500
Money market funds	915,800	—	—	915,800
Other current assets	8,203	—	—	8,203
Total assets at fair value	**$ 924,003**	**$ 6,500**	**$ —**	**$ 930,503**
Liabilities:				
Other long-term liabilities	(8,203)	—	—	(8,203)
Total liabilities at fair value	**$ (8,203)**	**$ —**	**$ —**	**$ (8,203)**

NOTE 13 – DEBT AGREEMENTS

The Company's outstanding debt balances as of December 31, 2019 and 2018 consisted of the following (in thousands):

	As of December 31,	
	2019	2018
Term Loan Facility	$ 418,026	$ 818,026
2027 Senior Notes	600,000	—
2023 Senior Notes	—	475,000
2024 Senior Notes	—	300,000
Exchangeable Senior Notes	400,000	400,000
Total face value	**1,418,026**	**1,993,026**
Debt discount	(59,922)	(87,038)
Deferred financing fees	(5,263)	(9,304)
Total long-term debt and exchangeable notes	**1,352,841**	**1,896,684**
Less: long-term debt - current portion	—	—
Long-term debt and exchangeable notes, net of current portion	**$ 1,352,841**	**$ 1,896,684**

Scheduled maturities with respect to the Company's long-term debt are as follows (in thousands):

2020	$ —
2021	—
2022	(400,000)
2023	—
2024	—
Thereafter	(1,018,026)
Total	**$ (1,418,026)**

Term Loan Facility and Revolving Credit Facility

On December 18, 2019, Horizon Therapeutics USA, Inc. (formerly known as Horizon Pharma USA, Inc.) (the "Borrower"), a wholly owned subsidiary of the Company, borrowed approximately $418.0 million aggregate principal amount of loans (the "December 2019 Refinancing Loans") pursuant to an amendment (the "December 2019 Refinancing Amendment") to the credit agreement, dated as of May 7, 2015, by and among the Borrower, the Company and certain of its subsidiaries as guarantors, the lenders party thereto from time to time and Citibank, N.A., as administrative agent and collateral agent, as amended by Amendment No. 1, dated as of October 25, 2016, Amendment No. 2, dated March 29, 2017, Amendment No. 3, dated October 23, 2017, Amendment No. 4, dated October 19, 2018, Amendment No. 5, dated March 11, 2019 and Amendment No. 6, dated May 22, 2019 (the "Term Loan Facility"). Pursuant to Amendment No. 5, the Borrower received $200.0 million aggregate principal amount of revolving commitments (the "Incremental Revolving Commitments"). The Incremental Revolving Commitments were established pursuant to an incremental facility (the "Revolving Credit Facility") and provide the Borrower with $200.0 million of additional borrowing capacity, which includes a $50.0 million letter of credit sub-facility. The Incremental Revolving Commitments will terminate in March 2024. Borrowings under the Revolving Credit Facility are available for general corporate purposes. As of December 31, 2019, the Revolving Credit Facility was undrawn. As used herein, all references to the "Credit Agreement" are references to the original credit agreement, dated as of May 7, 2015, as amended through the December 2019 Refinancing Amendment.

The December 2019 Refinancing Loans were incurred as a separate new class of term loans under the Credit Agreement with substantially the same terms as the previously outstanding senior secured term loans incurred on May 22, 2019 (the "Refinanced Loans") to effectuate a repricing of the Refinanced Loans. The Borrower used the proceeds of the December 2019 Refinancing Loans to repay the Refinanced Loans, which totaled approximately $418.0 million. The December 2019 Refinancing Loans bear interest at a rate, at the Borrower's option, equal to the London Inter-Bank Offered Rate ("LIBOR"), plus 2.25% per annum (subject to a 0.00% LIBOR floor) or the adjusted base rate plus 1.25% per annum, with a step-down to LIBOR plus 2.00% per annum or the adjusted base rate plus 1.00% per annum at the time the Company's leverage ratio is less than or equal to 2.00 to 1.00. The adjusted base rate is defined as the greatest of (a) LIBOR (using one-month interest period) plus 1.00%, (b) the prime rate, (c) the federal funds rate plus 0.50%, and (d) 1.00%.

The loans under the Revolving Credit Facility bear interest, at the Borrower's option, at a rate equal to either LIBOR plus an applicable margin of 2.25% per annum (subject to a LIBOR floor of 0.00%), or the adjusted base rate plus 1.25% per annum, with a step-down to LIBOR plus 2.00% per annum or the adjusted base rate plus 1.00% per annum at the time the Company's leverage ratio is less than or equal to 2.00 to 1.00. The Credit Agreement provides for (i) the December 2019 Refinancing Loans, (ii) the Revolving Credit Facility, (iii) one or more uncommitted additional incremental loan facilities subject to the satisfaction of certain financial and other conditions, and (iv) one or more uncommitted refinancing loan facilities with respect to loans thereunder. The Credit Agreement allows for the Company and certain of its subsidiaries to become additional borrowers under incremental or refinancing facilities.

The obligations under the Credit Agreement (including obligations in respect of the December 2019 Refinancing Loans and the Revolving Credit Facility) and any swap obligations and cash management obligations owing to a lender (or an affiliate of a lender) are guaranteed by the Company and each of the Company's existing and subsequently acquired or formed direct and indirect subsidiaries (other than certain immaterial subsidiaries, subsidiaries whose guarantee would result in material adverse tax consequences and subsidiaries whose guarantee is prohibited by applicable law). The obligations under the Credit Agreement (including obligations in respect of the December 2019 Refinancing Loans and the Revolving Credit Facility) and any related swap and cash management obligations are secured, subject to customary permitted liens and other agreed upon exceptions, by a perfected security interest in (i) all tangible and intangible assets of the Borrower and the guarantors, except for certain customary excluded assets, and (ii) all of the capital stock owned by the Borrower and guarantors thereunder (limited, in the case of the stock of certain non-U.S. subsidiaries of the Borrower, to 65% of the capital stock of such subsidiaries). The Borrower and the guarantors under the Credit Agreement are individually and collectively referred to herein as a "Loan Party" and the "Loan Parties," as applicable.

The Company elected to exercise its reinvestment rights under the mandatory prepayment provisions of the Credit Agreement with respect to the net proceeds from the Company's sale of its rights to PROCYSBI and QUINSAIR in the Europe, Middle East and Africa regions to Chiesi Farmaceutici S.p.A. To the extent the Company had not applied such net proceeds to permitted acquisitions (including the acquisition of rights to products and products lines) and/or the acquisition of capital assets within 365 days of the receipt thereof (or committed to so apply and then applied within 180 days after the end of such 365-day period), the Company was required to make a mandatory prepayment under the Credit Agreement in an amount equal to the unapplied net proceeds. In June 2018, the Company repaid $23.5 million under the mandatory prepayment provisions of the Credit Agreement.

On March 18, 2019, the Company completed the repayment of $300.0 million of the outstanding principal amount of term loans under the Credit Agreement following the closing of its underwritten public equity offering on March 11, 2019. In July 2019, the Company repaid an additional $100.0 million of term loans under the Credit Agreement following the private placement of the 2027 Senior Notes. Following these repayments, the outstanding principal balance of term loans under the Credit Agreement was $418.0 million.

Additionally, the Company elected to exercise its reinvestment rights under the mandatory prepayment provisions of the Credit Agreement with respect to the net proceeds from the Immedica transaction. To the extent the Company had not applied such net proceeds to permitted acquisitions (including the acquisition of rights to products and products lines) and/or the acquisition of capital assets within 365 days of the receipt of proceeds from the Immedica transaction (or commit to so apply and then apply within 180 days after the end of such 365-day period), the Company was required to make a mandatory prepayment under the Credit Agreement in an amount equal to the unapplied net proceeds. In March 2019, the Company repaid $35.0 million under the mandatory prepayment provisions of the Credit Agreement which was included in the $300.0 million repayment referred to above.

The Borrower is permitted to make voluntary prepayments of the loans under the Credit Agreement at any time without payment of a premium, except that with respect to the December 2019 Refinancing Loans, a 1% premium will apply to a repayment of the December 2019 Refinancing Loans in connection with a repricing of, or any amendment to the Credit Agreement in a repricing of, such loans effected on or prior to the date that is six months following December 18, 2019. The Borrower is required to make mandatory prepayments of loans under the Credit Agreement (without payment of a premium) with (a) net cash proceeds from certain non-ordinary course asset sales (subject to reinvestment rights and other exceptions), (b) casualty proceeds and condemnation awards (subject to reinvestment rights and other exceptions), (c) net cash proceeds from issuances of debt (other than certain permitted debt), and (d) 50% of the Company's excess cash flow (subject to decrease to 25% or 0% if the Company's first lien leverage ratio is less than 2.25:1 or 1.75:1, respectively). The principal amount of the December 2019 Refinancing Loans are due and payable on May 22, 2026, the final maturity date of the December 2019 Refinancing Loans.

The Credit Agreement contains customary representations and warranties and customary affirmative and negative covenants, including, among other things, restrictions on indebtedness, liens, investments, mergers, dispositions, prepayment of other indebtedness and dividends and other distributions. The Credit Agreement also contains a springing financial maintenance covenant, which requires that the Company maintain a specified leverage ratio at the end of each fiscal quarter. The covenant is tested if both the outstanding loans and letters of credit under the Revolving Credit Facility, subject to certain exceptions, exceed 25% of the total commitments under the Revolving Credit Facility as of the last day of any fiscal quarter. If the Company fails to meet this covenant, the commitments under the Revolving Credit Facility could be terminated and any outstanding borrowings, together with accrued interest, under the Revolving Credit Facility could be declared immediately due and payable.

Other events of default under the Credit Agreement include: (i) the failure by the Borrower to timely make payments due under the Credit Agreement; (ii) material misrepresentations or misstatements in any representation or warranty by any Loan Party when made; (iii) failure by any Loan Party to comply with the covenants under the Credit Agreement and other related agreements; (iv) certain defaults under a specified amount of other indebtedness of the Company or its subsidiaries; (v) insolvency or bankruptcy-related events with respect to the Company or any of its material subsidiaries; (vi) certain undischarged judgments against the Company or any of its restricted subsidiaries; (vii) certain ERISA-related events reasonably expected to have a material adverse effect on the Company and its restricted subsidiaries taken as a whole; (viii) certain security interests or liens under the loan documents ceasing to be, or being asserted by the Company or its restricted subsidiaries not to be, in full force and effect; (ix) any loan document or material provision thereof ceasing to be, or any challenge or assertion by any Loan Party that such loan document or material provision is not, in full force and effect; and (x) the occurrence of a change of control. If one or more events of default occurs and continues beyond any applicable cure period, the administrative agent may, with the consent of the lenders holding a majority of the loans and commitments under the facilities, or will, at the request of such lenders, terminate the commitments of the lenders to make further loans and declare all of the obligations of the Loan Parties under the Credit Agreement to be immediately due and payable.

The interest on the Term Loan Facility is variable and as of December 31, 2019, the interest rate on the Term Loan Facility was 3.94% and the effective interest rate was 4.31%.

As of December 31, 2019, the fair value of the amounts outstanding under the Term Loan Facility was approximately $420.1 million, categorized as a Level 2 instrument, as defined in Note 12.

2027 Senior Notes

On July 16, 2019, Horizon Therapeutics USA, Inc. (formerly known as Horizon Pharma USA, Inc.), the Company's wholly owned subsidiary ("HTUSA"), completed a private placement of $600.0 million aggregate principal amount of 5.5% Senior Notes due 2027 (the "2027 Senior Notes") to several investment banks acting as initial purchasers, who subsequently resold the 2027 Senior Notes to persons reasonably believed to be qualified institutional buyers.

The Company used the net proceeds from the offering of the 2027 Senior Notes, together with approximately $65.0 million in cash on hand, to redeem or prepay $625.0 million of its outstanding debt, consisting of (i) the outstanding $225.0 million principal amount of its 6.625% Senior Notes due 2023 (the "2023 Senior Notes"), (ii) the outstanding $300.0 million principal amount of its 8.750% Senior Notes due 2024 (the "2024 Senior Notes") and (iii) $100.0 million of the outstanding principal amount of senior secured term loans under the Credit Agreement, as well as to pay the related premiums and fees and expenses, excluding accrued interest, associated with such redemption and prepayment.

The 2027 Senior Notes are HTUSA's general unsecured senior obligations, rank equally in right of payment with all existing and future senior debt of HTUSA and rank senior in right of payment to any existing and future subordinated debt of HTUSA. The 2027 Senior Notes are effectively subordinate to all of the existing and future secured debt of HTUSA to the extent of the value of the collateral securing such debt.

The 2027 Senior Notes are unconditionally guaranteed on a senior basis by the Company and all of the Company's restricted subsidiaries, other than HTUSA and certain immaterial subsidiaries, that guarantee the Credit Agreement. The guarantees are each guarantor's senior unsecured obligations and rank equally in right of payment with such guarantor's existing and future senior debt and senior in right of payment to any existing and future subordinated debt of such guarantor. The guarantees are effectively subordinated to all of the existing and future secured debt of each guarantor, including such guarantor's guarantee under the Credit Agreement, to the extent of the value of the collateral securing such debt. The guarantees of a guarantor may be released under certain circumstances. The 2027 Senior Notes are structurally subordinated to all of the liabilities of the Company's subsidiaries that do not guarantee the 2027 Senior Notes.

The 2027 Senior Notes accrue interest at an annual rate of 5.5% payable semiannually in arrears on February 1 and August 1 of each year, beginning on February 1, 2020. The 2027 Senior Notes will mature on August 1, 2027, unless earlier exchanged, repurchased or redeemed.

Except as described below, the 2027 Senior Notes may not be redeemed before August 1, 2022. Thereafter, some or all of the 2027 Senior Notes may be redeemed at any time at specified redemption prices, plus accrued and unpaid interest to the redemption date. At any time prior to August 1, 2022, some or all of the 2027 Senior Notes may be redeemed at a price equal to 100% of the aggregate principal amount thereof, plus a make-whole premium and accrued and unpaid interest to the redemption date. Also prior to August 1, 2022, up to 40% of the aggregate principal amount of the 2027 Senior Notes may be redeemed at a redemption price of 105.5% of the aggregate principal amount thereof, plus accrued and unpaid interest, with the net proceeds of certain equity offerings. In addition, the 2027 Senior Notes may be redeemed in whole but not in part at a redemption price equal to 100% of the principal amount plus accrued and unpaid interest and additional amounts, if any, to, but excluding, the redemption date, if on the next date on which any amount would be payable in respect of the 2027 Senior Notes, HTUSA or any guarantor is or would be required to pay additional amounts as a result of certain tax related events.

If the Company undergoes a change of control, HTUSA will be required to make an offer to purchase all of the 2027 Senior Notes at a price in cash equal to 101% of the aggregate principal amount thereof plus accrued and unpaid interest to, but not including, the repurchase date, subject to certain exceptions. If the Company or certain of its subsidiaries engages in certain asset sales, HTUSA will be required under certain circumstances to make an offer to purchase the 2027 Senior Notes at 100% of the principal amount thereof, plus accrued and unpaid interest to the repurchase date.

The indenture governing the 2027 Senior Notes contains covenants that limit the ability of the Company and its restricted subsidiaries to, among other things, pay dividends or distributions, repurchase equity, prepay junior debt and make certain investments, incur additional debt and issue certain preferred stock, incur liens on assets, engage in certain asset sales, merge, consolidate with or merge or sell all or substantially all of their assets, enter into transactions with affiliates, designate subsidiaries as unrestricted subsidiaries, and allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to the Company. Certain of the covenants will be suspended during any period in which the 2027 Senior Notes receive investment grade ratings. The indenture governing the 2027 Senior Notes also includes customary events of default.

As of December 31, 2019, the interest rate on the 2027 Senior Notes was 5.50% and the effective interest rate was 5.76%.

As of December 31, 2019, the fair value of the 2027 Senior Notes was approximately $645.8 million, categorized as a Level 2 instrument, as defined in Note 12.

2023 Senior Notes

On April 29, 2015, Horizon Pharma Financing Inc. ("Horizon Financing"), a wholly owned subsidiary of the Company, completed a private placement of $475.0 million aggregate principal amount of 2023 Senior Notes to certain investment banks acting as initial purchasers who subsequently resold the 2023 Senior Notes to qualified institutional buyers as defined in Rule 144A under the Securities Act of 1933, as amended (the "Securities Act"), and in offshore transactions to non-U.S. persons in reliance on Regulation S under the Securities Act. The net proceeds from the offering of the 2023 Senior Notes were approximately $462.3 million, after deducting the initial purchasers' discount and offering expenses payable by Horizon Financing.

In connection with the closing of the acquisition of Hyperion Therapeutics, Inc. ("Hyperion") on May 7, 2015, Horizon Financing merged with and into Horizon Pharma, Inc. ("HPI") and on October 31, 2018, HPI merged with and into HTUSA. As a result, the 2023 Senior Notes became the general unsecured senior obligations of HTUSA, which was previously a guarantor under the 2023 Senior Notes. The obligations under the 2023 Senior Notes were fully and unconditionally guaranteed on a senior unsecured basis by the Company and all of the Company's direct and indirect subsidiaries that were guarantors from time to time under the Credit Agreement.

The Company redeemed $250.0 million of 2023 Senior Notes on May 1, 2019. In connection with this early redemption, the Company paid a premium of $8.3 million on May 1, 2019. Following this redemption, $225.0 million of the 2023 Senior Notes remained outstanding.

On August 9, 2019, the Company redeemed the remaining $225.0 million of 2023 Senior Notes. In connection with this early redemption, the Company paid a premium of $7.5 million on August 9, 2019.

2024 Senior Notes

On October 25, 2016, HPI and HTUSA (together, in such capacity, the "2024 Issuers"), completed a private placement of $300.0 million aggregate principal amount of 2024 Senior Notes to certain investment banks acting as initial purchasers who subsequently resold the 2024 Senior Notes to qualified institutional buyers as defined in Rule 144A under the Securities Act. The net proceeds from the offering of the 2024 Senior Notes were approximately $291.9 million, after deducting the initial purchasers' discount and offering expenses payable by the 2024 Issuers. On October 31, 2018, HPI merged with and into HTUSA, and as a result, HPI's obligations as co-issuer under the 2024 Senior Notes became HTUSA's general unsecured senior obligations.

The obligations under the 2024 Senior Notes were HTUSA's general unsecured senior obligations and were fully and unconditionally guaranteed on a senior unsecured basis by the Company and all of the Company's direct and indirect subsidiaries that were guarantors from time to time under the Credit Agreement.

On August 9, 2019, the Company redeemed all $300.0 million of 2024 Senior Notes. In connection with this early redemption, the Company paid a premium of $23.7 million on August 9, 2019.

Exchangeable Senior Notes

On March 13, 2015, Horizon Investment completed a private placement of $400.0 million aggregate principal amount of Exchangeable Senior Notes to certain investment banks acting as initial purchasers who subsequently resold the Exchangeable Senior Notes to qualified institutional buyers as defined in Rule 144A under the Securities Act. The net proceeds from the offering of the Exchangeable Senior Notes were approximately $387.2 million, after deducting the initial purchasers' discount and offering expenses payable by Horizon Investment.

The Exchangeable Senior Notes are fully and unconditionally guaranteed, on a senior unsecured basis, by the Company (the "Guarantee"). The Exchangeable Senior Notes and the Guarantee are Horizon Investment's and the Company's senior unsecured obligations. The Exchangeable Senior Notes accrue interest at an annual rate of 2.50% payable semiannually in arrears on March 15 and September 15 of each year, beginning on September 15, 2015. The Exchangeable Senior Notes will mature on March 15, 2022, unless earlier exchanged, repurchased or redeemed. The initial exchange rate is 34.8979 ordinary shares of the Company per $1,000 principal amount of the Exchangeable Senior Notes (equivalent to an initial exchange price of approximately $28.66 per ordinary share). The exchange rate will be subject to adjustment in some events but will not be adjusted for any accrued and unpaid interest. In addition, following certain corporate events that occur prior to the maturity date or upon a tax redemption, Horizon Investment will increase the exchange rate for a holder who elects to exchange its Exchangeable Senior Notes in connection with such a corporate event or a tax redemption in certain circumstances.

Other than as described below, the Exchangeable Senior Notes may not be redeemed by the Company.

Issuer Redemptions:

Optional Redemption for Changes in the Tax Laws of a Relevant Taxing Jurisdiction: Horizon Investment may redeem the Exchangeable Senior Notes at its option, prior to March 15, 2022, in whole but not in part, in connection with certain tax-related events.

Provisional Redemption: Horizon Investment may redeem for cash all or a portion of the Exchangeable Senior Notes if the last reported sale price of ordinary shares of the Company has been at least 130% of the exchange price then in effect for at least twenty trading days whether or not consecutive) during any thirty consecutive trading day period ending on, and including, the trading day immediately preceding the date on which Horizon Investment provide written notice of redemption. The redemption price will be equal to 100% of the principal amount of the Exchangeable Senior Notes to be redeemed, plus accrued and unpaid interest to, but not including, the redemption date; provided that if the redemption date occurs after a regular record date and on or prior to the corresponding interest payment date, Horizon Investment will pay the full amount of accrued and unpaid interest due on such interest payment date to the record holder of the Exchangeable Senior Notes on the regular record date corresponding to such interest payment date, and the redemption price payable to the holder who presents an Exchangeable Senior Note for redemption will be equal to 100% of the principal amount of such Exchangeable Senior Note.

Holder Exchange Rights:

Holders may exchange all or any portion of their Exchangeable Senior Notes at their option at any time prior to the close of business on the business day immediately preceding December 15, 2021 only upon satisfaction of one or more of the following conditions:

1. Exchange upon Satisfaction of Sale Price Condition – During any calendar quarter, if the last reported sale price of ordinary shares of the Company for at least twenty trading days (whether or not consecutive) during the period of thirty consecutive trading days ending on the last trading day of the immediately preceding calendar quarter is greater than or equal to 130% of the applicable exchange price on each applicable trading day.
2. Exchange upon Satisfaction of Trading Price Condition – During the five business day period after any ten consecutive trading day period in which the trading price per $1,000 principal amount of Exchangeable Senior Notes for each trading day of such period was less than 98% of the product of the last reported sale price of ordinary shares of the Company and the applicable exchange rate on such trading day.
3. Exchange upon Notice of Redemption – Prior to the close of business on the business day immediately preceding December 15, 2021, if Horizon Investment provides a notice of redemption, at any time prior to the close of business on the second scheduled trading day immediately preceding the redemption date.

As of December 31, 2019, none of the above conditions had been satisfied and no exchange of Exchangeable Senior Notes had been triggered.

On or after December 15, 2021, a holder may exchange all or any portion of its Exchangeable Senior Notes at any time prior to the close of business on the second scheduled trading day immediately preceding the maturity date regardless of the foregoing conditions.

Upon exchange, Horizon Investment will settle exchanges of the Exchangeable Senior Notes by paying or causing to be delivered, as the case may be, cash, ordinary shares or a combination of cash and ordinary shares, at its election.

The Company recorded the Exchangeable Senior Notes under the guidance in ASC Topic 470-20, *Debt with Conversion and Other Options*, and separated them into a liability component and equity component. The carrying amount of the liability component of $268.9 million was determined by measuring the fair value of a similar liability that does not have an associated equity component. The carrying amount of the equity component of $119.1 million represented by the embedded conversion option was determined by deducting the fair value of the liability component of $268.9 million from the initial proceeds of $387.2 million ascribed to the convertible debt instrument as a whole. The initial debt discount of $131.1 million is being charged to interest expense over the life of the Exchangeable Senior Notes using the effective interest rate method.

As of December 31, 2019, the interest rate on the Exchangeable Senior Notes was 2.50% and the effective interest rate was 8.88%.

As of December 31, 2019, the fair value of the Exchangeable Senior Notes was approximately $528.2 million, categorized as a Level 2 instrument, as defined in Note 12.

Loss on debt extinguishment

During the year ended December 31, 2019, the Company recorded a loss on debt extinguishment of $58.8 million in the consolidated statement of comprehensive income (loss), which reflected the early redemption premiums and the write-off of the deferred financing fees and debt discount fees related to the prepayment of $775.0 million of the 2023 Senior Notes and 2024 Senior Notes and the write-off of the deferred financing fees and debt discount fees related to the $400.0 million of term loan repayments.

NOTE 14 – LEASE OBLIGATIONS

As discussed in Note 2, the Company elected the Topic 842 transition provision that allows entities to continue to apply the legacy guidance in Topic 840, Leases, including its disclosure requirements, in the comparative periods presented in the year of adoption. Accordingly, the Topic 842 disclosures below are presented as of and for the twelve-month period ended December 31, 2019 only.

The Company has the following office space lease agreements in place for real properties:

Location	Approximate Square Feet	Lease Expiry Date
Dublin, Ireland	18,900	November 4, 2029
Lake Forest, Illinois	160,000	March 31, 2031
Novato, California	61,000	August 31, 2021
South San Francisco, California	20,000	January 31, 2030
Chicago, Illinois	9,200	December 31, 2028
Mannheim, Germany	4,800	December 31, 2020
Other	12,400	May 31, 2020 to September 15, 2022

The above table does not include details of an agreement to lease entered into on October 14, 2019, relating to approximately 63,000 square feet of office space under construction in Dublin, Ireland. Lease commencement will begin when construction of the offices are completed by the lessor and the Company has access to begin the construction of leasehold improvements. The Company expects to incur leasehold improvement costs during 2020 and 2021 in order to prepare the building for occupancy.

As of December 31, 2019, the Company held $39.8 million of right-of-use lease assets, $4.4 million of the current portion of lease liabilities and $46.5 million of long-term lease liabilities.

The Company recognizes rent expense on a monthly basis over the lease term based on a straight-line method. Rent expense was $6.2 million, $5.6 million and $6.4 million for the years ended December 31, 2019, 2018 and 2017, respectively.

The table below reconciles the undiscounted cash flows for each of the first five years and total of the remaining years to the operating lease liabilities recorded on the Company's consolidated balance sheet as of December 31, 2019 (in thousands):

2020	$	7,804
2021		7,116
2022		5,940
2023		5,867
2024		6,485
Thereafter		39,607
Total lease payments		72,819
Imputed interest		(21,935)
Total operating lease liabilities	**$**	**50,884**

The weighted-average discount rate and remaining lease term for operating leases as of December 31, 2019 was 7.11% and 10.4 years, respectively.

The following table, which was included in the Company's 2018 Annual Report on Form 10-K, depicts the minimum future cash payments due under lease obligations at December 31, 2018 (in thousands):

2019	$	6,228
2020		6,680
2021		5,788
2022		4,565
2023		4,442
Thereafter		36,696
Total	**$**	**64,399**

NOTE 15 – COMMITMENTS AND CONTINGENCIES

Purchase Commitments

Under the Company's agreement with AGC Biologics A/S (formerly known as CMC Biologics A/S) ("AGC Biologics"), the Company has agreed to purchase certain minimum annual order quantities of TEPEZZA drug substance. In addition, the Company must provide AGC Biologics with rolling forecasts of TEPEZZA drug substance requirements, with a portion of the forecast being a firm and binding order. Under the Company's agreement with Catalent Indiana, LLC ("Catalent"), the Company must provide Catalent with rolling forecasts of TEPEZZA drug product requirements, with a portion of the forecast being a firm and binding order. At December 31, 2019, the Company had binding purchase commitments with AGC Biologics for TEPEZZA drug substance of €66.3 million ($74.3 million converted at an exchange rate as of December 31, 2019 of 1.1215), to be delivered through the second half of 2021. In addition, the Company had binding purchase commitments with Catalent for TEPEZZA drug product of $7.7 million, to be delivered through December 2020.

Patheon Pharmaceuticals Inc. ("Patheon") is obligated to manufacture PROCYSBI for the Company through December 31, 2021. The Company must provide Patheon with rolling, non-binding forecasts of PROCYSBI, with a portion of the forecast being a firm written order. Cambrex Profarmaco Milano ("Cambrex") is obligated to manufacture PROCYSBI active pharmaceutical ingredient ("API") for the Company through November 2, 2020. The Company must provide Cambrex with rolling, non-binding forecasts, with a portion of the forecast being the minimum floor of the firm order that must be placed. At December 31, 2019, the Company had a binding purchase commitment with Patheon for PROCYSBI of $3.1 million, to be delivered through March 2020 and with Cambrex for PROCYSBI API of $0.6 million, to be delivered through February 2020.

Under an agreement with Boehringer Ingelheim Biopharmaceuticals GmbH ("Boehringer Ingelheim Biopharmaceuticals"), Boehringer Ingelheim Biopharmaceuticals is required to manufacture and supply ACTIMMUNE and IMUKIN to the Company. Following the IMUKIN sale, purchases of IMUKIN inventory are expected to be onward sold to Clinigen. The Company is required to purchase minimum quantities of finished medicine during the term of the agreement, which term extends to at least June 30, 2024. As of December 31, 2019, the minimum binding purchase commitment to Boehringer Ingelheim Biopharmaceuticals was $15.6 million (converted using a Dollar-to-Euro exchange rate of 1.1215) through July 2024. As of December 31, 2019, the Company also committed to incur an additional $0.7 million for the harmonization of the drug substance manufacturing process with Boehringer Ingelheim Biopharmaceuticals.

Under the Company's agreement with Bio-Technology General (Israel) Ltd ("BTG Israel"), the Company has agreed to purchase certain minimum annual order quantities and is obligated to purchase at least 80 percent of its annual world-wide bulk product requirements for KRYSTEXXA from BTG Israel. The term of the agreement runs until December 31, 2030, and will automatically renew for successive three-year periods unless earlier terminated by either party upon three years' prior written notice. The agreement may be terminated earlier by either party in the event of a force majeure, liquidation, dissolution, bankruptcy or insolvency of the other party, uncured material breach by the other party or after January 1, 2024, upon three years' prior written notice. Under the agreement, if the manufacture of the bulk product is moved out of Israel, the Company may be required to obtain the approval of the Israel Innovation Authority (formerly known as Israeli Office of the Chief Scientist) ("IIA") because certain KRYSTEXXA intellectual property was initially developed with a grant funded by the IIA. The Company issues eighteen-month forecasts of the volume of KRYSTEXXA that the Company expects to order. The first nine months of the forecast are considered binding firm orders. At December 31, 2019, the Company had a binding purchase commitment with BTG Israel for KRYSTEXXA of $44.0 million, to be delivered through December 31, 2026. Additionally, there were other purchase orders relating to the manufacture of KRYSTEXXA of $3.4 million outstanding at December 31, 2019.

Jagotec or its affiliates are required to manufacture and supply RAYOS exclusively to the Company in bulk. The earliest the agreement can expire is December 31, 2023, and the minimum purchase commitment is in force until December 2023. At December 31, 2019, the minimum purchase commitment based on tablet pricing in effect under the agreement was $3.2 million through December 2023. Additionally, purchase orders relating to the manufacture of RAYOS of $0.3 million were outstanding at December 31, 2019. Effective January 1, 2019, the Company amended its license and supply agreements with Jagotec and Skyepharma AG, which are affiliates of Vectura. Under these amendments, from January 1, 2020, the Company is no longer subject to a minimum purchase commitment in respect of the supply agreement with Jagotec.

Nuvo Pharmaceuticals Inc. (formerly known as Nuvo Research Inc.) (“Nuvo”) is obligated to manufacture and supply PENNSAID 2% to the Company. The term of the supply agreement is through December 31, 2029, but the agreement may be terminated earlier by either party for any uncured material breach by the other party of its obligations under the supply agreement or upon the bankruptcy or similar proceeding of the other party. At least ninety days prior to the first day of each calendar month during the term of the supply agreement, the Company submits a binding written purchase order to Nuvo for PENNSAID 2% in minimum batch quantities. At December 31, 2019, the Company had a binding purchase commitment with Nuvo for PENNSAID 2% of $2.0 million, to be delivered through March 2020.

Sanofi-Aventis U.S. LLC (“Sanofi-Aventis U.S.”) is obligated to manufacture and supply DUEXIS to the Company in final, packaged form and the Company is obligated to purchase DUEXIS exclusively from Sanofi-Aventis U.S. for the commercial requirements of DUEXIS in North America, South America and certain countries and territories in Europe, including the European Union (“EU”) member states and Scandinavia. The agreement term extends until May 2021 and automatically renews for successive two-year terms unless terminated by either party upon two years’ prior written notice. At December 31, 2019, the Company had a binding purchase commitment to Sanofi-Aventis U.S. for DUEXIS of $9.1 million, to be delivered through June 2020.

Excluding the above, additional purchase orders and other commitments relating to the manufacture of RAVICTI, BUPHENYL and QUINSAIR of $2.6 million were outstanding at December 31, 2019.

Royalty and Milestone Agreements

KRYSTEXXA

Under the terms of a license agreement with Duke and MVP, the Company is obligated to pay Duke a mid-single-digit royalty on its global net sales of KRYSTEXXA and a royalty of between 5% and 15% on any global sublicense revenue. The Company is also obligated to pay MVP a mid-single-digit royalty on its net sales of KRYSTEXXA outside of the United States and a royalty of between 5% and 15% on any sublicense revenue outside of the United States.

RAVICTI

Under the terms of an asset purchase agreement with Bausch Health Companies Inc. (formerly Ucyclyd Pharma, Inc.) (“Bausch”), the Company is obligated to pay to Bausch mid single-digit royalties on its global net sales of RAVICTI. Under the terms of a license agreement with Saul W. Brusilow, M.D. and Brusilow Enterprises, Inc. (“Brusilow”), the Company is obligated to pay low single-digit royalties to Brusilow on net sales of RAVICTI that are covered by a valid claim of a licensed patent.

PROCYSBI

Under the terms of an amended and restated license agreement with The Regents of the University of California, San Diego (“UCSD”), as amended, the Company is obligated to pay to UCSD tiered low to mid-single-digit royalties on its net sales of PROCYSBI, including a minimum annual royalty in an amount less than $0.1 million. The Company must also pay UCSD a percentage in the mid-teens of any fees it receives from its sublicensees under the agreement that are not earned royalties. The Company may also be obligated to pay UCSD aggregate developmental milestone payments of $0.3 million and aggregate regulatory milestone payments of $1.8 million for each orphan indication, and aggregate developmental milestone payments of $0.8 million and aggregate regulatory milestone payments of $3.5 million for each non-orphan indication.

ACTIMMUNE

Under a license agreement, as amended, with Genentech Inc. (“Genentech”), who was the original developer of ACTIMMUNE, the Company is obligated to pay a low single digit royalty to Genentech on its annual net sales of ACTIMMUNE.

Under the terms of an assignment and option agreement with Connetics Corporation (which was the predecessor parent company to InterMune Pharmaceuticals Inc. and is now part of GlaxoSmithKline), (“Connetics”), the Company is obligated to pay low single-digit royalties to Connetics on the Company’s net sales of ACTIMMUNE in the United States.

RAYOS and LODOTRA

During the years ended December 31, 2018 and 2017, the Company was obligated to pay Vectura a mid-single digit percentage royalty on its adjusted gross sales of RAYOS and LODOTRA and on any sub-licensing income, which includes any payments not calculated based on the adjusted gross sales of RAYOS and LODOTRA, such as license fees, and lump sum and milestone payments.

Under certain amendments to the Company's license and supply agreements with Vectura, the royalty payable by the Company to Vectura in respect of RAYOS sales in North America is amended whereby, effective January 1, 2019, the Company is obligated to pay Vectura a mid-teens percentage royalty on its net sales, subject to a minimum royalty of $8.0 million per year, with the minimum royalty requirement expiring on December 31, 2022. In addition, under the amendments, the Company ceased recording LODOTRA revenue and is no longer required to pay a royalty in respect of LODOTRA.

VIMOVO

The Company is required to pay Nuvo (formerly Aralez Pharmaceuticals Inc.) a 10 percent royalty on net sales of VIMOVO and other medicines sold by the Company, its affiliates or sublicensees during the royalty term that contain gastroprotective agents in a single fixed combination oral solid dosage form with nonsteroidal anti-inflammatory drugs, subject to minimum annual royalty obligations of $7.5 million. These minimum royalty obligations will continue for each year during which one of Nuvo's patents covers such medicines in the United States and there are no competing medicines in the United States. The royalty rate may be reduced to a mid-single digit royalty rate as a result of loss of market share to competing medicines. The Company's obligation to pay royalties to Nuvo will expire upon the later of (a) expiration of the last-to-expire of certain patents covering such medicines in the United States, and (b) ten years after the first commercial sale of such medicines in the United States.

TEPEZZA

Under the agreement for the acquisition of River Vision Development Corp., the Company is required to pay up to $325.0 million upon the attainment of various milestones, composed of $100.0 million related to FDA approval and $225.0 million related to net sales thresholds for TEPEZZA. The agreement also includes a royalty payment of 3 percent of the portion of annual worldwide net sales exceeding $300.0 million (if any). The Company will make a milestone payment of $100.0 million related to FDA approval, during the first quarter of 2020.

Under the Company's license agreement with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc. (together referred to as "Roche"), the Company is required to pay Roche up to CHF103.0 million ($106.5 million when converted using a CHF-to-Dollar exchange rate at December 31, 2019 of 1.0336) upon the attainment of various development, regulatory and sales milestones for TEPEZZA. During the years ended December 31, 2019 and 2017, CHF3.0 million ($3.0 million when converted using a CHF-to-Dollar exchange rate at the date of payment of 1.0023) and CHF2.0 million ($2.0 million when converted using a CHF-to-Dollar exchange rate at the date of payment of 1.0169), respectively, was paid in relation to these milestones. The Company will make a milestone payment of CHF5.0 million ($5.2 million when converted using a CHF-to-Dollar exchange rate at December 31, 2019 of 1.0336), during the first quarter of 2020. The agreement with Roche also includes pay tiered royalties on annual worldwide net sales between 9 and 12 percent.

Under the Company's license agreement with Lundquist Institute (formerly known as Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center) ("Lundquist"), the Company is required to pay Lundquist a royalty payment of less than 1 percent of TEPEZZA net sales.

Under the Company's license agreement with Boehringer Ingelheim Biopharmaceuticals, the Company is required to pay Boehringer Ingelheim Biopharmaceuticals milestone payments totaling low-single-digit million euros upon the achievement of certain TEPEZZA sales milestones.

For all of the royalty agreements entered into by the Company, a total royalty expense of $71.5 million was recorded in cost of goods sold in the consolidated statements of comprehensive income (loss) during the year ended December 31, 2019. A total net expense of $66.6 million was recorded during the year ended December 31, 2018, of which an expense of $68.5 million was recorded in "cost of goods sold" and a reduction of $1.9 million was recorded in "selling, general and administrative" expenses in the consolidated statements of comprehensive income (loss). A total net expense of $73.5 million was recorded during the year ended December 31, 2017, of which $72.8 million was recorded in "cost of goods sold" and $0.7 million was recorded in "selling, general and administrative" expenses in the consolidated statements of comprehensive income (loss).

Contingencies

The Company is subject to claims and assessments from time to time in the ordinary course of business. The Company's management does not believe that any such matters, individually or in the aggregate, will have a material adverse effect on the Company's business, financial condition, results of operations or cash flows. In addition, the Company from time to time has billing disputes with vendors in which amounts invoiced are not in accordance with the terms of their contracts.

In November 2015, the Company received a subpoena from the U.S. Attorney's Office for the Southern District of New York requesting documents and information related to its patient assistance programs and other aspects of its marketing and commercialization activities. The Company is unable to predict how long this investigation will continue or its outcome, but it anticipates that it may continue to incur significant costs in connection with the investigation, regardless of the outcome. The Company may also become subject to similar investigations by other governmental agencies. The investigation by the U.S. Attorney's Office and any additional investigations of the Company's patient assistance programs and sales and marketing activities may result in damages, fines, penalties or other administrative sanctions against the Company.

On March 5, 2019, the Company received a civil investigative demand ("CID") from the United States Department of Justice ("DOJ") pursuant to the Federal False Claims Act regarding assertions that certain of the Company's payments to pharmacy benefit managers ("PBMs") were potentially in violation of the Anti-Kickback Statute. The CID requests certain documents and information related to the Company's payments to PBMs, pricing and the Company's patient assistance program regarding DUEXIS, VIMOVO and PENNSAID 2%. The Company is cooperating with the investigation. While the Company believes that its payments and programs are compliant with the Anti-Kickback Statute, no assurance can be given as to the timing or outcome of the DOJ's investigation, or that it will not result in a material adverse effect on the Company's business.

Other Agreements

On December 12, 2017, the Company entered into an agreement to license HZN-003 (formerly MEDI4945), a rheumatology pipeline program with the objective of enhancing the Company's leadership position in the uncontrolled gout market, from MedImmune. Under the terms of the agreement, the Company paid MedImmune an upfront cash payment of $12.0 million. Under the license agreement, the Company is required to pay up to $153.5 million upon the attainment of various milestones linked to the initiation of clinical trials and the attainment of net sales thresholds, and royalties on net sales.

Indemnification

In the normal course of business, the Company enters into contracts and agreements that contain a variety of representations and warranties and provide for general indemnifications. The Company's exposure under these agreements is unknown because it involves claims that may be made against the Company in the future, but have not yet been made. The Company may record charges in the future as a result of these indemnification obligations.

In accordance with its memorandum and articles of association, the Company has indemnification obligations to its officers and directors for certain events or occurrences, subject to certain limits, while they are serving at the Company's request in such capacity. Additionally, the Company has entered into, and intends to continue to enter into, separate indemnification agreements with its directors and executive officers. These agreements, among other things, require the Company to indemnify its directors and executive officers for certain expenses, including attorneys' fees, judgments, fines and settlement amounts incurred by a director or executive officer in any action or proceeding arising out of their services as one of the Company's directors or executive officers, or any of the Company's subsidiaries or any other company or enterprise to which the person provides services at the Company's request. The Company also has a director and officer insurance policy that enables it to recover a portion of any amounts paid for current and future potential claims. All of the Company's officers and directors have also entered into separate indemnification agreements with HTUSA.

NOTE 16 - LEGAL PROCEEDINGS

PENNSAID 2%

On November 13, 2014, the Company received a Paragraph IV Patent Certification from Watson Laboratories, Inc., now known as Actavis Laboratories UT, Inc. ("Actavis UT"), advising that Actavis UT had filed an Abbreviated New Drug Application ("ANDA") with the FDA for a generic version of PENNSAID 2%. On December 23, 2014, June 30, 2015, August 11, 2015 and September 17, 2015, the Company filed four separate suits against Actavis UT and Actavis plc (collectively "Actavis"), in the United States District Court for the District of New Jersey, with each of the suits seeking an injunction to prevent approval of the ANDA. The lawsuits alleged that Actavis has infringed nine of the Company's patents covering PENNSAID 2% by filing an ANDA seeking approval from the FDA to market a generic version of PENNSAID 2% prior to the expiration of certain of the Company's patents listed in the FDA's Orange Book (the "Orange Book"). These four suits were consolidated into a single suit. On October 27, 2015 and on February 5, 2016, the Company filed two additional suits against Actavis, in the United States District Court for the District of New Jersey, for patent infringement of three additional Company patents covering PENNSAID 2%.

On August 17, 2016, the District Court issued a *Markman* opinion holding certain of the asserted claims of seven of the Company's patents covering PENNSAID 2% invalid as indefinite. On March 16, 2017, the Court granted Actavis' motion for summary judgment of non-infringement of the asserted claims of three of the Company's patents covering PENNSAID 2%. In view of the *Markman* and summary judgment decisions, a bench trial was held from March 21, 2017 through March 30, 2017, regarding a claim of one of the Company's patents covering PENNSAID 2%. On May 14, 2017, the Court issued its opinion upholding the validity of claim of the patent, which Actavis had previously admitted its proposed generic diclofenac sodium topical solution product would infringe. Actavis filed its Notice of Appeal on June 16, 2017. The Company also filed its Notice of Appeal of the District Court's rulings on certain claims of the Company's patents covering PENNSAID 2%. On October 10, 2019, the Federal Circuit Court affirmed the District Court's judgment of validity of U.S Patent No. 9,066,913 (the "'913 patent"), and its finding that the Actavis generic product would infringe the '913 patent. The Federal Circuit also affirmed the District Court's summary judgment finding that certain patents are invalid for indefiniteness and would not be infringed. The Company filed a Petition for Rehearing, asking the Federal Circuit to reconsider the latter order invalidating certain patents.

On August 18, 2016, the Company filed suit in the United States District Court for the District of New Jersey against Actavis for patent infringement of four of the Company's newly issued patents covering PENNSAID 2%. All four of such patents are listed in the Orange Book. This litigation is currently stayed by agreement of the parties. The Company received from Actavis a Paragraph IV Patent Certification notice, dated September 27, 2016, against an additional newly issued patent covering PENNSAID 2%, advising that Actavis had filed an ANDA with the FDA for a generic version of PENNSAID 2%. The subject patent is listed in the Orange Book.

On March 29, 2019, the Company received notice from Aurolife Pharma, Inc. ("Aurolife") that it had filed an ANDA with the FDA seeking approval of a generic version of PENNSAID 2%. The ANDA contained a Paragraph IV Patent Certification alleging that the patents covering PENNSAID 2% are invalid and/or will not be infringed by Aurolife's manufacture, use or sale of its generic version of PENNSAID 2%.

DUEXIS

On May 29, 2018, the Company received notice from Alkem Laboratories, Inc. ("Alkem") that it had filed an ANDA with the FDA seeking approval of a generic version of DUEXIS. The ANDA contained a Paragraph IV Patent Certification alleging that the patents covering DUEXIS are invalid and/or will not be infringed by Alkem's manufacture, use or sale of the medicine for which the ANDA was submitted. The Company filed suit in the United States District Court of Delaware against Alkem on July 9, 2018, seeking an injunction to prevent the approval of Alkem's ANDA and/or to prevent Alkem from selling a generic version of DUEXIS. The litigation is scheduled for a bench trial beginning on September 14, 2020.

On September 27, 2018, the Company received notice from Teva Pharmaceuticals USA, Inc. ("Teva") that it had filed an ANDA with the FDA seeking approval of a generic version of DUEXIS. The ANDA contained a Paragraph IV Patent Certification alleging that the patents covering DUEXIS are invalid and/or will not be infringed by Teva's manufacture, use or sale of its generic version of DUEXIS.

VIMOVO

Currently, patent litigation is pending in the United States District Court for the District of New Jersey and the Court of Appeals for the Federal Circuit against Dr. Reddy's Laboratories Inc. and Dr. Reddy's Laboratories Ltd. (collectively, "Dr. Reddy's") which seeks to market VIMOVO prior to the expiration of certain of the Company's patents listed in the Orange Book. Settlements have been reached with three other generic companies: (i) Teva Pharmaceuticals Industries Limited (formerly known as Actavis Laboratories FL, Inc., which itself was formerly known as Watson Laboratories, Inc. – Florida) and Actavis Pharma, Inc. (collectively, "Actavis Pharma") (ii) Lupin; and (iii) Mylan Pharmaceuticals Inc., Mylan Laboratories Limited, and Mylan Inc. (collectively, "Mylan"). Under the Settlement Agreements, the license entry date is now August 1, 2024; however, all three may be able to enter the market earlier in certain circumstances.

The Company understands that Dr. Reddy's has entered into a settlement with AstraZeneca with respect to patent rights directed to Nexium® (esomeprazole) for the commercialization of VIMOVO. The settlement agreement, however, has no effect on the Nuvo VIMOVO patents, which are still the subject of patent litigations. As part of the Company's acquisition of the U.S. rights to VIMOVO, the Company has taken over and is responsible for the patent litigation that includes the Nuvo patents licensed to the Company under the amended and restated collaboration and license agreement for the United States with Nuvo.

The VIMOVO cases were filed on April 21, 2011, July 25, 2011, October 28, 2011, January 4, 2013, May 10, 2013, June 28, 2013, October 23, 2013, May 13, 2015 and November 24, 2015 and collectively include allegations of infringement of certain of the Company's patents covering VIMOVO.

The District Court consolidated all of the cases pending against the generic companies into two separate cases for purposes of discovery. The District Court entered final judgment for one of the consolidated cases on July 21, 2017, upholding the validity of U.S. Patent No. 6,926,907 (the "'907 patent") and U.S. Patent No. 8,557,285 (the "'285 patent"), and finding the generic products would infringe one or both of the two patents. Both sides appealed the District Court's judgment to the Court of Appeals for the Federal Circuit. On May 15, 2019, the Federal Circuit reversed the District Court's judgment in favor of the Company, and entered judgment that the '285 and '907 patents are invalid for lack of a sufficient written description. On July 30, 2019, the Federal Circuit Court of Appeals denied the Company's request for a rehearing of the Court's invalidity ruling against the '285 and '907 patents for VIMOVO coordinated-release tablets. As a result, the District Court entered judgment invalidating the '285 and '907 patents in September 2019, which could subsequently result in Dr. Reddy's initiating an at-risk launch of a generic version of VIMOVO. On February 18, 2020, the FDA granted final approval for Dr. Reddy's generic version of VIMOVO. The Company anticipates that Dr. Reddy's will immediately launch its product at-risk notwithstanding the ongoing patent litigation. The Company continues to assert claims of infringement against Dr. Reddy's based on U.S. Patent No. 8,858,996 (the "'996 patent") and U.S. Patent No. 9,161,920 (the "'920 patent") in the District Court.

On November 19, 2018, the District Court granted Dr. Reddy's and Mylan's summary judgment ruling that U.S Patent Numbers 9,220,698 and 9,393,208 are invalid, and on January 21, 2019, it entered final judgment against the '698, '208, and U.S. Patent Number 8,945,621. On February 21, 2019, the Company appealed the adverse judgments on the '208 and '698 patents to the Federal Circuit Court of Appeals.

On December 4, 2017, Mylan filed a Petition for inter partes review ("IPR") against the '208 patent. The Patent Trial and Appeals Board ("PTAB") instituted an IPR proceeding on Mylan's Petition on June 14, 2018. On July 2, 2018, Dr. Reddy's filed a motion seeking to join Mylan's '208 IPR. On April 1, 2019, the PTAB granted Dr. Reddy's request to join the Mylan '208 IPR. On September 6, 2019, the PTAB issued a Final Written Decision invalidating the '208 patent on the basis of obviousness. On November 18, 2019, the Company filed an appeal with the Federal Circuit Court of Appeals to review the PTAB's ruling invalidating the '208 patent.

On August 20, 2019, the Company received notice from Ajanta Pharma LTD ("Ajanta") that it had filed an ANDA with the FDA seeking approval of a generic version of VIMOVO. The ANDA contained a Paragraph IV Patent Certification alleging that the patents covering VIMOVO are invalid and/or will not be infringed by Ajanta's manufacture, use or sale of the medicine for which the ANDA was submitted. The Company filed suit in the United States District Court of New Jersey against Ajanta on September 30, 2019, seeking an injunction to prevent the approval of Ajanta's ANDA and/or to prevent Ajanta from selling a generic version of VIMOVO.

NOTE 17 – SHAREHOLDERS' EQUITY

On February 28, 2019, the Company entered into a Rights Agreement (the "Rights Agreement"), with Computershare Trust Company, N.A., as rights agent. The Board of Directors of the Company (the "Board") has authorized the issuance of one ordinary share purchase right (a "Right") for each outstanding ordinary share of the Company. Each Right represents the right to purchase one-fifth of an ordinary share of the Company, upon the terms and subject to the conditions of the Rights Agreement. The Rights were issued to the shareholders of record on March 11, 2019 and will expire on February 28, 2020.

The Board has adopted the Rights Agreement to enable all shareholders of the Company to realize the long-term value of their investment in the Company and to guard against attempts to acquire control of the Company at an inadequate price. In general terms, the Rights Agreement works by causing significant dilution to any person or group that acquires 10% (or 15% in the case of an existing "13G Investor" as defined in the Rights Agreement) or more of the outstanding ordinary shares of the Company without the prior approval of the Board. The Rights Agreement is not intended to prevent an acquisition of the Company on terms that the Board considers favorable to, and in the best interests of, all shareholders. Rather, the Rights Agreement aims to provide the Board with adequate time to fully assess any takeover proposal and therefore comply with its fiduciary duties and to encourage anyone seeking to acquire the Company to negotiate with the Board prior to attempting a takeover. The Rights Agreement was adopted in response to the takeover environment in general, particularly in light of the Company's evolution into a biopharma company focused on rare diseases and rheumatology, the Phase 3 clinical trial results of its rare disease medicine candidate TEPEZZA announced on February 28, 2019 and the market opportunity for KRYSTEXXA and TEPEZZA and was not in response to any specific approach to the Company or perceived imminent takeover proposal for the Company. The issuance of Rights is not taxable to the Company or to shareholders and does not affect reported earnings per share.

During the year ended December 31, 2019, the Company issued an aggregate of 14.1 million of ordinary shares in connection with the closing of its underwritten public equity offering on March 11, 2019. The Company received a total of approximately $326.8 million after deducting underwriting discounts and other estimated offering expenses payable by the Company in connection with such offering.

During the year ended December 31, 2019, the Company issued an aggregate of 5.1 million of ordinary shares in connection with stock option exercises, the vesting of restricted stock units and performance stock units, and employee share purchase plan purchases. The Company received a total of $36.2 million in net proceeds in connection with such issuances.

During the year ended December 31, 2019, the Company made payments of $31.6 million for employee withholding taxes relating to share-based awards.

On May 2, 2019, the shareholders of the Company approved an increase in the Company's authorized share capital of an additional 300,000,000 ordinary shares of nominal value $0.0001 per share.

On May 2, 2019, the shareholders of the Company approved the renewal of the Board's existing authority to allot and issue ordinary shares for cash and non-cash considerations under Irish law for a five-year period to expire on May 2, 2024. Additionally, on May 2, 2019, the shareholders of the Company approved the renewal of the Board's existing authority to allot and issue ordinary shares for cash without first offering those ordinary shares to existing shareholders pursuant to the statutory pre-emption right that would otherwise apply under Irish law for a five-year period to expire on May 2, 2024.

NOTE 18 – SHARE-BASED AND LONG-TERM INCENTIVE PLANS

Employee Stock Purchase Plan

2014 Employee Stock Purchase Plan. On May 17, 2014, HPI's board of directors adopted the 2014 Employee Stock Purchase Plan (the "2014 ESPP"). On September 18, 2014, at a special meeting of the stockholders of HPI (the "Special Meeting"), HPI's stockholders approved the 2014 ESPP. Upon consummation of the Company's merger transaction with Vidara (the "Vidara Merger"), the Company assumed the 2014 ESPP.

As of December 31, 2019, an aggregate of 1,236,775 ordinary shares were authorized and available for future issuance under the 2014 ESPP.

Share-Based Compensation Plans

2005 Stock Plan. In October 2005, HPI adopted the 2005 Stock Plan (the "2005 Plan"). Upon the signing of the underwriting agreement related to HPI's initial public offering, on July 28, 2011, no further option grants were made under the 2005 Plan. All stock awards granted under the 2005 Plan prior to July 28, 2011 continue to be governed by the terms of the 2005 Plan. Upon consummation of the Vidara Merger, the Company assumed the 2005 Plan.

2011 Equity Incentive Plan. In July 2010, HPI's board of directors adopted the 2011 Equity Incentive Plan (the "2011 EIP"). In June 2011, HPI's stockholders approved the 2011 EIP, and it became effective upon the signing of the underwriting agreement related to HPI's initial public offering on July 28, 2011. Upon consummation of the Vidara Merger, the Company assumed the 2011 EIP, and upon the effectiveness of the Horizon Therapeutics Public Limited Company 2014 Equity Incentive Plan (the "2014 EIP"), no additional stock awards were or will be made under the 2011 Plan, although all outstanding stock awards granted under the 2011 Plan continue to be governed by the terms of the 2011 Plan.

2014 Equity Incentive Plan and 2014 Non-Employee Equity Plan. On May 17, 2014, HPI's board of directors adopted the 2014 EIP and the Horizon Therapeutics Public Limited Company 2014 Non-Employee Equity Plan (the "2014 Non-Employee Equity Plan"). At the Special Meeting, HPI's stockholders approved the 2014 EIP and 2014 Non-Employee Equity Plan. Upon consummation of the Vidara Merger, the Company assumed the 2014 EIP and 2014 Non-Employee Equity Plan, which serve as successors to the 2011 EIP.

The 2014 EIP provides for the grant of incentive and nonstatutory stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards, performance awards and other stock awards that may be settled in cash, shares or other property to the employees of the Company (or a subsidiary company). During the year ended December 31, 2017, the compensation committee of the Company's board of directors (the "Compensation Committee") approved an amendment to the 2014 EIP to reserve additional shares to be used exclusively for grants of awards to individuals who were not previously employees or non-employee directors of the Company (or following a bona fide period of non-employment with the Company) (the "2017 Inducement Pool"), as an inducement material to the individual's entry into employment with the Company within the meaning of Rule 5635(c)(4) of the Nasdaq Listing Rules, ("Rule 5635(c)(4)"). The 2014 EIP was amended by the Compensation Committee without shareholder approval pursuant to Rule 5635(c)(4). An amendment to the 2014 EIP increasing the number of ordinary shares that may be issued under the 2014 EIP by 10,800,000 ordinary shares was approved by the Compensation Committee on February 21, 2018 and by the shareholders of the Company on May 3, 2018.

On February 20, 2019, the Compensation Committee approved, subject to shareholder approval, an amendment to the 2014 EIP, increasing the number of ordinary shares that may be issued under the 2014 EIP by 9,000,000 ordinary shares, subject to adjustment for certain changes in our capitalization. On May 2, 2019, the shareholders of the Company approved such amendment to the 2014 EIP.

The 2014 Non-Employee Equity Plan provides for the grant of non-statutory stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards and other forms of stock awards that may be settled in cash, shares or other property to the non-employee directors and consultants of the Company (or a subsidiary company). The Company's board of directors has authority to suspend or terminate the 2014 Non-Employee Equity Plan at any time.

On February 20, 2019, the Compensation Committee approved, subject to shareholder approval, an amendment to the 2014 Non-Employee Equity Plan, increasing the number of ordinary shares that may be issued under the 2014 Non-Employee Equity Plan by 750,000 ordinary shares, subject to adjustment for certain changes in our capitalization. On May 2, 2019, the shareholders of the Company approved such amendment to the 2014 Non-Employee Equity Plan.

As of December 31, 2019, an aggregate of 9,087,671 ordinary shares were authorized and available for future grants under the 2014 EIP, of which 424,421 shares relate to the 2017 Inducement Pool. As of December 31, 2019, 698,491 ordinary shares were authorized and available for future grants under the 2014 Non-Employee Equity Plan.

Stock Options

The following table summarizes stock option activity during the year ended December 31, 2019:

	Options	Weighted Average Exercise Price	Weighted Average Contractual Term Remaining (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2018	11,827,765	$ 19.06	6.24	$ 37,257
Granted	69,752	29.52		
Exercised	(1,863,093)	13.31		
Forfeited	(118,982)	22.32		
Expired	(351,240)	28.98		
Outstanding as of December 31, 2019	**9,564,202**	**19.85**	**5.43**	**156,270**
Exercisable as of December 31, 2019	**8,986,221**	**$ 19.99**	**5.29**	**$ 145,621**

Stock options typically have a contractual term of ten years from grant date.

The following table summarizes the Company's outstanding stock options at December 31, 2019:

	Options Outstanding			Options Exercisable		
Exercise Price Ranges	Number of options outstanding	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (in years)	Number Exercisable	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (in years)
$2.01 - $4.00	240,451	$ 2.83	2.66	240,451	$ 2.83	2.66
$4.01- $8.00	267,898	6.97	2.98	267,898	6.97	2.98
$8.01 - $12.00	317,975	9.07	4.44	317,975	9.07	4.44
$12.01 - $17.00	1,976,577	14.30	5.81	1,757,320	14.26	5.59
$17.01 - $22.00	1,822,998	18.07	6.35	1,534,026	18.20	6.22
$22.01 - $28.00	2,928,868	22.28	5.15	2,928,868	22.28	5.15
$28.01 - $36.00	2,009,435	28.86	5.43	1,939,683	28.84	5.27
	9,564,202	**$ 19.85**	**5.43**	**8,986,221**	**$ 19.99**	**5.29**

During the years ended December 31, 2019, 2018 and 2017, the Company granted stock options to purchase an aggregate of 69,752, 403,973 and 2,077,215 ordinary shares, respectively, with a weighted average grant date fair value of $15.77, $6.93 and $7.96, respectively.

The total intrinsic value of the options exercised during the years ended December 31, 2019, 2018 and 2017 was $28.2 million, $17.0 million and $2.6 million, respectively. The total fair value of stock options vested during the years ended December 31, 2019, 2018 and 2017 was $13.8 million, $36.6 million and $41.3 million, respectively.

The fair value of each stock option award is estimated on the date of grant using the Black-Scholes option pricing model. The determination of the fair value of each stock option is affected by the Company's share price on the date of grant, as well as assumptions regarding a number of highly complex and subjective variables. These variables include, but are not limited to, the Company's expected share price volatility over the expected term of the awards and actual and projected stock option exercise behavior. The weighted average fair value per share of stock option awards granted during the years ended December 31, 2019, 2018 and 2017, and assumptions used to value stock options, are as follows:

	2019	2018	2017
Dividend yield	—	—	—
Risk-free interest rate	1.6%	2.3%-2.8%	1.8%-2.2%
Weighted average volatility	56.5%	49.5%	49.1%
Expected term (in years)	6.00	5.56	5.99
Weighted average grant date fair value per share of options granted	$ 15.77	$ 6.93	$ 7.96

Dividend yields

The Company has never paid dividends and does not anticipate paying any dividends in the near future. Additionally, the Credit Agreement (described in Note 13 above), as well as the indentures governing the 2027 Senior Notes, (described in Note 13 above), contain covenants that restrict the Company from issuing dividends.

Risk-Free Interest Rate

The Company determined the risk-free interest rate by using a weighted average assumption equivalent to the expected term based on the U.S. Treasury constant maturity rate as of the date of grant.

Volatility

The Company used an average historical share price volatility of comparable companies to be representative of future share price volatility, as the Company did not have sufficient trading history for its ordinary shares.

Expected Term

Given the Company's limited historical exercise behavior, the expected term of options granted was determined using the "simplified" method since the Company does not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term. Under this approach, the expected term is presumed to be the average of the vesting term and the contractual life of the option.

Forfeitures

As share-based compensation expense recognized in the consolidated statements of comprehensive income (loss) is based on awards ultimately expected to vest, it has been reduced for estimated forfeitures based on actual forfeiture experience, analysis of employee turnover and other factors. The Company adopted ASU No. 2016-09 on January 1, 2017 and has elected to retain a forfeiture rate after adoption.

Restricted Stock Units

The following table summarizes restricted stock unit activity for the year ended December 31, 2019:

	Number of Units	Weighted Average Grant-Date Fair Value Per Units
Outstanding as of December 31, 2018	6,772,818	$ 15.56
Granted	3,581,848	21.69
Vested	(3,197,941)	15.38
Forfeited	(615,501)	18.06
Outstanding as of December 31, 2019	**6,541,224**	**$ 18.77**

The grant-date fair value of restricted stock units is the closing price of the Company's shares on the date of grant.

During the years ended December 31, 2019, 2018 and 2017, the Company granted 3,581,848, 4,983,368 and 3,732,035 restricted stock units to acquire shares of the Company's ordinary shares to its employees and non-executive directors, respectively, with a weighted average grant date fair value of $21.69, $15.85 and $12.44, respectively. The restricted stock units vest annually, with a vesting period ranging from two to four years. The Company accounts for the restricted stock units as equity-settled awards in accordance with ASU No. 2017-09. The total fair value of restricted stock units vested during the years ended December 31, 2019, 2018 and 2017 was $76.4 million, $43.6 million and $18.0 million, respectively.

Performance Stock Unit Awards

The following table summarizes performance stock unit awards ("PSUs") activity for the year ended December 31, 2019:

	Number of Units	Weighted Average Grant-Date Fair Value Per Unit	Average Illiquidity Discount	Recorded Weighted Average Fair Value Per Unit
Outstanding as of December 31, 2018	1,393,943			
Granted	2,290,632	$ 25.31	0.75%	$ 25.12
Forfeited	(170,792)	23.52	0.23%	23.47
Vested	(515,629)	13.87	0.00%	13.87
Performance based adjustment (1)	560,746	13.87	0.00%	13.87
Outstanding as of December 31, 2019	**3,558,900**			

(1) Represents adjustment based on the net sales performance criteria meeting 157.4% of target as of December 31, 2018 for the 2018 PSUs (as defined below).

On January 5, 2018, the Company awarded PSUs to key executive participants ("2018 PSUs"). Vesting of the 2018 PSUs was contingent upon receiving shareholder approval of amendments to the 2014 EIP, which were approved on May 3, 2018. The 2018 PSUs utilize two performance metrics, a short-term component tied to business performance and a long-term component tied to total compounded annual shareholder rate of return ("TSR"), as follows:

- 30% of the granted 2018 PSUs that may vest (such portion of the PSU award, the "2018 Relative TSR PSUs") are determined by reference to the level of the Company's relative TSR over the three-year period ending December 31, 2020, as measured against the TSR of each company included in the Nasdaq Biotechnology Index (NBI) during such three-year period. Generally, in order to earn any portion of the 2018 Relative TSR PSUs, the participant must also remain in continuous service with the Company through the earlier of January 1, 2021 or the date immediately prior to a change in control. If a change in control occurs prior to December 31, 2020, the level of the Company's relative TSR will be measured through the date of the change in control.

- 70% of the granted 2018 PSUs that may vest (such portion of the PSU award, the "2018 Net Sales PSUs"), are determined by reference to the Company's net sales for its segments during 2018 (being the orphan and rheumatology segment and inflammation segment), weighted with the orphan and rheumatology segment comprising the majority of the target sales (with respect to the total PSU award). During the year ended December 31, 2018, the net sales performance criteria was met at 157.4% of target. Accordingly, the two-thirds of the 2018 Net Sales PSUs earned portion have vested and the remaining one-third will vest in January 2021, subject to the participant's continued service with the Company through such vesting date.

On January 4, 2019, the Company awarded PSUs to key executive participants ("2019 PSUs"). The 2019 PSUs utilize two performance metrics, a short-term component tied to business performance and a long-term component tied to relative compounded annual TSR, as follows:

- 30% of the granted 2019 PSUs that may vest (such portion of the PSU award, the "2019 Relative TSR PSUs") are determined by reference to the level of the Company's relative TSR over the three-year period ending December 31, 2021, as measured against the TSR of each company included in the Nasdaq Biotechnology Index (NBI) during such three-year period. Generally, in order to earn any portion of the 2019 Relative TSR PSUs, the participant must also remain in continuous service with the Company through the earlier of January 1, 2022 or the date immediately prior to a change in control. If a change in control occurs prior to December 31, 2021, the level of the Company's relative TSR will be measured through the date of the change in control.

- 70% of the granted 2019 PSUs that may vest (such portion of the PSU award, the "2019 Net Sales PSUs"), are determined by reference to the Company's net sales for its orphan and rheumatology segment. During the year ended December 31, 2019, the net sales performance criteria was met at 119.2% of target. Accordingly, one-third of the net sales PSUs portion have vested and the remaining two-thirds will vest in equal installments in January 2021 and January 2022, subject to the participant's continued service with the Company through the applicable vesting dates.

All PSUs outstanding at December 31, 2019, may vest in a range of between 0% and 200%, based on the performance metrics described above. The Company accounts for the 2018 PSUs and 2019 PSUs as equity-settled awards in accordance with ASC 718. Because the value of the 2018 Relative TSR PSUs and 2019 Relative TSR PSUs are dependent upon the attainment of a level of TSR, it requires the impact of the market condition to be considered when estimating the fair value of the 2018 Relative TSR PSUs and 2019 Relative TSR PSUs. As a result, the Monte Carlo model is applied and the most significant valuation assumptions used related to the 2019 PSUs during the year ended December 31, 2019, include:

Valuation date stock price	$	20.39
Expected volatility		38.9%
Risk-free rate		2.6%

The value of the 2018 Net Sales PSUs and 2019 Net Sales PSUs is calculated at the end of each quarter based on the expected payout percentage based on estimated full-period performance against targets, and the Company adjusts the expense quarterly.

On January 4, 2019, the Company awarded a company-wide grant of PSUs (the "TEPEZZA PSUs"). Vesting of the TEPEZZA PSUs was contingent upon receiving shareholder approval of amendments to the 2014 EIP, which approval was received on May 2, 2019. The TEPEZZA PSUs are generally eligible to vest contingent upon receiving approval of the TEPEZZA BLA from the FDA no later than September 30, 2020 and the employee's continued service with the Company. At December 31, 2019, there were 1,472,961 TEPEZZA PSUs outstanding. In January 2020, the Company received TEPEZZA approval from the FDA and the Company started recognizing the expense related to the TEPEZZA PSUs on that date. For members of the executive committee, one-third of the TEPEZZA PSUs vested on the FDA approval date and one-third will vest on each of the first two anniversaries of the FDA approval date, subject to the employee's continued service through the applicable vesting dates. For all other participants, one-half of the TEPEZZA PSUs vested on the FDA approval date and one-half will vest on the one-year anniversary of the FDA approval date, subject to the employee's continued service through the applicable vesting dates.

Share-Based Compensation Expense

The following table summarizes share-based compensation expense included in the Company's consolidated statements of operations for the years ended December 31, 2019, 2018 and 2017 (in thousands):

	For the Years Ended December 31,		
	2019	**2018**	**2017**
Share-based compensation expense:			
Cost of goods sold	$ 3,818	$ 3,699	$ 2,469
Research and development	9,117	8,880	9,263
Selling, general and administrative	78,280	102,281	109,821
Total share-based compensation expense	**$ 91,215**	**$ 114,860**	**$ 121,553**

During the years ended December 31, 2019 and 2018, the Company recognized $9.1 million and $2.0 million of a tax benefit, respectively, related to share-based compensation resulting from the current share prices in effect at the time of the exercise of stock options and vesting of restricted stock units. As of December 31, 2019, the Company estimates that pre-tax unrecognized compensation expense of $103.5 million for all unvested share-based awards, including stock options, restricted stock units and PSUs, will be recognized through the third quarter of 2022. The Company expects to satisfy the exercise of stock options and future distribution of shares for restricted stock units and PSUs by issuing new ordinary shares which have been reserved under the 2014 EIP.

The above table does not include expense related to the TEPEZZA PSUs as the recognition of expense related to these awards will commence when approval of the TEPEZZA BLA from the FDA is considered probable. As of December 31, 2019, the Company was not able to make a determination as to whether the TEPEZZA Phase 3 positive research results represented sufficient evidence to support a conclusion that achievement of the performance condition was probable and as such, the Company did not recognize an expense related to the TEPEZZA PSU's during the year ended December 31, 2019. In January 2020, the Company received TEPEZZA approval from the FDA and the Company started recognizing the expense related to the TEPEZZA PSUs beginning on that date.

Cash Incentive Program

On January 5, 2018, the Compensation Committee approved a performance cash incentive program for the Company's executive leadership team, including its executive officers (the "Cash Incentive Program"). Participants receiving awards under the Cash Incentive Program are eligible to earn a cash bonus based upon the achievement of specified Company goals, which both performance criteria were met on or before December 31, 2018. The Company determined that the cash bonus award under the Cash Incentive Program is to be paid out at the maximum 150% target level of $14.1 million. The first and second installments were paid in January 2019 and January 2020, respectively, and the remaining installment will vest and become payable in January 2021, subject to the participant's continued services with the Company through such vesting date, the date of any earlier change in control, or a termination due to death or disability.

The Company accounted for the Cash Incentive Program as a deferred compensation plan under ASC 710 and is recognizing the payout expense using straight-line recognition through the end of the 36-month vesting period. During the year ended December 31, 2019, the Company recorded an expense of $4.2 million, to the consolidated statement of comprehensive income (loss) related to the Cash Incentive Program.

NOTE 19 – INCOME TAXES

The Company's loss before benefit for income taxes by jurisdiction for the years ended December 31, 2019, 2018 and 2017 is as follows (in thousands):

	For the Years Ended December 31,		
	2019	2018	2017
Ireland	$ 77,272	$ (10,944)	$ (16,956)
United States	(21,269)	(179,388)	(266,857)
Other foreign	(76,227)	107,200	(174,998)
Loss before benefit for income taxes	**$ (20,224)**	**$ (83,132)**	**$ (458,811)**

The components of the benefit for income taxes were as follows for the years ended December 31, 2019, 2018 and 2017 (in thousands):

	For the Years Ended December 31,		
	2019	2018	2017
Current (benefit) provision			
Ireland	$ (1,233)	$ (245)	$ 2,922
U.S. – Federal and State	(4,663)	42,791	12,085
Other foreign	1,257	843	831
Total current (benefit) provision	(4,639)	43,389	15,838
Deferred (benefit) provision			
Ireland	$ (556,370)	$ (14,184)	$ (6,294)
U.S. – Federal and State	(7,581)	(62,788)	(126,048)
Other foreign	(24,654)	(11,169)	7,818
Total deferred benefit	(588,605)	(88,141)	(124,524)
Total benefit for income taxes	**$ (593,244)**	**$ (44,752)**	**$ (108,686)**

Total benefit for income taxes was $593.2 million, $44.8 million and $108.7 million for the years ended December 31, 2019, 2018 and 2017, respectively. The current tax benefit of $4.6 million for the year ended December 31, 2019 was primarily attributable to the tax benefit recognized on the amortization of the deferred credit of $6.7 million, partially offset by the U.S. state tax liabilities of $1.7 million. The deferred tax benefit of $588.6 million for the year ended December 31, 2019, was primarily attributable to the recognition of a deferred tax asset resulting from an intra-company transfer of intellectual property assets to an Irish subsidiary of $553.3 million, the tax benefit recognized on intra-company inventory transfers of $24.7 million and the U.S federal and state tax credits generated during the year of $10.5 million. The Company recognized a deferred tax asset and related income tax benefit of $553.3 million, which represents the difference between the book and tax basis of the transferred assets multiplied by the Irish statutory income tax rate. The tax deductions for the amortization of the assets will be recognized in the future up to 80% of the current year's taxable income and any amortization not deducted for tax purposes in a particular year is allowed to be carried forward indefinitely under Irish tax law. The Company has evaluated the need for a valuation allowance with respect to this deferred tax asset, and as part of that analysis, the Company reviewed its projected earnings in the foreseeable future. Based upon all available evidence it is more likely than not that we would be able to fully realize the tax benefit on the deferred tax asset resulting from the intra-company transfer of intellectual property assets.

A reconciliation between the Irish statutory income tax rate to the Company's effective tax rate for 2019, 2018 and 2017 is as follows (in thousands):

	For the Years Ended December 31,		
	2019	2018	2017
Irish income tax at statutory rate (12.5%)	$ (2,528)	$ (10,392)	$ (57,351)
Foreign tax rate differential	14,111	8,927	(13,479)
Intra-company transfer of IP assets	(553,334)	45,780	—
Intra-company inventory transfers	(24,654)	(11,169)	(8,888)
Notional interest deduction	(19,982)	(24,455)	(27,020)
U.S. federal and state tax credits	(16,752)	(4,405)	(3,608)
Share-based compensation	(4,614)	21,383	26,811
Change in U.S. state effective tax rate	(1,551)	8,103	(2,329)
Uncertain tax positions	(382)	2,456	4,976
U.S state income taxes	(135)	(6,515)	214
Liquidation of foreign partnership	—	(42,689)	—
Write-off and reinstatement of U.S. deferred tax asset related to interest expense carryforwards due to the Tax Act	—	(37,392)	59,243
Impact of the Tax Act on deferred taxes	—	—	(143,254)
Non-deductible in-process research and development costs	—	—	51,148
Disallowed interest	1,749	3,023	2,990
Change in valuation allowances	4,069	(1,115)	(1,378)
Disqualified compensation expense	7,219	4,831	1,305
Other, net	3,540	(1,123)	1,934
Benefit for income taxes	**$ (593,244)**	**$ (44,752)**	**$ (108,686)**
Effective income tax rate	**2933.5%**	**53.8%**	**23.7%**

The overall effective income tax rate for 2019 of 2,933.5% was a higher benefit rate than the Irish statutory rate of 12.5% primarily attributable to the recognition of a $553.3 million deferred tax asset resulting from an intra-company transfer of intellectual property assets to an Irish subsidiary, a $24.7 million tax benefit recognized on intra-company inventory transfers, a $20.0 million tax benefit recognized on the Company's notional interest deduction, $16.8 million of U.S. Federal and state tax credits generated during the year (inclusive of the deferred credit amortization) and the excess tax benefits recognized on share-based compensation of $4.6 million. These tax benefits are partially offset by tax expense of $14.1 million on the pre-tax income and losses generated in jurisdictions with statutory tax rates different than the Irish statutory tax rate, a tax expense of $7.2 million on non-deductible officer's compensation and a tax expense of $4.1 million on increases in net valuation allowances.

The overall effective income tax rate for 2018 of 53.8% was a higher benefit rate than the Irish statutory rate of 12.5% primarily due to a $42.7 million U.S. federal tax benefit and $7.9 million U.S. state tax benefit was recorded with respect to the liquidation of a foreign partnership, a $37.4 million tax benefit resulting from a measurement period adjustment under SAB 118 to reinstate the deferred tax asset related to our U.S. interest expense carryforwards under Section 163(j) of the Internal Revenue Code ("Section 163(j)") to reflect the guidance issued by the U.S. Treasury Department and the U.S. Internal Revenue Service in Notice 2018-28, a $24.5 million tax benefit on the Company's notional interest deduction and a $11.2 million tax benefit recognized on intra-company inventory transfers. These tax benefits are partially offset by tax expense of $45.8 million on an intra-company transfer of asset other than inventory, a tax expense of $21.4 million on non-deductible share-based compensation expenses, which includes the previously recognized share-based compensation expense relating to PSUs which was charged to income tax expense during the year ended December 31, 2018, of $23.3 million, a tax expense of $8.9 million on the income earned in higher tax rate jurisdictions and a tax expense of $8.1 million resulting from the remeasurement of net U.S. deferred tax liabilities attributable to state legislation as enacted during the current year.

The overall effective income tax rate for 2017 of 23.7% was a higher benefit rate than the Irish statutory rate of 12.5% primarily due to a provisional $84.0 million net benefit recorded following the enactment of the Tax Act, which net benefit included a $143.3 million tax benefit from the revaluation of the Company's U.S. net deferred tax liability based on the revised U.S. federal tax rate of 21%, partially offset by the write-off of a $59.2 million deferred tax asset related to the Company's U.S. interest expense carryforwards. The higher 2017 benefit rate was also attributable to losses incurred in higher tax rate jurisdictions, the benefit realized on the notional interest deduction of $27.0 million, a tax benefit recognized on intra-company inventory transfers of $8.9 million, U.S. federal and state tax credits of $3.6 million and $2.3 million due to a decrease in the U.S. state effective tax rate. These benefits to income taxes are partially offset by non-deductible IPR&D expenses of $51.1 million recorded in connection with the acquisition of River Vision, non-deductible share-based compensation expenses of $26.8 million, including the write-off of $16.4 million of deferred taxes related to previously recognized share-based compensation expense related to PSUs that expired unvested in December 2017, and an increase in uncertain tax positions of $5.0 million.

The increase in the effective income tax rate in 2019 compared to that in 2018 was primarily due to the recognition of a deferred tax asset of $553.3 million resulting from an intra-company transfer of intellectual property assets to an Irish subsidiary.

The increase in the effective income tax rate in 2018 compared to that in 2017 was primarily due to a tax benefit of $42.7 million U.S. federal and $7.9 million U.S. state tax benefit generated on the liquidation of a foreign partnership during the year ended December 31, 2018, a tax benefit of $37.4 million recorded during the year ended December 31, 2018, as a measurement period adjustment under SAB 118, to reinstate the deferred tax asset related to our U.S. interest expense carryforwards under Section 163(j) to reflect the guidance issued by the U.S. Treasury Department and the U.S. Internal Revenue Service in Notice 2018-28, and a non-deductible IPR&D expenses of $51.1 million recorded during the year ended December 31, 2017, recorded in connection with the acquisition of River Vision.

Significant components of the Company's net deferred tax assets and liabilities, are as follows (in thousands):

	As of December 31,	
	2019	2018
Deferred tax assets:		
Intangible assets	$ 332,764	$ —
Net operating loss carryforwards	35,762	51,264
Intercompany interest	60,885	52,605
Accrued compensation	40,851	40,942
Accruals and reserves	14,097	3,284
U.S. federal and state credits	12,977	43,789
Capital loss carryforwards	1,893	3,139
Alternative minimum tax credit	—	2,816
Other	3,452	738
Total deferred tax assets	**502,681**	**198,577**
Valuation allowance	(29,268)	(26,472)
Deferred tax assets, net of valuation allowance	**$ 473,413**	**$ 172,105**
Deferred tax liabilities:		
Debt discount	$ 12,495	$ 18,795
Intangible assets	—	257,930
Total deferred tax liabilities	12,495	276,725
Net deferred income tax (asset) liability	**$ (460,918)**	**$ 104,620**

On December 22, 2017, the SEC staff issued SAB 118, which provides guidance on accounting for the tax effects of the Tax Act. SAB 118 provided a measurement period that should not extend beyond one year from the date of enactment for companies to complete the accounting under ASC 740, *Income Taxes*. In accordance with SAB 118, during the year ended December 31, 2017, the Company reflected the income tax effects of those aspects of the Tax Act for which the accounting under ASC 740 was complete. To the extent that the Company's accounting for certain income tax effects of the Tax Act was incomplete but it was able to determine a reasonable estimate, the Company recorded a provisional estimate in the consolidated financial statements for the year ended December 31, 2017. As of December 31, 2017, the Company had not completed its accounting for the effects of the Tax Act. However, the Company had made reasonable estimates of the effects on its income tax provision with respect to certain items, primarily the revaluation of its existing U.S. deferred tax balances and the write-off of its U.S. deferred tax assets resulting from interest expense carryforwards under Section 163(j). The Company recognized a net income tax benefit of $84.0 million for the year ended December 31, 2017, associated with the items it could reasonably estimate. This benefit reflects the revaluation of its U.S. net deferred tax liability based on the U.S. federal tax rate of 21%, partially offset by the write-off of the deferred tax asset related to its U.S. interest expense carryforwards.

On April 2, 2018, the U.S. Treasury Department and the U.S. Internal Revenue Service issued Notice 2018-28 ("the Notice") which provides guidance for computing the business interest expense limitation under the Tax Act and clarifies the treatment of interest disallowed and carried forward under Section 163(j), prior to enactment of the Tax Act. In accordance with the measurement period provisions under SAB 118 and the guidance in the Notice the Company reinstated the deferred tax asset related to its U.S. interest expense carryforwards under Section 163(j) based on the revised U.S. federal tax rate of 21% plus applicable state tax rates. The impact of the deferred tax asset reinstatement in accordance with SAB 118 was a $37.4 million increase to the Company's benefit for income taxes and a corresponding decrease to the U.S. group net deferred tax liability position. The impact of this reinstatement has been recognized as a discrete tax adjustment during the year ended December 31, 2018 and resulted in a 45.0% increase in the Company's effective tax rate during the period. In the fourth quarter of 2018, the Company completed our analysis to determine the effect of the Tax Act and recorded immaterial adjustments as of December 31, 2018 which related to return to provision adjustments which impacted the U.S. net deferred tax liabilities.

No provision has been made for income taxes on undistributed earnings of subsidiaries because it is the Company's intention to indefinitely reinvest outside of Ireland undistributed earnings of its subsidiaries. In the event of the distribution of those earnings to Ireland in the form of dividends, a sale of the subsidiaries, or certain other transactions, the Company may be liable for income taxes in Ireland. The cumulative unremitted earnings of the Company as of December 31, 2019, were approximately $4.3 billion, and the Company estimates that it would incur approximately $2.0 million of additional income tax on unremitted earnings were they to be remitted to Ireland.

As of December 31, 2019, the Company had net operating loss carryforwards of approximately $69.4 million for U.S. federal, $24.4 million for various U.S. states and $9.2 million for non-U.S. losses. Net operating loss carryforwards for U.S. federal income tax purposes that were generated prior to January 1, 2018, have a twenty-year carryforward life and the earliest layers will begin to expire in 2031. Under the Tax Act, U.S. federal net operating losses incurred in 2018 and in future years may be carried forward indefinitely, but the deductibility of such net operating losses is limited to 80% of the current year's taxable income. It is uncertain if and to what extent various U.S. states will conform to the Tax Act. U.S. state net operating losses will start to expire in 2020 for the earliest net operating loss layers to the extent there is not sufficient state taxable income to utilize those net operating loss carryovers. Irish net operating losses may be carried forward indefinitely and therefore have no expiration. Utilization of the U.S. net operating loss carryforwards may be subject to annual limitations as prescribed by federal and state statutory provisions. The imposition of the annual limitations may result in a portion of the net operating loss carryforwards expiring unused.

Utilization of certain net operating loss and tax credit carryforwards in the United States is subject to an annual limitation due to ownership change limitations provided by Sections 382 and 383 of the Internal Revenue Code. The Company is limited under the annual limitation of $7.7 million from the year 2019 until 2028 on certain net operating losses generated before an August 2, 2012 ownership change. The U.S. federal net operating loss carryforward and U.S. federal tax credit carryforward limitation is cumulative such that any use of the carryforwards below the limitation in a particular tax year will result in a corresponding increase in the limitation for the subsequent tax year.

At December 31, 2019, the Company had $18.2 million and $12.9 million of U.S. federal and state income tax credits, respectively, to reduce future tax liabilities. The federal income tax credits consisted of orphan drug credits and research and development credits. The U.S. state income tax credits consisted primarily of California research and development credits and the Illinois Economic Development for a Growing Economy ("EDGE") tax credits. Both the U.S. federal orphan drug credits and research and development credits have a twenty-year carryforward life. The U.S. federal orphan drug credits will begin to expire in 2037 and the U.S. federal research and development credits will begin to expire in 2039. The California research and development credits have indefinite lives and therefore are not subject to expiration. The EDGE credits have a five-year carryforward life following the year of generation and will begin to expire in 2020.

A reconciliation of the beginning and ending amounts of valuation allowances for the years ended December 31, 2019, 2018 and 2017 is as follows (in thousands):

Valuation allowances at December 31, 2016	**$**	**(32,532)**
Increase for 2016 activity		(6,835)
Release of valuation allowances		5,313
Decreases to valuation allowances due to divestiture		8,404
Valuation allowances at December 31, 2017	**$**	**(25,650)**
Increase for 2017 activity		(3,328)
Release of valuation allowances		2,506
Valuation allowances at December 31, 2018	**$**	**(26,472)**
Increase for 2019 activity		(5,693)
Release of valuation allowances		2,897
Valuation allowances at December 31, 2019	**$**	**(29,268)**

Deferred tax valuation allowances increased by $2.8 million during the year ended December 31, 2019, increased by $0.8 million during the year ended December 31, 2018 and decreased by $6.9 million during the year ended December 31, 2017. For the year ended December 31, 2019, the net increase in valuation allowances resulted primarily from additional U.S. state tax credits and state net operating losses which are unlikely to be realized in the foreseeable future, partially offset by the release of a portion of the valuation allowances with respect to the U.S. capital loss carryforwards which expired unused.

The changes in the Company's uncertain income tax positions for the years ended December 31, 2019, 2018 and 2017, excluding interest and penalties, consisted of the following (in thousands):

	For the Years Ended December 31,		
	2019	2018	2017
Beginning balance – uncertain tax positions	$ 26,306	$ 23,404	$ 17,747
Tax positions in the year:			
Additions	2,553	1,899	2,451
Acquired uncertain tax positions	—	—	—
Tax positions related to prior years:			
Additions	1,663	1,531	4,145
Settlements and lapses	(3,094)	(528)	(939)
Ending balance – uncertain tax positions	**$ 27,428**	**$ 26,306**	**$ 23,404**

For the year ended December 31, 2019, the net increase in uncertain tax positions was primarily attributable to additional U.S. federal orphan drug credits and U.S. federal research and development credits generated during the year, partially offset by lapses in statute for a portion of uncertain tax positions in jurisdictions outside of the United States. In the Company’s consolidated balance sheet, uncertain tax positions (including interest and penalties) of $9.1 million were included in other long-term liabilities, $2.4 million were included in accrued expenses and an additional $18.1 million was included in deferred tax assets.

At December 31, 2019, penalties of $0.2 million and interest of $2.0 million are included in the balance of the uncertain tax positions and penalties of $0.2 million and interest of $2.0 million were included in the balance of uncertain tax positions at December 31, 2018. The Company classifies interest and penalties with respect to income tax liabilities as a component of income tax expense. The Company assessed that its liability for uncertain tax positions will not significantly change within the next twelve months. If these uncertain tax positions are released, the impact on the Company’s tax provision would be a benefit of $28.4 million, including interest and penalties.

The Company files income tax returns in Ireland, in the United States for federal and various states, as well as in certain other jurisdictions. At December 31, 2019, all open tax years in U.S. federal and certain state jurisdictions date back to 2006 due to the taxing authorities’ ability to adjust operating loss carryforwards. In Ireland, the statute of limitations expires five years from the end of the tax year or four years from the time a tax return is filed, whichever is later. Therefore, the earliest year open to examination is 2015 with the lapse of statute occurring in 2020. No changes in settled tax years have occurred to date.

NOTE 20 – EMPLOYEE BENEFIT PLANS

The Company sponsors a defined contribution 401(k) retirement savings plan covering all of its U.S. employees, whereby an eligible employee may elect to contribute a portion of his or her salary on a pre-tax basis, subject to applicable federal limitations. The Company is not required to make any discretionary matching of employee contributions. The Company makes a matching contribution equal to 100% of each employee's elective contribution to the plan of up to 3% of the employee's eligible pay, and 50% for the next 2% of the employee's eligible pay. The full amount of this employer contribution is immediately vested in the plan. For the years ended December 31, 2019, 2018 and 2017, the Company recorded defined contribution expense of $6.2 million, $5.2 million and $4.9 million, respectively.

The Company's wholly owned Irish subsidiary sponsors a defined contribution plan covering all of its employees in Ireland. For the years ended December 31, 2019, 2018 and 2017, the Company recognized expenses of $0.6 million, $0.6 million and $0.4 million, respectively, under this plan.

The Company has a non-qualified deferred compensation plan for executives. The deferred compensation plan obligations are payable in cash upon retirement, termination of employment and/or certain other times in a lump-sum distribution or in installments, as elected by the participant in accordance with the plan. As of December 31, 2019 and 2018, the deferred compensation plan liabilities totaled $12.7 million and $8.2 million, respectively, and are included in "other long-term liabilities" in the consolidated balance sheet. The Company held funds of approximately $12.7 million and $8.2 million in an irrevocable grantor's rabbi trust as of December 31, 2019 and 2018, respectively, related to this plan. Rabbi trust assets are classified as trading marketable securities and are included in "other current assets" in the consolidated balance sheets. Unrealized gains and losses on these marketable securities are included in "other income" in the consolidated statements of comprehensive income (loss). For the years ended December 31, 2019, 2018 and 2017, the Company recognized expenses of $1.1 million, $0.9 million and $0.8 million, respectively, under this plan.

NOTE 21 – SELECTED QUARTERLY FINANCIAL INFORMATION (UNAUDITED)

The following table provides a summary of selected financial results of operations by quarter for the years ended December 31, 2019 and 2018 (in thousands, except per share data):

2019	First	Second	Third	Fourth (1)
Net sales	$ 280,371	$ 320,647	$ 335,466	$ 363,545
Gross profit	192,229	231,484	245,517	268,624
Operating (loss) income	(1,795)	25,112	48,619	54,675
Net (loss) income	(32,863)	(5,120)	18,234	592,769
Net (loss) income per ordinary share - basic	$ (0.19)	$ (0.03)	$ 0.10	$ 3.16
Net (loss) income per ordinary share - diluted	(0.19)	(0.03)	0.09	2.84

2018	First	Second	Third	Fourth
Net sales	$ 223,881	$ 302,835	$ 325,311	$ 355,543
Gross profit	113,593	211,498	234,234	256,944
Operating (loss) income	(117,298)	10,559	62,180	82,468
Net (loss) income	(148,656)	(24,751)	33,381	101,648
Net (loss) income per ordinary share - basic	$ (0.90)	$ (0.15)	$ 0.20	$ 0.60
Net (loss) income per ordinary share - diluted	(0.90)	(0.15)	0.19	0.58

(1) During the year ended December 31, 2019, the Company prospectively applied the if-converted method to the Exchangeable Senior Notes when determining the diluted net income (loss) per share.

Change in Accounting Method

Effective January 1, 2019, the Company retrospectively changed its accounting for business combinations and now records acquired intangible assets and their related third-party contingent royalties on a net basis. See Note 1, for further details of this accounting change and the related revisions to the Company's consolidated balance sheet as at December 31, 2018, and the consolidated statement of comprehensive income (loss) and cash flows for the years ended December 31, 2018 and 2017. The impact of the accounting change resulted in certain adjustments to the consolidated statements of comprehensive income (loss) for the quarters during the year ended December 31, 2018. The first three quarters during the year 2018 were presented as adjusted in the Company's Quarterly Reports on Form 10-Q that were filed during 2019. Additionally, the following are selected line items from the Company's unaudited consolidated financial information for the three months ended December 31, 2018 illustrating the effect of the change in accounting method (in thousands, except per share data):

	Consolidated Statements of Comprehensive Loss For the Three Months Ended December 31, 2018		
	As Previously Reported	Impact of Accounting Change (1)	As Adjusted
Cost of goods sold	$ 109,520	$ (10,921)	$ 98,599
Gross profit	246,023	10,921	256,944
Gain on sale of assets	(30,385)	(297)	(30,682)
Total operating expenses	174,773	(297)	174,476
Operating income	71,250	11,218	82,468
Other income, net	(632)	640	8
Total other expenses, net	(30,514)	640	(29,874)
Income before benefit for income taxes	40,736	11,858	52,594
Benefit for income taxes	(46,822)	(2,232)	(49,054)
Net income	87,558	14,090	101,648
Net income per ordinary share—basic	0.52	0.08	0.60
Net income per ordinary share—diluted	0.50	0.08	0.58
Comprehensive income	87,296	14,090	101,386

(1) The change in accounting principle resulted in the Company re-performing its purchase price allocations as of the respective acquisition dates for prior business combinations. The adjustments to the purchase price allocations primarily resulted in a net decrease in cost of goods sold reflecting lower intangible asset amortization and the elimination of royalty accretion and remeasurement expenses, partially offset by the royalty expense based on the periods' net sales. The re-performance of purchase price allocations also directly impacted impairments of long-lived assets and benefit/expense for income taxes, as shown in the tables above. In addition, the elimination of royalty reimbursement assets and accrued contingent royalty liabilities that were recorded in connection with divestitures resulted in adjustments to other income, net.

SCHEDULE II – VALUATION AND QUALIFYING ACCOUNTS

For Each of the Three Fiscal Years Ended December 31, 2019, 2018 and 2017:

Valuation and Qualifying Accounts (in thousands)	Balance at beginning of period	Additions charged to costs and expenses	Deductions from reserves	Balance at end of period
Year ended December 31, 2019:				
Allowance for returns	39,041	25,813	(19,772)	45,082
Allowance for prompt pay discounts	9,113	64,968	(66,892)	7,189
Year ended December 31, 2018:				
Allowance for returns	37,862	25,111	(23,932)	39,041
Allowance for prompt pay discounts	9,234	75,121	(75,242)	9,113
Year ended December 31, 2017:				
Allowance for returns	15,246	45,648	(23,032)	37,862
Allowance for prompt pay discounts	6,670	80,203	(77,639)	9,234

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities and Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

HORIZON THERAPEUTICS PLC

Dated: February 26, 2020

By: /s/ TIMOTHY WALBERT
Timothy Walbert

President, Chief Executive Officer and
Chairman of the Board

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Timothy Walbert and Paul W. Hoelscher, and each of them, his or her true and lawful attorneys-in-fact and agents, with full power of substitution and resubstitution, for him or her and in his or her name, place and stead, in any and all capacities, to sign any and all amendments (including post-effective amendments) to this report, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or either of them, or their or his or her substitutes or substitute, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

SIGNATURE	TITLE	DATE
/s/ TIMOTHY WALBERT Timothy Walbert	President, Chief Executive Officer and Chairman of the Board *(Principal Executive Officer)*	February 26, 2020
/s/ PAUL W. HOELSCHER Paul W. Hoelscher	Executive Vice President and Chief Financial Officer *(Principal Financial Officer)*	February 26, 2020
/s/ MILES W. MCHUGH Miles W. McHugh	Senior Vice President and Chief Accounting Officer *(Principal Accounting Officer)*	February 26, 2020
/s/ MICHAEL GREY Michael Grey	Director	February 26, 2020
/s/ WILLIAM F. DANIEL William F. Daniel	Director	February 26, 2020
/s/ JEFF HIMAWAN Jeff Himawan, Ph.D.	Director	February 26, 2020
/s/ SUSAN MAHONY Susan Mahony, Ph.D.	Director	February 26, 2020
/s/ GINO SANTINI Gino Santini	Director	February 26, 2020
/s/ JAMES SHANNON James Shannon, M.D.	Director	February 26, 2020
/s/ H. THOMAS WATKINS H. Thomas Watkins	Director	February 26, 2020
/s/ PASCALE WITZ Pascale Witz	Director	February 26, 2020

DESCRIPTION OF SHARE CAPITAL

The following description of the share capital of Horizon Therapeutics public limited company (the "Company") is a summary. This summary does not purport to be complete and is qualified in its entirety by reference to the Irish Companies Act 2014 (as amended) (the "Companies Act"), and the complete text of the Company's constitution, which is comprised of its amended and restated memorandum and articles of association (hereinafter referred to as "constitution" or, as appropriate, the "memorandum" and/or the "articles of association") and which constitution is filed as Exhibit 3.1 to the Company's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on May 8, 2019. You should read those laws and documents carefully.

Capital Structure

Authorized Share Capital

The authorized share capital of the Company is €40,000 and $60,000, divided into 40,000 deferred shares with nominal value of €1.00 per share and 600,000,000 U.S. dollar denominated ordinary shares with nominal value of U.S. $0.0001 per share. The authorized share capital includes 40,000 deferred shares with nominal value of €1.00 per share in order to satisfy statutory requirements for all Irish public limited companies upon incorporation or re-registration.

The Company may issue shares subject to the maximum authorized share capital contained in the Company's constitution. The authorized share capital may be increased or reduced by a resolution approved by a simple majority of the votes cast at a general meeting of the Company's shareholders (referred to under Irish law as an "ordinary resolution"). The shares comprising the authorized share capital of the Company may be divided into shares of such nominal value as the ordinary resolution shall prescribe. As a matter of Irish law, the directors of a company may issue new ordinary or preferred shares without shareholder approval once authorized to do so by the constitution or by an ordinary resolution adopted by the shareholders at a general meeting. The authorization may be granted for a maximum period of five years, at which point it must be renewed by the shareholders by an ordinary resolution.

The Company's constitution authorizes the Company's board of directors to issue new ordinary or preferred shares without shareholder approval for a period of five years from the date of adoption of such constitution, which adoption was effective in September 2014. The authorization was renewed at a general meeting of the Company's shareholders on May 2, 2019 and will expire on May 2, 2024.

The rights and restrictions to which the Company's ordinary shares are subject are prescribed in the Company's constitution. The Company's constitution provides that the terms of the preferred shares which may be issued by the Company shall be determined by means of an ordinary resolution. The creation of a new class of shares of the Company would also require a special resolution to amend the constitution of the Company.

Irish law does not recognize fractional shares held of record. Accordingly, the Company's constitution does not provide for the issuance of fractional shares of the Company, and the official Irish register of the Company will not reflect any fractional interest in shares. Whenever an alteration or reorganization of the share capital of the Company would result in any Company shareholder becoming entitled to fractions of a share, the Company's board of directors may, on behalf of those shareholders that would become entitled to fractions of a share, sell the shares representing the fractions for the best price reasonably obtainable, to any person and distribute the proceeds of the sale in due proportion among those members.

Preemption Rights, Share Warrants and Share Options

Under Irish law, certain statutory preemption rights apply automatically in favor of shareholders where shares are to be issued for cash. The Company disapplied these preemption rights in its constitution for a period of five years from the date of adoption of such constitution, which adoption was effective in September 2014, as permitted under Irish law. This disapplication was renewed at a general meeting of the Company's shareholders on May 2, 2019 by a resolution approved by not less than 75% of the votes cast (referred to under Irish law as a "special

resolution"), and will expire on May 2, 2024. If the disapplication is not renewed before then, shares issued for cash must be offered to existing shareholders of the Company on a pro rata basis to their existing shareholding before the shares may be issued to any new shareholders. The statutory preemption rights do not apply (i) where shares are issued for non-cash consideration (such as in a stock-for-stock acquisition), (ii) to the issue of non-equity shares (that is, shares that have the right to participate only up to a specified amount in any income or capital distribution) or (iii) where shares are issued pursuant to an employee stock option or similar equity plan.

The Company's constitution provides that, subject to any shareholder approval requirement under any laws, regulations or the rules of any stock exchange to which the Company is subject, the Company's board of directors is authorized, from time to time, in its discretion, to grant such persons, for such periods and upon such terms as it deems advisable, options to purchase or subscribe for such number of shares of any class or classes or of any series of any class as the Company's board of directors may deem advisable, and to cause warrants or other appropriate instruments evidencing such options to be issued. The Company is subject to the rules of The Nasdaq Stock Market LLC and the U.S. Internal Revenue Code of 1986 (the "Code"), which require shareholder approval of certain equity plan and share issuances.

Dividends

Under Irish law, dividends and distributions may only be made from distributable reserves. Distributable reserves generally means accumulated realized profits less accumulated realized losses and includes reserves created by way of capital reduction. In addition, no distribution or dividend may be made unless the net assets of the Company are equal to, or in excess of, the aggregate of the Company's called up share capital plus undistributable reserves and the distribution does not reduce the Company's net assets below such aggregate. Undistributable reserves include the share premium account, the capital redemption reserve fund and the amount by which the Company's accumulated unrealized profits, so far as not previously utilized by any capitalization, exceed the Company's accumulated unrealized losses, so far as not previously written off in a reduction or reorganization of capital.

The determination as to whether or not the Company has sufficient distributable reserves to fund a dividend must be made by reference to the "relevant accounts" of the Company. The "relevant accounts" are either the last set of unconsolidated annual audited financial statements or other financial statements properly prepared in accordance with the Companies Act, which give a "true and fair view" of the Company's unconsolidated financial position and accord with accepted accounting practice. The relevant accounts must be filed in the Companies Registration Office (the official public registry for companies in Ireland).

The Company's constitution authorizes the directors to declare dividends without shareholder approval to the extent they may be paid out of funds of the Company which are lawfully available for such purposes. The Company's board of directors may also recommend a dividend to be approved and declared by the shareholders at a general meeting. The Company's board of directors or any general meeting declaring a dividend may direct that the payment be made by distribution of assets, shares or cash, and no dividend issued may exceed the amount recommended by the directors. Dividends may be declared and paid in the form of cash or non-cash assets and may be paid in dollars or any other currency.

The Company's board of directors may deduct from any dividend payable to any shareholder any amounts payable by such shareholder to the Company in relation to the shares of the Company.

Share Repurchases, Redemptions and Conversions

Overview

The Company's constitution provides that any ordinary share that the Company has agreed to acquire shall be deemed to be a redeemable share. Accordingly, for Irish law purposes, the repurchase of ordinary shares by the Company may technically be effected as a redemption of those shares as described below under "*—Repurchases and*

Redemptions by the Company." If the Company's constitution did not contain such provision, repurchases by the Company would be subject to many of the same rules that apply to purchases of the Company's ordinary shares by subsidiaries described below under "*—Purchases by Subsidiaries of the Company*," including the shareholder approval requirements described below, and the requirement that any on market purchases be effected on a "recognized stock exchange," which, for purposes of the Companies Act, includes Nasdaq.

Neither Irish law nor any constituent document of the Company places limitations on the right of nonresident or foreign owners to vote or hold the Company ordinary shares. Except where otherwise noted, references herein to repurchasing or buying back ordinary shares of the Company refer to the redemption of ordinary shares by the Company or the purchase of ordinary shares of the Company by a subsidiary of the Company, in each case in accordance with the Company's constitution and Irish law as described below.

Repurchases and Redemptions by the Company

Under Irish law, a company may issue redeemable shares and redeem them out of distributable reserves or the proceeds of a new issue of shares issued for that purpose. Please see also "*—Dividends.*" The Company may only issue redeemable shares if the nominal value of the issued share capital that is not redeemable is not less than 10% of the nominal value of the total issued share capital of the Company. No shares may be redeemed unless they are fully-paid and the terms of redemption of the shares must provide for payment on redemption. Redeemable shares may, upon redemption, be cancelled or held in treasury. Based on the provisions of the Company's constitution, shareholder approval will not be required to redeem the Company's shares.

The Company may also be given an additional general authority to purchase its own shares on market by way of ordinary resolution, which would take effect on the same terms and be subject to the same conditions as applicable to purchases by the Company subsidiaries as described below.

Repurchased and redeemed shares may be cancelled or held as treasury shares. The nominal value of treasury shares held by the Company at any time must not exceed 10% of the Company's capital (consisting of the aggregate of all amounts of nominal value plus premium paid for the Company's shares, plus certain other sums that may be credited as such).

The Company may not exercise any voting rights in respect of any shares held as treasury shares. Treasury shares may be canceled by the Company or re-issued subject to certain conditions.

Purchases by Subsidiaries of the Company

Under Irish law, an Irish or non-Irish subsidiary may purchase shares of the Company either on market or off market. For a subsidiary of the Company to make purchases on market of the Company's ordinary shares, the Company's shareholders must provide general authorization for such purchase by way of ordinary resolution. However, as long as this general authority has been granted, no specific shareholder authority for a particular on market purchase by a subsidiary of the Company's ordinary shares is required. For a purchase by a subsidiary of the Company off market, the proposed purchase contract must be authorized by special resolution of the Company's shareholders before the contract is entered into and the purchase contract must be furnished to the Company's shareholders on request and be made available for inspection by the Company's shareholders at the registered office of the Company from the date of the notice of the meeting at which the special resolution is to be proposed and at the meeting itself.

In order for a subsidiary of the Company to make an on market purchase of the Company's shares, such shares must be purchased on a "recognized stock exchange." Nasdaq, on which the Company's ordinary shares are currently listed, is specified as a recognized stock exchange for this purpose by Irish law.

The number of shares held by the subsidiaries of the Company at any time will count as treasury shares and will be included in any calculation of the permitted treasury share threshold of 10% of the Company's permitted treasury share threshold described above. While a subsidiary holds shares of the Company, it cannot exercise any voting rights in respect of those shares. The acquisition of the Company's ordinary shares by an Irish subsidiary must be funded out of distributable reserves of the subsidiary.

Lien on Shares, Calls on Shares and Forfeiture of Shares

The Company's constitution provides that the Company has a first and paramount lien on every share that is not a fully paid up share for all amounts payable at a fixed time or called in respect of that share. Subject to the terms of their allotment, directors may call for any unpaid amounts in respect of any shares to be paid, and if payment is not made, the shares may be forfeited. These provisions are standard inclusions in the constitution of an Irish public company limited by shares such as the Company and are only applicable to shares of the Company that have not been fully paid up.

Consolidation and Division; Subdivision

Under its constitution, the Company may, by ordinary resolution, consolidate and divide all or any of its share capital into shares of larger nominal value than its existing shares or subdivide its shares into smaller amounts than are fixed by its constitution.

Reduction of Share Capital

The Company may, by special resolution, reduce its authorized but unissued share capital in any way. The Company also may, by special resolution and subject to confirmation by the Irish High Court, reduce or cancel its issued share capital in any manner permitted by the Companies Act.

Annual Meetings of Shareholders

The Company is required to hold an annual general meeting at intervals of no more than 15 months from the previous annual general meeting, provided that an annual general meeting is held in each calendar year following the first annual general meeting and no more than nine months after the Company's fiscal year-end. Any annual general meeting of the Company may be held outside Ireland if a resolution so authorizing has been passed at the preceding annual general meeting and the articles of association do not prohibit the holding of annual general meetings outside of Ireland.

Notice of an annual general meeting must be given to all of the Company's shareholders and to the auditors of the Company. The Company's constitution provides for a minimum notice period of 21 days, which is the minimum permitted under Irish law.

The only matters which must, as a matter of Irish law, be transacted at an annual general meeting are: (i) the consideration of the Company's statutory financial statements; (ii) the review by Company's shareholders of the Company's affairs; (iii) the election and reelection of Company's board of directors in accordance with the constitution; (iv) the appointment or reappointment of the Irish statutory auditors; (v) the authorization of Company's board of directors to approve the remuneration of the Irish statutory auditors; and (vi) the declaration of dividends (other than interim dividends).

Extraordinary General Meetings of Shareholders

Extraordinary general meetings of the Company may be convened by (i) the Company's board of directors, (ii) on requisition of the Company's shareholders holding not less than 10% of the paid up share capital of the Company carrying voting rights, (iii) by a shareholder or shareholders holding not less than 50% of the paid-up share capital of the Company carrying voting rights, (iv) on requisition of the Company's auditors, or (v) in exceptional cases, by order of the court. Extraordinary general meetings are generally held for the purpose of approving shareholder resolutions as may be required from time to time. At any extraordinary general meeting only such business shall be conducted as is set forth in the notice thereof.

Notice of an extraordinary general meeting must be given to all of the Company's shareholders and to the auditors of the Company. Under Irish law and the Company's constitution, the minimum notice periods are 21 days' notice in writing for an extraordinary general meeting to approve a special resolution and 14 days' notice in writing for any other extraordinary general meeting.

In the case of an extraordinary general meeting convened by the Company's shareholders, the proposed purpose of the meeting must be set out in the requisition notice. Upon receipt of any such valid requisition notice, the Company's board of directors has 21 days to convene a meeting of the Company's shareholders to vote on the matters set out in the requisition notice. This meeting must be held within two months of the receipt of the requisition notice. If the Company's board of directors does not convene the meeting within such 21-day period, the requisitioning shareholders, or any of them representing more than one half of the total voting rights of all of them, may themselves convene a meeting, which meeting must be held within three months of the Company's receipt of the requisition notice.

If the Company's board of directors becomes aware that the net assets of the Company are not greater than half of the amount of the Company's called-up share capital, it must convene an extraordinary general meeting of the Company's shareholders not later than 28 days from the date that they learn of this fact to consider how to address the situation.

Quorum for General Meetings

The Company's constitution provides that no business shall be transacted at any general meeting unless a quorum is present. One or more of the Company's shareholders present in person or by proxy holding not less than a majority of the issued and outstanding shares of the Company entitled to vote at the meeting in question constitute a quorum.

Voting

The Company's constitution provides that the Company's board of directors or its chairman may determine the manner in which the poll is to be taken and the manner in which the votes are to be counted.

Each Company shareholder is entitled to one vote for each ordinary share that he or she holds as of the record date for the meeting. Voting rights may be exercised by shareholders registered in the Company's share register as of the record date for the meeting or by a duly appointed proxy, which proxy need not be a Company shareholder. Where interests in shares are held by a nominee trust company, such company may exercise the rights of the beneficial holders on their behalf as their proxy. All proxies must be appointed in the manner prescribed by the Company's constitution, which permit shareholders to notify the Company of their proxy appointments electronically in such manner as may be approved by the Company's board of directors.

In accordance with the Company's constitution, the Company may from time to time be authorized by ordinary resolution to issue preferred shares. These preferred shares may have such voting rights as may be specified in the terms of such preferred shares (e.g., they may carry more votes per share than ordinary shares or may entitle their holders to a class vote on such matters as may be specified in the terms of the preferred shares). Treasury shares or shares of the Company that are held by subsidiaries of the Company are not entitled to vote at general meetings of shareholders.

Irish law requires special resolutions of the Company's shareholders at a general meeting to approve certain matters. Examples of matters requiring special resolutions include:

- amending the objects of the Company;
- amending the constitution of the Company;
- approving a change of name of the Company;
- authorizing the entering into of a guarantee or provision of security in connection with a loan, quasi-loan or credit transaction to a director or connected person;
- opting out of preemption rights on the issuance of new shares;
- re-registration of the Company from a public limited company to a private company;
- variation of class rights attaching to classes of shares (where the articles of association do not provide otherwise);

- purchase of the Company shares off market;
- reduction of issued share capital;
- sanctioning a compromise/scheme of arrangement with creditors or shareholders;
- resolving that the Company be wound up by the Irish courts;
- resolving in favor of a shareholders' voluntary winding-up; and
- setting the re-issue price of treasury shares.

Variation of Rights Attaching to a Class or Series of Shares

Under the Company's constitution and the Companies Act, any variation of class rights attaching to the issued shares of the Company must be approved by a special resolution of the Company's shareholders of the affected class or with the consent in writing of the holders of three-quarters of all the votes of that class of shares.

Inspection of Books and Records

Under Irish law, shareholders have the right to: (i) receive a copy of the constitution of the Company and any act of the Irish Government which alters the constitution; (ii) inspect and obtain copies of the minutes of general meetings and resolutions of the Company; (iii) inspect and receive a copy of the register of shareholders, register of directors and secretaries, register of directors' interests and other statutory registers maintained by the Company; (iv) receive copies of balance sheets and directors' and auditors' reports which have previously been sent to shareholders prior to an annual general meeting; and (v) receive balance sheets of any subsidiary of the Company which have previously been sent to shareholders prior to an annual general meeting for the preceding ten years. The auditors of the Company will also have the right to inspect all books, records and vouchers of the Company. The auditors' report must be circulated to the shareholders with the Company's financial statements prepared in accordance with Irish law 21 days before the annual general meeting and must be read to the shareholders at the Company's annual general meeting.

Acquisitions

Irish law recognizes the concept of a statutory merger in three situations: (i) a domestic merger where an Irish private limited company merges with another Irish company (which is not a public limited company) under Part 9 of the Companies Act; (ii) a domestic merger where an Irish public limited company merges with another Irish company under Part 17 of the Companies Act; and (iii) a cross-border merger where an Irish company merges with another company based in the European Economic Area (the "EEA") under the European Communities (Cross Border Merger) Regulations 2008 of Ireland.

Under Irish law, where the Company proposes to acquire another company, approval of the Company's shareholders will not be required unless effected as a direct domestic merger or direct cross-border merger as referred to above. Under Irish law, where another company proposes to acquire the Company, the requirement of the approval of the Company's shareholders will depend on the method of acquisition. Under Irish law, there is no requirement for a company's shareholders to approve a sale, lease or exchange of all or substantially all of a company's property and assets.

Takeover Offer

Under a takeover offer, the bidder will make a general offer to the target shareholders to acquire their shares. The offer must be conditional on the bidder acquiring, or having agreed to acquire (pursuant to the offer, or otherwise) securities conferring more than 50% of the voting rights of the target. The bidder may require any remaining shareholders to transfer their shares on the terms of the offer (i.e., a "squeeze out") if it has acquired, pursuant to the offer, not less than a specific percentage of the target shares to which the offer relates. The percentage for companies listed on regulated markets in the EEA is 90%. As the Company is not listed on an EEA

regulated market, the relevant applicable percentage for the Company is 80%. Dissenting shareholders have the right to apply to the High Court of Ireland for relief.

Scheme of Arrangement

A scheme of arrangement is a statutory procedure which can be utilized to acquire an Irish company. A scheme of arrangement involves the target company putting an acquisition proposal to its shareholders, which can be (i) a transfer scheme, pursuant to which their shares are transferred to the bidder in return for the relevant consideration or (ii) a cancellation scheme, pursuant to which their shares are cancelled in return for the relevant consideration, with the result in each case that the bidder will become the 100% owner of the target company. A scheme of arrangement requires the approval of a majority in number of the shareholders of each class, representing at least 75% of the shares of each class, present and voting, in person or by proxy, at a general, or relevant class, meeting of the target company. The scheme also requires the sanction of the High Court of Ireland. Subject to the requisite shareholder approval and sanction of the High Court of Ireland, the scheme will be binding on all shareholders. Dissenting shareholders have the right to appear at the High Court of Ireland hearing and make representations in objection to the scheme.

Statutory Merger

It is possible for the Company to be acquired by way of a domestic or cross-border statutory merger, as described above. Such mergers must be approved by a special resolution of the Company's shareholders. If the consideration being paid to the Company shareholders is not entirely cash, dissenting shareholders may be entitled to require that their shares be acquired for cash.

Appraisal Rights

Irish law generally does not provide for "appraisal rights." However, it does provide for dissenters' rights in certain situations, as described below.

Under a tender or takeover offer, the bidder may require any remaining shareholders to transfer their shares on the terms of the offer (i.e., a "squeeze out") if it has acquired, pursuant to the offer, not less than 80% of the target shares to which the offer relates (in the case of a company that is not listed on an EEA regulated market). Dissenting shareholders have the right to apply to the High Court of Ireland for relief.

A scheme of arrangement which has been approved by the requisite shareholder majority and sanctioned by the High Court of Ireland will be binding on all shareholders. Dissenting shareholders have the right to appear at the High Court of Ireland hearing and make representations in objection to the scheme.

Under the European Communities (Cross-Border Mergers) Regulations 2008 governing the merger of an Irish public limited company such as the Company and a company incorporated in the EEA, a shareholder (i) who voted against the special resolution approving the merger or (ii) of a company in which 90% of the shares are held by the other party to the merger, has the right to request that the company acquire his or her shares for cash at a price determined in accordance with the share exchange ratio set forth in the merger agreement.

Similar rights apply in the case of a merger of an Irish public limited company into another company to which the provisions of the Companies Act apply.

Disclosure of Interests in Shares

Under the Companies Act, the Company's shareholders must notify the Company if, as a result of a transaction, the shareholder will become interested in three percent or more of the voting shares of the Company, or if as a result of a transaction a shareholder who was interested in more than three percent of the voting shares of the Company ceases to be so interested. Under the Companies Act, "interested" is broadly defined and includes direct and indirect holdings, beneficial interests and, in some cases, derivative interests. Furthermore, a person's interests are aggregated with the interests of certain related persons and entities (including controlled companies). Where a

shareholder is interested in more than three percent of the voting shares of the Company, the shareholder must notify the Company of any alteration of his or her interest that brings his or her total holding through the nearest whole percentage number, whether an increase or a reduction.

The relevant percentage figure is calculated by reference to the aggregate nominal value of the voting shares in which the shareholder is interested as a proportion of the entire nominal value of the issued share capital of the Company (or any such class of share capital in issue). Where the percentage level of the shareholder's interest does not amount to a whole percentage, this figure may be rounded down to the next whole number. The Company must be notified within five business days of the transaction or alteration of the shareholder's interests that gave rise to the notification requirement. If a shareholder fails to comply with these notification requirements, the shareholder's rights in respect of any Company shares it holds will not be enforceable, either directly or indirectly. However, such person may apply to the court to have the rights attaching to such shares reinstated.

In addition to these disclosure requirements, the Company, under the Companies Act, may, by notice in writing, require a person whom the Company knows or has reasonable cause to believe to be, or at any time during the three years immediately preceding the date on which such notice is issued to have been, interested in shares comprised in the Company's relevant share capital to: (i) indicate whether or not it is the case; and (ii) where such person holds or has during that time held an interest in the shares of the Company, to provide additional information, including the person's own past or present interests in shares of the Company. If the recipient of the notice fails to respond within the reasonable time period specified in the notice, the Company may apply to court for an order directing that the affected shares be subject to certain restrictions, as prescribed by the Companies Act, as follows:

- any transfer of those shares or, in the case of unissued shares, any transfer of the right to be issued with shares and any issue of shares, shall be void;
- no voting rights shall be exercisable in respect of those shares;
- no further shares shall be issued in right of those shares or in pursuance of any offer made to the holder of those shares; and
- no payment shall be made of any sums due from the Company on those shares, whether in respect of capital or otherwise.

The court may also order that shares subject to any of these restrictions be sold with the restrictions terminating upon the completion of the sale.

In the event the Company is in an offer period pursuant to the Irish takeover rules, accelerated disclosure provisions apply for persons holding an interest in the Company securities of one percent or more.

Anti-Takeover Provisions

Irish Takeover Rules and Substantial Acquisition Rules

The Company is subject to the Irish Takeover Panel Act 1997, as amended, and the Irish Takeover Rules made thereunder (the "Irish Takeover Rules"), which regulate the conduct of takeovers of, and certain other relevant transactions affecting, Irish public limited companies listed on certain stock exchanges, including Nasdaq. The Irish Takeover Rules are administered by the Irish Takeover Panel, which has supervisory jurisdiction over such transactions. Among other matters, the Irish Takeover Rules operate to ensure that no offer is frustrated or unfairly prejudiced and, in the case of multiple bidders, that there is a level playing field.

A transaction in which a third party seeks to acquire 30% or more of the voting rights in the Company and any other acquisitions of securities of the Company will be governed by the Irish Takeover Panel Act 1997, as amended, and the Irish Takeover Rules and will be regulated by the Irish Takeover Panel. The "General Principles," and certain important aspects, of the Irish Takeover Rules are described below.

General Principles

The Irish Takeover Rules are built on the following General Principles which will apply to any transaction regulated by the Irish Takeover Panel:

- in the event of an offer, all holders of securities of the target company must be afforded equivalent treatment and, if a person acquires control of a company, the other holders of securities must be protected;
- the holders of securities in the target company must have sufficient time and information to enable them to reach a properly informed decision on the offer; where it advises the holders of securities, the board of directors of the target company must give its views on the effects of the implementation of the offer on employment, employment conditions and the locations of the target company's place of business;
- a target company's board of directors must act in the interests of the company as a whole and must not deny the holders of securities the opportunity to decide on the merits of the offer;
- false markets (i.e., a market based on erroneous, imperfect or unequally disclosed information) must not be created in the securities of the target company, the bidder or any other company concerned by the offer in such a way that the rise or fall of the prices of the securities becomes artificial and the normal functioning of the markets is distorted;
- a bidder can only announce an offer after ensuring that he or she can fulfill in full the consideration offered, if such is offered, and after taking all reasonable measures to secure the implementation of any other type of consideration;
- a target company may not be hindered in the conduct of its affairs longer than is reasonable by an offer for its securities; and
- a "substantial acquisition" of securities (whether such acquisition is to be effected by one transaction or a series of transactions) shall take place only at an acceptable speed and shall be subject to adequate and timely disclosure.

Mandatory Bid

Under certain circumstances, a person who acquires shares, or other voting securities, of the Company may be required under the Irish Takeover Rules to make a mandatory cash offer for the remaining outstanding voting securities in the Company at a price not less than the highest price paid for the securities by the acquiror, or any parties acting in concert with the acquiror, during the previous 12 months. This mandatory bid requirement is triggered if an acquisition of securities would increase the aggregate holding of an acquiror, including the holdings of any parties acting in concert with the acquiror, to securities representing 30% or more of the voting rights in the Company, unless the Irish Takeover Panel otherwise consents. An acquisition of securities by a person holding, together with its concert parties, securities representing between 30% and 50% of the voting rights in the Company would also trigger the mandatory bid requirement if, after giving effect to the acquisition, the percentage of the voting rights held by that person (together with its concert parties) would increase by 0.05% within a 12-month period. Any person (excluding any parties acting in concert with the holder) holding securities representing more than 50% of the voting rights of a company is not subject to these mandatory offer requirements in purchasing additional securities.

Voluntary Bid; Requirements to Make a Cash Offer and Minimum Price Requirements

If a person makes a voluntary offer to acquire outstanding ordinary shares of the Company, the offer price must not be less than the highest price paid for the Company's ordinary shares by the bidder or its concert parties during the three-month period prior to the commencement of the offer period. The Irish Takeover Panel has the power to extend the "look back" period to 12 months if the Irish Takeover Panel, taking into account the General Principles, believes it is appropriate to do so.

If the bidder or any of its concert parties has acquired ordinary shares of the Company (i) during the period of 12 months prior to the commencement of the offer period that represent more than 10% of the total ordinary shares of the Company or (ii) at any time after the commencement of the offer period, the offer must be in cash (or accompanied by a full cash alternative) and the price per ordinary share of the Company must not be less than the

highest price paid by the bidder or its concert parties during, in the case of (i), the 12-month period prior to the commencement of the offer period or, in the case of (ii), the offer period. The Irish Takeover Panel may apply this rule to a bidder who, together with its concert parties, has acquired less than 10% of the total ordinary shares of the Company in the 12-month period prior to the commencement of the offer period if the Irish Takeover Panel, taking into account the General Principles, considers it just and proper to do so.

An offer period will generally commence from the date of the first announcement of the offer or proposed offer.

Substantial Acquisition Rules

The Irish Takeover Rules also contain rules governing substantial acquisitions of shares and other voting securities which restrict the speed at which a person may increase his or her holding of shares and rights over shares to an aggregate of between 15% and 30% of the voting rights of the Company. Except in certain circumstances, an acquisition or series of acquisitions of shares or rights over shares representing 10% or more of the voting rights of the Company is prohibited, if such acquisition(s), when aggregated with shares or rights already held, would result in the acquirer holding 15% or more but less than 30% of the voting rights of the Company and such acquisitions are made within a period of seven days. These rules also require accelerated disclosure of acquisitions of shares or rights over shares relating to such holdings.

Frustrating Action

Under the Irish Takeover Rules, the Company's board of directors is not permitted to take any action that might frustrate an offer for the shares of the Company once the Company's board of directors has received an approach that may lead to an offer or has reason to believe that such an offer is or may be imminent, subject to certain exceptions. Potentially frustrating actions such as (i) the issue of shares, options or convertible securities, (ii) material acquisitions or disposals, (iii) entering into contracts other than in the ordinary course of business or (iv) any action, other than seeking alternative offers, which may result in frustration of an offer, are prohibited during the course of an offer or at any earlier time during which the Company's board of directors has reason to believe an offer is or may be imminent. Exceptions to this prohibition are available where:

- the action is approved by the Company's shareholders at a general meeting;
- the Irish Takeover Panel has given its consent where it is satisfied the action would not constitute frustrating action;
- the Company's shareholders holding more than 50% of the voting rights state in writing that they approve the proposed action and would vote in favor of it at a general meeting;
- the action is taken in accordance with a contract entered into prior to the announcement of the offer (or any earlier time at which the Company's board of directors considered the offer to be imminent); or
- the decision to take such action was made before the announcement of the offer and either has been at least partially implemented or is in the ordinary course of business.

Certain other provisions of Irish law or the Company's constitution may be considered to have anti-takeover effects, including advance notice requirements for director nominations and other shareholder proposals, as well as those described under the following captions: "*—Preemption Rights, Share Warrants and Share Options*," "*—Disclosure of Interests in Shares*," "*—Shareholder Rights Plan*" and "*—Corporate Governance*."

Shareholder Rights Plan

Irish law does not expressly authorize or prohibit companies from issuing share purchase rights or adopting a shareholder rights plan as an anti-takeover measure, although the ability of the Company's board of directors to do so would be subject to its fiduciary duties and, during the course of an offer, the Irish Takeover Rules. However, there is no directly relevant Irish case law on this issue. The constitution expressly authorizes the Company's board of directors to adopt a shareholder rights plan upon such terms and conditions as it deems expedient in the interests of Company, subject to applicable law.

Corporate Governance

The Company's constitution allocates authority over the day-to-day management of the Company to its board of directors. The Company's board of directors may then delegate the management of the Company to committees of the board of directors (consisting of one or more members of the board of directors) but regardless, the Company's board of directors remains responsible, as a matter of Irish law, for the proper management of the affairs of the Company. Committees may meet and adjourn as they determine proper. A vote at any committee meeting will be determined by a majority of votes of the members present.

The board of directors of the Company has a standing Audit Committee, a Compensation Committee, a Transaction Committee and a Nominating and Corporate Governance Committee, with each committee comprised solely of independent directors, as prescribed by the Nasdaq listing standards and SEC rules and regulations. The Company has adopted corporate governance policies, including a code of conduct and an insider trading policy, as well as an open door reporting policy and a comprehensive compliance program.

The Companies Act provide for a minimum of two directors. The Company's constitution provides that, subject to the Companies Act, the board may determine the size of the board from time to time.

The Company's board of directors is divided into three classes, designated Class I, Class II and Class III. Each class has a three-year term, with the terms expiring in staggered years on the date of the annual general meeting of shareholders for the applicable year. At each annual general meeting of shareholders, successors to the class of directors whose term expires at that annual general meeting are eligible for election for a successive three-year term. If the number of directors is changed, any increase or decrease shall be apportioned among the classes so as to maintain the number of directors in each class as nearly as possible or as the chairman of the board of directors may otherwise direct. In no case will a decrease in the number of directors shorten the term of any incumbent director. A director may hold office until the annual general meeting of the year in which his or her term expires and until his or her successor is elected and duly qualified, subject to his or her prior death, resignation, retirement, disqualification or removal from office.

Directors are elected by ordinary resolution at a general meeting. Irish law requires majority voting for the election of directors, which could result in the number of directors falling below the prescribed minimum number of directors due to the failure of nominees to be elected. Accordingly, the Company's constitution provides that if, at any general meeting of shareholders, the number of directors is reduced below the minimum prescribed by the constitution due to the failure of any person nominated to be a director to be elected, then, in such circumstances, the nominee or nominees who receive the highest number of votes in favor of election will be elected in order to maintain such prescribed minimum number of directors. Each director elected in this manner will remain a director (subject to the provisions of the Companies Act and the articles of association) only until the conclusion of the next annual general meeting of the Company unless he or she is reelected.

Under the Companies Act and notwithstanding anything contained in the constitution or in any agreement between the Company and a director, the shareholders may, by an ordinary resolution, remove a director from office before the expiration of his or her term at a meeting held on no less than 28 days' notice and at which the director is entitled to be heard. The power of removal is without prejudice to any claim for damages for breach of contract (e.g. employment contract) that the director may have against the Company in respect of his removal.

The Company's constitution provides that, subject to the terms of any one or more classes or series of preferred shares, the board of directors may fill any vacancy occurring on the board of directors. Any director of any class

elected to fill a vacancy resulting from an increase in the number of directors of such class will hold office for a term that will coincide with the remaining term of that class. Any director elected to fill a vacancy not resulting from an increase in the number of directors shall have the same remaining term as that of his predecessor. A vacancy on the board of directors created by the removal of a director may be filled by the shareholders at the meeting at which such director is removed and, in the absence of such election or appointment, the remaining directors may fill the vacancy.

Legal Name; Formation; Fiscal Year; Registered Office

Horizon Therapeutics public limited company, the current legal and commercial name of the Company, was incorporated in Ireland on December 20, 2011 as a private limited company (registration number 507678) under the name Aravis Therapeutics International Limited. Aravis Therapeutics International Limited was renamed Vidara Therapeutics International Limited on April 3, 2012. Vidara Therapeutics International Limited was re-registered as a public limited company named Vidara Therapeutics International plc effective August 1, 2014, and was subsequently renamed Horizon Pharma plc on September 17, 2014. Horizon Pharma plc was subsequently renamed Horizon Therapeutics plc on May 2, 2019. The Company's fiscal year ends on December 31st and the Company's registered address is Connaught House, 1st Floor, 1 Burlington Road, Dublin 4, D04 C5Y6, Ireland.

Duration; Dissolution; Rights upon Liquidation

The Company's corporate existence has unlimited duration. The Company may be dissolved and wound up at any time by way of a shareholders' voluntary winding up or a creditors' winding up. In the case of a shareholders' voluntary winding up, a special resolution of shareholders is required. The Company may also be dissolved by way of court order on the application of a creditor, or by the Companies Registration Office as an enforcement measure where the Company has failed to file certain returns.

The Company may also be dissolved by the Director of Corporate Enforcement in Ireland where the affairs of the Company have been investigated by an inspector and it appears from the report or any information obtained by the Director of Corporate Enforcement that the Company should be wound up.

If the Company's constitution contain no specific provisions in respect of a dissolution or winding up, then, subject to the priorities of any creditors, the assets will be distributed to the Company's shareholders in proportion to the paid-up nominal value of the shares held. The Company's constitution provides that the ordinary shareholders of the Company are entitled to participate pro rata in a winding up, but their right to do so may be subject to the rights of any preferred shareholders to participate under the terms of any series or class of preferred shares.

Uncertificated Shares

Under the constitution, but subject to the provisions of the Companies Act, no shareholder of the Company is entitled to receive certificates for their shares, except for legended shares, and the Company will only issue uncertificated ordinary shares.

Stock Exchange Listing

The Company's ordinary shares are listed on the Nasdaq Global Select Market under the trading symbol "HZNP." The Company's ordinary shares are not currently intended to be listed on the Irish Stock Exchange.

No Sinking Fund

The Company's ordinary shares have no sinking fund provisions.

Transfer and Registration of Shares

The transfer agent and Registrar for the Company's ordinary shares is Computershare Trust Company, N.A. Its address is 150 Royall Street, Canton, MA 02021. The transfer agent maintains the share register, registration in which is determinative of ownership of shares of the Company. A shareholder who holds shares beneficially is not the holder of record of such shares. Instead, the depository (for example, Cede & Co., as nominee for DTC) or other nominee is the holder of record of those shares. Accordingly, a transfer of shares from a person who holds such shares beneficially to a person who also holds such shares beneficially through a depository or other nominee will not be registered in the Company's official share register, as the depository or other nominee will remain the record holder of any such shares.

A written instrument of transfer is required under Irish law in order to register on the Company's official share register any transfer of shares (i) from a person who holds such shares directly to any other person, (ii) from a person who holds such shares beneficially but not directly to a person who holds such shares directly, or (iii) from a person who holds such shares beneficially to another person who holds such shares beneficially where the transfer involves a change in the depository or other nominee that is the record owner of the transferred shares. An instrument of transfer is also required for a shareholder who directly holds shares to transfer those shares into his or her own broker account (or vice versa). Such instruments of transfer may give rise to Irish stamp duty, which must be paid prior to registration of the transfer on the Company's official Irish share register. However, a shareholder who directly holds shares may transfer those shares into his or her own broker account (or vice versa) without giving rise to Irish stamp duty provided there is no change in the ultimate beneficial ownership of the shares as a result of the transfer and the transfer is not made in contemplation of a sale of the shares.

Any transfer of the Company's ordinary shares that is subject to Irish stamp duty will not be registered in the name of the buyer unless an instrument of transfer is duly stamped and provided to the transfer agent. The Company, in its absolute discretion and insofar as the Companies Act or any other applicable law permit, may, or may provide that a subsidiary of the Company will, pay Irish stamp duty arising on a transfer of the Company's ordinary shares on behalf of the transferee of such ordinary shares. If stamp duty resulting from the transfer of the Company's ordinary shares which would otherwise be payable by the transferee is paid by the Company or any subsidiary of the Company on behalf of the transferee, then in those circumstances, the Company will, on its behalf or on behalf of its subsidiary (as the case may be), be entitled to (i) seek reimbursement of the stamp duty from the transferee, (ii) set-off the stamp duty against any dividends payable to the transferee of those Company ordinary shares and (iii) to claim a first and permanent lien on the Company ordinary shares on which stamp duty has been paid by the Company or its subsidiary for the amount of stamp duty paid. The Company's lien shall extend to all dividends paid on those Company ordinary shares.

The Company's constitution delegates to any director, the secretary or any assistant secretary of the Company the authority, on behalf of the Company, to execute an instrument of transfer on behalf of a transferring party.

In order to help ensure that the official share register is regularly updated to reflect trading of the Company's ordinary shares occurring through normal electronic systems, the Company intends to regularly produce any required instruments of transfer in connection with any transactions for which it pays stamp duty (subject to the reimbursement and set-off rights described above). In the event that the Company notifies one or both of the parties to a share transfer that it believes stamp duty is required to be paid in connection with the transfer and that it will not pay the stamp duty, the parties may either themselves arrange for the execution of the required instrument of transfer (and may request a form of instrument of transfer from the Company for this purpose) or request that the Company execute an instrument of transfer on behalf of the transferring party in a form determined by the Company. In either event, if the parties to the share transfer have the instrument of transfer duly stamped (to the extent required) and then provide it to the Company's transfer agent, the buyer will be registered as the legal owner of the relevant shares on the Company's official Irish share register (subject to the suspension right described below).

The directors may suspend registration of transfers from time to time, not exceeding 30 days in aggregate each year.

January 23, 2020

Shao Lee Lin, MD PhD
1111 Evergreen Dr.
Lake Forest, IL 60045

Dear Shao-Lee:

Pursuant to Section 4.1.3 of the Executive Employment Agreement, effective January 8, 2018, by and between Horizon Therapeutics Inc. (formerly known as Horizon Pharma, Inc.), Horizon Therapeutics USA, Inc. (formerly known as Horizon Pharma USA, Inc.) (collectively referred to as "Horizon Therapeutics") and you, Shao-Lee Lin, Horizon Therapeutics is terminating your employment without cause. This termination shall be effective today, January 23, 2020.

Based on this action, and in accordance with Sections 4.4.3(i) and 4.4.4(i), and subject to your obligations, which include but are not limited to signing the Release, which is attached as Exhibit A, and the Non-Compete Agreement, which is attached as Exhibit B, and certain other continuing obligations under your Executive Employment Agreement, you will be entitled to certain additional payments and equity acceleration, which are summarized in Exhibit C.

Please remember that the benefits described in Exhibit C are conditioned on your execution of Exhibits A & B. Additionally, you should be aware of your continuing contractual commitments to the Company and legal obligations, and the importance with which the Company views these obligations. Specifically, you have contractually agreed, for a period of 12 months, to refrain from directly or indirectly soliciting or encouraging any Horizon Therapeutics employee to leave their employment with the Company. Secondly, per your Employee Confidentiality and Inventions Agreement you have a continuing legal and contractual obligation not to disclose, publish, or otherwise use for any purpose the Company's Confidential Information.

Sincerely,

/s/ Brian K. Beeler
Brian K. Beeler
Executive Vice President, General Counsel

cc human resource file

EXHIBIT A

RELEASE AND WAIVER OF CLAIMS

In consideration of the payments and other benefits set forth in Section 4.4 of the Executive Employment Agreement dated January 8, 2018 (the "***Employment Agreement***"), to which this form is attached, and the consideration described in Exhibit C attached thereto, I, Shao-Lee Lin, hereby furnish Horizon Therapeutics, Inc. and Horizon Therapeutics USA, Inc. (together the "***Company***"), with the following release and waiver ("***Release and Waiver***").

In exchange for the consideration provided to me by the Employment Agreement that I am not otherwise entitled to receive, I hereby generally and completely release the Company and its directors, officers, employees, shareholders, partners, agents, attorneys, predecessors, successors, parent and subsidiary entities, insurers, Affiliates, and assigns from any and all claims, liabilities and obligations, both known and unknown, that arise out of or are in any way related to events, acts, conduct, or omissions occurring relating to my employment or the termination thereof prior to my signing this Release and Waiver. This general release includes, but is not limited to: (1) all claims arising out of or in any way related to my employment with the Company or the termination of that employment; (2) all claims related to my compensation or benefits from the Company, including, but not limited to, salary bonuses, commissions, vacation pay, expense reimbursements, severance pay, fringe benefits, stock, stock options, or any other ownership interests in the Company; (3) all claims for breach of contract, wrongful termination, and breach of the implied covenant of good faith and fair dealing; (4) all tort claims, including, but not limited to, claims for fraud, defamation, emotional distress, and discharge in violation of public policy; and (5) all federal, state, and local statutory claims, including, but not limited to, claims for discrimination, harassment, retaliation, attorney's fees, or other claims arising under the federal Civil Rights Act of 1964 (as amended), the federal Americans with Disabilities Act of 1990, the federal Age Discrimination in Employment Act of 1967 (as amended) ("***ADEA***"), the Illinois Human Rights Act, the Illinois Equal Pay Act, the Illinois Religious Freedom Restoration Act, and the Illinois Genetic Information Privacy Act. Notwithstanding the foregoing, this Release and Waiver, shall not release or waive my rights to indemnification under the articles and bylaws of the Company or applicable law; to payments under Sections 4.4.3 of the Employment Agreement; under any provision of the Employment Agreement that survives the termination of that agreement; under any applicable workers' compensation statute; under any option, restricted share or other agreement concerning any equity interest in the Company; as a shareholder of the Company or any other right that is not waivable under applicable law. I acknowledge that, among other rights, I am waiving and releasing any rights I may have under ADEA, that this Release and Waiver is knowing and voluntary, and that the consideration given for this Release and Waiver is in addition to anything of value to which I was already entitled as an executive of the Company. If I am 40 years of age or older upon execution of this Release and Waiver, I further acknowledge that I have been advised, as required by the Older Workers Benefit Protection Act, that: (a) the release and waiver granted herein does not relate to claims under the ADEA which may arise after this Release and Waiver is executed; (b) I should consult with an attorney prior to executing this Release and Waiver; and (c) I have twenty-one (21) days from the date of termination of my employment with the Company in which to consider this Release and Waiver (although I may choose voluntarily to execute this Release and Waiver earlier); (d) I have seven (7) days following the execution of this Release and Waiver to revoke my consent to this Release and Waiver; and (e) this Release and Waiver shall not be effective

until the seven (7) day revocation period has expired unexercised. If I am less than 40 years of age upon execution of this Release and Waiver, I acknowledge that I have the right to consult with an attorney prior to executing this, Release and Waiver (although I may choose voluntarily not to do so); and (c) I have five (5) days from the date of termination of my employment with the Company in which to consider this Release and Waiver (although I may choose voluntarily to execute this Release and Waiver earlier). I acknowledge my continuing obligations under my Confidential Information and Inventions Agreement dated January 8, 2018. Pursuant to the Confidential Information and Inventions Agreement I understand that among other things, I must not use or disclose any confidential or proprietary information of the Company and I must immediately return all Company property and documents (including all embodiments of proprietary information) and all copies thereof in my possession or control. I understand and agree that my right to the payments and other benefits I am receiving in exchange for my agreement to the terms of this Release and Waiver is contingent upon my continued compliance with my Confidential Information and Inventions Agreement.

This Release and Waiver, including my Confidential Information and Inventions Agreement dated January 8, 2018 constitutes the complete, final and exclusive embodiment of the entire agreement between the Company and me with regard to the subject matter hereof. I am not relying on any promise or representation by the Company that is not expressly stated herein. This Release and Waiver may only be modified by a writing signed by both me and a duty authorized officer of the Company.

Date: February 14, 2020

By: /s/ Shao-Lee Lin
Shao-Lee Lin

EXHIBIT B

NON-COMPETITION AGREEMENT

In consideration of the payments and other benefits set forth in Section 4.4 of the Executive Employment Agreement, effective January 8, 2018, by and between Horizon Therapeutics Inc. (formerly known as Horizon Pharma, Inc.), Horizon Therapeutics USA, Inc. (formerly known as Horizon Pharma USA, Inc.) (collectively referred to as "Horizon Therapeutics") and you, Shao-Lee Lin (the "***Employment Agreement***"), pursuant to Section 4.4.3(i), I, Shao-Lee Lin, for a period of twelve (12) months following my termination on January 23, 2020, agree not to acquire, assume or participate in, directly or indirectly, any position, investment or interest known by me to be adverse or antagonistic to Horizon Therapeutics, its business or prospects, financial or otherwise, or in any company, person or entity that is, directly or indirectly, in competition with the business of the Horizon Therapeutics or any of its affiliates. Notwithstanding the foregoing, I may invest and/or maintain investments in any public or private entity up to an amount of 2% of an entity's fully diluted shares and on a passive basis.

Date: February 14, 2020

By: /s/ Shao-Lee Lin
Shao-Lee Lin

EXHIBIT C

TERMS OF SEPARATION

Pursuant to your Employment Agreement:

- Last day of service 1/23/2020
- 12 months of base salary ($643,750)
- 12 months of COBRA
- 1/5/2020 Vesting – 2019 Grant – PSU – 12,588 shares – The portion of these performance grants that have vested as of 1/5/2020 will payout as soon as the determination of metrics is completed. The share number may differ based on the performance factors that were achieved.
- 12 months accelerated vesting on all time based awards including options and RSUs, including the following:
    - 1/4/2021 Vesting – 2018 Grant – RSU – 17,892 shares – Per 12 months accelerated vesting on all time-based awards including options and RSUs.
    - 1/5/2021 Vesting – 2018 Grant – RSU – 32,363 shares – Per 12 months accelerated vesting on all time-based awards including options and RSUs.
    - 1/5/2021 Vesting – 2019 Grant – RSU – 17,983 shares – Per 12 months accelerated vesting an all time-based awards including options and RSUs.
    - 1/5/2021 Vesting – 2020 Grant – RSU – 12,094 shares – Per 12 months accelerated vesting on all time-based awards including options and RSUs.
    - Accelerated vesting of all stock options that would have vested through 1/23/2021- Per 12 months accelerated-vesting on all time-based.
- Payment of five (5) days of PTO (maximum carryover from 2019)
- Payment of 2019 Discretionary Bonus in the amount of $386,250.00 (60% of $643,750.00)

You will receive a package from HR that explains the transition from other company benefits you might currently be enrolled in.

Exhibit 10.70

CERTAIN CONFIDENTIAL INFORMATION CONTAINED IN THIS DOCUMENT, MARKED BY [***], HAS BEEN OMITTED BECAUSE HORIZON THERAPEUTICS PLC HAS DETERMINED THE INFORMATION (I) IS NOT MATERIAL AND (II) WOULD LIKELY CAUSE COMPETITIVE HARM TO HORIZON THERAPEUTICS PLC IF PUBLICLY DISCLOSED.

EXECUTION VERSION

License Agreement

by and among

F. Hoffmann-La Roche Ltd,

a Swiss corporation;

Hoffmann-La Roche Inc.

a New Jersey corporation

and

River Vision LLC, a Delaware limited liability company

License Agreement

THIS LICENSE AGREEMENT ("***Agreement***") is entered into as of the Effective Date by and among:

F. HOFFMANN-LA ROCHE LTD, a corporation organized and existing under the laws of Switzerland, with its principal office at Grenzacherstrasse 124, CH-4070 Basel, Switzerland ("***Roche Basel***") and **Hoffmann-La Roche Inc., a corporation organized and existing under the laws of New Jersey**, with its principle office at 340 Kingsland Street, Nutley, New Jersey 07110, U.S.A. ("***Roche Nutley***"; Roche Basel and Roche Nutley together referred to as "***Roche***")

and

RIVER VISION LLC, a limited liability company organized and existing under the laws of Delaware, with its principal office at One Rockefeller Plaza, New York NY, 10020, U.S.A. ("***River Vision***").

Recitals

WHEREAS, Roche has conducted certain research and development related to, and possesses certain intellectual property rights with respect to teprotumumab, an antibody to IGF-1R ("***Compound***" as further defined below) ; and

WHEREAS, River Vision desires to obtain, and Roche is willing to grant to River Vision, an exclusive, royalty-bearing license, with the right to sublicense, under the Roche Patents and Roche Know-How (as defined below), to develop, have developed, commercialize, have commercialized, make, have made, use, have used, sell, have sold, offer for sale, have offered for sale, import and have imported Compound and/or Product, as appropriate, in the Field in the Territory, subject to the terms and conditions hereof; and

WHEREAS, Roche desires to obtain, and River Vision is willing to grant to Roche, certain rights with respect to Compound and Product, subject to the terms and conditions hereof.

Agreement

NOW, THEREFORE, in consideration of the foregoing premises and mutual promises, terms, conditions, and covenants contained herein and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties agree as follows:

1. DEFINITIONS

1.1 "***Affiliate***" shall mean, with respect to either party: (i) an entity which owns, directly or indirectly, a controlling interest in such party; (ii) an entity in which such party owns, either directly or indirectly, a controlling interest; or (iii) an entity, in which a controlling ownership, directly or indirectly, is common to the controlling ownership in such party, whereby "controlling interest" shall mean more than 50% (or if the jurisdiction where such entity is domiciled prohibits majority foreign ownership of such entity, the maximum foreign ownership interest permitted under such laws, provided that such ownership actually allows control of such entity) of the securities or other ownership interest representing the equity with the rights to vote in the designation of the governing bodies of such entity, or any other agreement or arrangement allowing the factual or legal control

of the decisions of such entity or its governing bodies. Anything to the contrary in this paragraph notwithstanding (i) Chugai Pharmaceutical Co., Ltd, 1-9, Kyobashi 2-chome, Chuo-ku, Tokyo, 104-8301, Japan ("***Chugai***") shall not be deemed an Affiliate of Roche unless Roche notifies River Vision that Roche wishes for Chugai to be deemed an Affiliate of Roche, and (ii) any entities that are Affiliated with River Vision as a result of NRM's Affiliation with River Vision, shall not be deemed an Affiliate of River Vision unless River Vision notifies Roche that River Vision wishes for any such entity to be deemed an Affiliate of River Vision.

1.2 "***Alliance Manager***" shall have the meaning provided in Section 2.7.

1.3 "***Agreement***" shall mean this agreement.

1.4 "***Appendix***" shall mean an appendix to this Agreement.

1.5 "***Approval***" shall mean the first approval, license, registration, or authorization of any country, federal, supranational, state or local regulatory agency, department, bureau or other government entity that are necessary for the manufacture, use, storage, import, transport and/or sale of a Product in such jurisdiction.

1.6 "***BLA***" shall mean a Biologics License Application, or similar application for marketing approval of the Product in the Field submitted to the FDA, or a foreign equivalent of the FDA.

1.7 "***BLA Filing***" shall mean the date on which the first BLA for Product in any country of the Territory has been submitted which BLA has been accepted (but not yet approved) by the applicable Regulatory Authority.

1.8 "***Business Day***" shall mean 9.00am to 5.00pm local time on a day other than a Saturday, Sunday or bank or other public or federal holiday in Switzerland or USA.

1.9 "***Cabilly License Agreement***" shall mean the agreement entered into between River Vision and Roche on or before the Effective Date, as amended now or in the future.

1.10 "***Calendar Year***" shall mean the period of time beginning on January 1 and ending December 31, except for the first year which shall begin on the Effective Date and end on December 31.

1.11 "***Calendar Quarter***" shall mean the four quarters of a Calendar Year, each Calendar Quarter starting on January 1, April 1, July 1 and October 1.

1.12 "***Change of Control***" shall have the meaning provided in Section 18.5.

1.13 "***Chugai Agreement***" shall mean the License Agreement relating to the Compound between Chugai and F. Hoffmann-La Roche Ltd dated March 7, 2008 for the territory of Japan, as amended now or in the future.

1.14 "***Combination Product***" shall mean any product that contains, in addition to a Compound, one or more other pharmaceutically active ingredients.

1.15 "***Commercially Reasonable Efforts***" shall mean (i) with respect to River Vision's obligation under this Agreement to develop or commercialize Product, the level of efforts required to carry out such obligation in a sustained manner consistent with the efforts a similarly situated biopharmaceutical company or pharmaceutical company, as the case may be, devotes to its products of similar market potential, profit potential or strategic value, based on conditions then prevailing and (ii) with respect to Roche, the level of efforts required to carry out a particular obligation under this Agreement in a sustained manner consistent with the efforts a similarly situated biopharmaceutical company or pharmaceutical company, as the case may be, devotes to its products of similar market potential, profit potential or strategic value, based on conditions then prevailing.

1.16 "***Compound***" shall mean Roche's proprietary compound teprotumumab, as specified in Appendix 1

1.17 "***Confidential Information***" shall mean any and all information, data or know-how (including but not limited to Know-How), whether technical or non-technical, oral or written (and if disclosed orally, memorialized in writing within [***] days of such oral disclosure), that is disclosed by one party or its Affiliates ("***Disclosing Party***") to the other party or its Affiliates ("***Receiving Party***"). Information shall not include any information, data or know-how which:

(i) was generally available to the public at the time of disclosure, or information which becomes available to the public after disclosure by the Disclosing Party other than through fault (whether by action or inaction) of the Receiving Party,

(ii) can be shown by cogent written records to have been already known to the Receiving Party prior to its receipt from the Disclosing Party,

(iii) is obtained at any time lawfully from a Third Party under circumstances permitting its use or disclosure,

(iv) is developed independently by the Receiving Party as evidenced by written records other than through knowledge of Confidential Information,

(v) is required to be disclosed by the Receiving Party to comply with a court or administrative order providing the Receiving Party furnishes prompt notice (in no event less than [***] days) to the Disclosing Party to enable it to resist such disclosure, or

(vi) is approved in writing by the Disclosing Party for release by the Receiving Party.

The terms of this Agreement shall be considered Confidential Information of both parties.

1.18 "***Control***" or "***Controlled***" shall mean, with respect to Compound, Product or any Know-How, Patents, Confidential Information or other intellectual property rights, possession by a party of the ability (whether by ownership, license or otherwise) to grant access to, to grant use of, or to grant a license or a sublicense to Compound or Product under such Know-How, Patents or intellectual property rights without violating the terms of any agreement or other arrangement with any Third Party.

*****Certain Confidential Information Omitted**

1.19 "***Data Room***" shall mean the due diligence data room containing all data and information Controlled by River Vision as of the applicable Review Period pertaining to Compound and/or Product, including but not limited to pre-clinical and clinical data, River Vision Patents, regulatory correspondence, CMC data related to the program River Vision generated since the Effective Date.

1.20 "***Drug Product***" shall mean Compound that has undergone all processing stages up to and including lyophilization but not including the labeling and secondary packaging.

1.21 "***Effective Date***" shall mean June 15, 2011.

1.22 "***EU***" shall mean the European Community and all its present and future member countries.

1.23 "***FDA***" shall mean the US Federal Food and Drug Administration and any successor agency thereof.

1.24 "***FDCA***" shall mean the Food, Drug and Cosmetics Act of the US.

1.25 "***Field***" shall mean treatment or prevention of human diseases and conditions, except Oncology.

1.26 "***First Commercial Sale***" shall mean the first sale of a Product by River Vision or its Affiliates to a Third Party for end use or consumption of such Product in a country after the Regulatory Authority of such country has granted Regulatory Approval or, if no such Regulatory Approval or similar marketing approval is required, the date upon which such Product first commercially launched in such country. Sale to an Affiliate shall not constitute a First Commercial Sale.

1.27 "**[**[***] ***Agreement***" shall mean the agreement between [***] and Roche dated June 6, 2002, as amended now or in the future.

1.28 "**[*** ***Agreement***" shall mean the agreement between [***] and Roche dated November 1, 2003, as amended now or in the future.

1.29 "***ICD-Classification***" shall mean the then current International Classifications of Diseases and Related Health Problems of the World Health Organization (WHO).

1.30 "***Indication***" shall mean those indications defined within a block (e.g. block H36 "Retinal disorders in diseases classified elsewhere") of the ICD Classification.

1.31 "***Initiation***" of a clinical trial shall mean the first administration of a Product to a patient in a clinical trial related to Compound or Product.

*****Certain Confidential Information Omitted**

1.32 "***Insolvency Event***" shall mean circumstances under which a party:

a) has a receiver, bankruptcy trustee or similar officer appointed over all or a material part of its assets or undertaking;

b) passes a resolution for winding-up (other than a winding-up for the purpose of, or in connection with, any solvent amalgamation or reconstruction) or a court makes an order to that effect or a court makes an order for administration (or any equivalent order in any jurisdiction); or

c) is subject to voluntary or involuntary bankruptcy or judicial restructuring proceedings.

1.33 "***Invention***" shall mean an invention that is conceived or reduced to practice in connection with any activity carried out pursuant to this Agreement. Under this definition, an Invention may be made by employees, agents or consultants of River Vision solely or jointly with a Third Party (a "***River Vision Invention***"), by employees, agents or consultants of the Roche Group solely or jointly with a Third Party (a "***Roche Invention***"), or jointly by employees, agents or consultants of River Vision and a member of the Roche Group with or without a Third Party (a "***Joint Invention***").

1.34 "***Joint Intellectual Property***" shall mean the Joint Patents and Joint Know-How.

1.35 "***Joint Know-How***" means Know-How that is developed by one or more employees, agents or consultants of River Vision or any of its Affiliates, on the one hand, and one or more employees, agents or consultants of Roche or any of its Affiliates, on the other hand, under this Agreement.

1.36 "***Joint Patents***" or "***Joint Patent Rights***" shall mean Patent Rights that claim Joint Know-How.

1.37 "***Know-How***" shall mean data, knowledge and information, and materials, including but not limited to all tangible and intangible techniques, technology, practices, trade secrets, inventions (whether patentable or not), methods, knowledge, know-how, skill, experience, analytical and quality control data, results, descriptions and compositions of matter, chemical manufacturing data, data and results from toxicological, pharmacological, preclinical and clinical testing and studies, assays, platforms, materials, samples, formulations, specifications, quality control testing data, that are necessary or useful for the discovery, manufacture, development or commercialization of Compound or Product.

1.38 "**[***]** ***Agreement***" shall be the agreement between [***] (along with any successors and assigns, "**[***]**") and Roche relating to NMB1 dated December 7, 2009, as amended now or in the future.

1.39 "***Net Sales***" shall mean, with respect to River Vision the amount of gross sales of a Product in the Territory invoiced by River Vision or its Affiliates or Partners to Third Parties, as reduced by the following deductions to the extent actually allowed or incurred with respect to such sales: [***]

*****Certain Confidential Information Omitted**

[***]. If Product is sold as part of a Combination Product (as defined below), then the parties shall meet approximately [***] prior to anticipated First Commercial Sale to negotiate, on a country-by-country basis, in good faith and agree to an appropriate adjustment to Net Sales, on a country-by-country basis, to reflect the relative significance of the Compound and other pharmaceutically active ingredients contained in the Combination Product. If the parties cannot reach agreement, then the Net Sales of the Combination Product, for the purposes of determining royalty payments, shall be determined by [***].

1.40 "***NRM***" shall mean Narrow River Management LLC.

1.41 "***Oncology***" shall mean any indication defined within Chapter II of the ICD Classification, or in a chapter that replaces Chapter II in successor versions of the ICD Classification. For the purposes of clarity, in the ICD-10 classification, any block within the range C01 to D48 shall fall within the definition of Oncology.

1.42 "***Patent Rights***" or "***Patents***" shall mean (a) patents, re-examinations, reissues, renewals, extensions, supplementary protection certificates, and term restorations, and (b) pending applications for patents, including, without limitation, provisional applications, continuations, continuations-in-part, divisional and substitute applications, including, without limitation, inventors' certificates.

1.43 "***Partner***" shall mean an entity with which River Vision will enter or has entered a Partner Agreement.

1.44 "***Partner Agreement***" shall mean any agreement between River Vision and a Third Party granting rights to develop and/or commercialise the Compound and/or the Product (including but not limited to a sub-license agreement with a Third Party or an assignment of this Agreement to a Third Party but not a Change of Control), other than a sub-contract pursuant to Section 2.4.

1.45 "***Pharmacovigilance Agreement***" shall mean an agreement entered into by the parties to set forth the responsibilities and obligations of the parties with respect to the procedures and timeframes for compliance with the applicable laws and regulations pertaining to safety reporting of the Products and related activities.

1.46 "***Phase 2 Trial***" shall mean a human clinical trial that would satisfy the requirements for a Phase 2 study as defined in 21 C.F.R. § 312.21(a), (or its successor regulation), and the foreign equivalent thereof.

1.47 "***Phase 3 Trial***" shall mean a human clinical trial that would satisfy the requirements for a Phase 3 study as defined in 21 CFR § 312.21(c) (or its successor regulation), and the foreign equivalent thereof.

1.48 "***Process Manufacture Transfer***" shall mean the actual transfer of the Process Manufacture Know-How listed in Appendix 3, such transfer to occur not earlier than the first anniversary of the Effective Date.

1.49 "***Process Manufacture Know-How***" shall mean the part of the Roche Know-How (described in Appendix 3) that will only be disclosed to River Vision after payment of the Process Manufacture Transfer Payment.

1.50 "***Process Manufacture Transfer Payment***" shall have the meaning provided in Section 9.3(a).

1.51 "***Product***" shall mean any pharmaceutical or therapeutic product containing the Compound, and includes without limitation Combination Products. If a given Product is commercialized in different formulations or dosage forms, then such formulations and dosage forms shall be considered as one single Product.

1.52 "***Regulatory Approval***" shall mean any and all approvals (including price and reimbursement approvals, if required), licenses, registrations, or authorizations of any country, federal, supranational, state or local regulatory agency, department, bureau or other government entity that are necessary for the manufacture, use, storage, import, transport and/or sale of a Product in such jurisdiction.

1.53 "***Regulatory Authority***" shall mean the FDA for the US and any equivalent governmental agency or body competent in a country (or group of countries like the European Union) to grant Regulatory Approval or other authorizations or licenses required for the development, manufacturing, marketing, reimbursement and/or pricing of pharmaceutical products in such country.

1.54 "***River Vision Intellectual Property***" shall mean the River Vision Patents, River Vision Know-How and River Vision's interest in the Joint Intellectual Property.

1.55 "***River Vision Know-How***" shall mean, to the extent used for the development, manufacture or commercialization of Compound or Product based thereon, information not included in the River Vision Patents that River Vision, any of its Partners or any of its Affiliates Controls on the Effective Date or during the Term, provided however that Roche Know-How shall not be deemed River Vision Know-How.

1.56 "***River Vision Patents***" shall mean, to the extent used for the development, manufacture or commercialization of Compound or Product based thereon, all Patents that River Vision, any of its Partners or any of its Affiliates Controls as of the Effective Date or during the Term, provided however that the Roche Patents shall not be deemed River Vision Patents.

1.57 "***River Vision Studies***" shall mean the studies to be performed by River Vision with Drug Product, as described in Appendix 4.

1.58 "***Roche Intellectual Property***" shall mean the Roche Patents, the Roche Know-How and Roche's interest in the Joint Intellectual Property.

1.59 "***Roche Know-How***" shall mean the Know-How Controlled by Roche listed in Appendix 3 of this Agreement. The term Roche Know-How shall include Process Manufacture Know-How.

1.60 "***Roche Patents***" shall mean the Patents or Patent Rights Controlled by Roche as exhaustively listed in Appendix 2 of this Agreement, along with all Patents and Patent Rights that claim priority to one or more of such Patents or Patent Rights so listed in such Appendix 2.

1.61 "***Royalty Term***" shall mean, in the case of any Product in any country of the Territory, the period of time commencing on the date of First Commercial Sale of such Product in such country and ending upon the later of:

(a) the expiration of the last-to-expire Valid Claim within the Roche Patents and/or Joint Patent Rights covering the composition, use or manufacture of such Product in such country where such activity occurs, or

(b) ten (10) years after the date of First Commercial Sale of such Product in such country.

1.62 "***Section***" shall mean a section of this Agreement.

1.63 "***Supported Shelf Age***" shall have the meaning provided in Section 6.1(c).

1.64 "***Term***" shall have the meaning provided in Section 15.1.

1.65 "***Territory***" shall mean all countries and territories of the world, except Japan.

1.66 "***Third Party***" shall mean an entity or person other than (a) Roche or its Affiliates and (b) River Vision or its Affiliates.

1.67 "***US***" or "***United States***" means the United States of America and its territories and possessions.

1.68 "***Valid Claim***" shall mean a claim contained in:

(a) an issued and unexpired Roche Patent or Joint Patent Rights which has not been held unenforceable, unpatentable or invalid by a decision of a court or other governmental agency of competent jurisdiction, unappealable or unappealed within the time allowed for appeal, and which has not been admitted to be invalid or unenforceable through abandonment, reissue, disclaimer or otherwise; or

(b) a patent application that is included in the Roche Patents or Joint Patent Rights that has been prosecuted in good faith and pending for less than [***] years. If a claim or a patent application that ceased to be a Valid Claim under clause (b) of the preceding sentence because of the passage of time later issues as a part of a patent within clause (a) of the preceding sentence, then it shall again be considered a Valid Claim effective as of the issuance of such patent.

2. RIVER VISION LICENSES

2.1 License grants.

(a) General. Subject to the terms and conditions of this Agreement, Roche hereby grants to River Vision (i) an exclusive (even as to Roche), royalty-bearing license, under the Roche Intellectual Property to develop, have developed, commercialize, have commercialized, make, have made, use, have used, sell, have sold, offer for sale, have offered for sale, import and have imported Compound and/or Product in the Field in the Territory, and (ii) subject to the terms of Section 11, an exclusive license and right to enforce the Roche Patents against anyone making, using, selling, offering for sale or importing any IGF-1 R antibody (in addition to Compound and Product) in the Field in the Territory, other than for this clause (ii) those IGF-1 R antibodies (but not including Compound or Product) developed and commercialized by Roche with its Affiliates and licensees. For clarity, River Vision is not granted any license or right to practice the Roche Patents under clause (ii), but rather to enforce the Roche Patents as provided in such clause (ii).

(b) Rights in Japan. If Chugai terminates its agreement with Roche relating to the Compound to Roche or such agreement otherwise terminates for any reason, then (i) the Territory shall automatically be deemed to include the territory of Japan, (ii) Roche shall automatically license and transfer to River Vision any Patents, Know-How, Regulatory Approvals, regulatory documentation or filings, and other rights or documentation Controlled by Roche or any of its Affiliates as a result of such termination, and (iii) such Patents and Know-how (including those within the Territory) shall be deemed Roche Patents and Roche Know-How. Roche hereby grants as of the Effective Date a non-exclusive sub-license to the improvements (as defined in the Chugai Agreement) made by Chugai under the Chugai Agreement to develop, have developed, make, have made, use, have used, sell, have sold, offer for sale, have offered for sale, import and have imported Compound and/or Product in the Field in the Territory. Such improvements shall be deemed Roche Patents and Roche Know-How, subject to any third party obligations.

(c) Rights in Oncology. If Roche, at its own discretion, elects to out-license the rights to the Compound in Oncology, then River Vision shall have the exclusive option right to extend the Field to Oncology. Roche will provide written notice to River Vision of its intent to license its rights with respect to Oncology. River Vision shall have [***] days after receipt of such notice to notify Roche of its intention to exercise its option right. If River Vision elects to exercises its option right, then the parties shall negotiate and enter into the terms for such extension of the Field in good faith.

2.2 Sub-Licenses.

(a) Under the [***] Agreement. Roche hereby grants an exclusive (even as to Roche) sub-license of the rights licensed to Roche under the [***] Agreement solely to develop, have developed, commercialize, have commercialized, make, have made, use, have used, sell, have sold, offer for sale, have offered for sale, import and have imported Compound and/or Product in the Field in the Territory. The sublicense granted under this Section 2.2 shall be subject to the rights and obligations and undertakings of Roche, as applicable and consistent with the [***] Agreement (a copy of which is attached hereto as Appendix 5, and incorporated herein by reference). Roche shall act as the sole direct contact with [***] in relation to the sub-license under this Section 2.2.

(b) Under the [***] Agreement. Roche hereby grants an exclusive (even as to Roche) sub-license of the rights licensed to Roche under the [***] Agreement solely to develop, have developed, commercialize, have commercialized, make, have made, use, have used, sell, have sold, offer for sale, have offered for sale, have imported and import Compound and/or Product in the Field in the Territory. The sublicense granted under this Section 2.2 shall be subject to the rights and obligations and undertakings of Roche, as applicable and consistent with the [***] Agreement (a copy of which is attached hereto as Appendix 6, and incorporated herein by reference). Roche shall act as the sole direct contact with [***] in relation to the sublicense under this Section 2.2.

(c) Under the [***] Agreement. Roche hereby grants an exclusive (even as to Roche) sub-license of the rights licensed to Roche under the [***] Agreement solely to develop, have developed, commercialize, have commercialized, make, have made, use, have used, sell, have sold, offer for sale, have offered for sale, import and have imported Compound and/or Product in the Field in the Territory. The sublicense granted under this Section 2.2 shall be subject to the rights and obligations and undertakings of Roche, as applicable and consistent with the [***] Agreement (a copy of which is attached hereto as Appendix 7, and incorporated herein by reference). Roche shall act as the sole direct contact with [***] in relation to the sublicense under this Section 2.2.

(d) Compliance with terms. River Vision shall comply with the terms of the [***] Agreement, the [***] License Agreement and the [***] License Agreement, to the extent such terms are disclosed in the respective Appendices attached hereto.

(e) Sub-license agreements. Roche shall not amend the [***] Agreement, the [***] Agreement or the [***] Agreement in a manner that materially affects any such sub-licenses hereunder, shall perform its obligations under such agreements, shall use Commercially Reasonable Efforts to enforce and maintain such agreements with respect to the Compound and/or the Product, and shall promptly notify River Vision in writing of any threatened or actual termination or notice regarding same with respect to such agreements with respect to the Compound and/or the Product. Roche shall provide copies of any amendments to such agreements (with reasonable redactions) to River Vision once executed. If any such agreement terminates or may terminate, Roche shall use Commercially Reasonable Efforts to maintain the applicable sub-license to River Vision; if Roche is not able to maintain the applicable sub-license, River Vision shall have the right to attempt to cure any breach giving rise to such actual or threatened termination and may credit any amounts paid by River Vision to maintain any such sub-license against any amounts owed to Roche hereunder, provided that such amounts credited against any amounts owned to Roche hereunder shall not exceed the amount owed by Roche for the respective license. River Vision shall inform Roche of any intended interactions with [***], [***] or [***], as applicable.

2.3 Right to Sublicense to its Affiliates. Subject to Roche's rights under Section 3, River Vision shall have the right to grant written sublicenses to its Affiliates under its rights granted under Section 2.1 and Section 2.2. without prior approval of Roche and solely to the extent necessary to develop, commercialize, make, use, offer for sale, sell or import (and have others do the same) Compound and/or Product in the Field in the Territory. If River Vision grants such a sublicense, River Vision shall ensure that all of the applicable terms and conditions of this Agreement shall apply to the Affiliate to the same extent as they apply to River Vision for all purposes. River Vision assumes full responsibility for the performance of all obligations and observance of all terms so imposed on such Affiliate and shall itself account to Roche for all payments due under this Agreement by reason of such sublicense.

2.4 Sub-Contractors. River Vision has the right to sub-contract the work performed under this Agreement. However, River Vision shall only sub-contract the manufacture of the Compound or Product [***]. Any sub-contract agreement shall include the right to disclose (i) a copy of the Agreement and confidential information to Roche and (ii) the right to assign the agreement to Roche, including the right to transfer of the ownership of data, information and results arising therefrom to Roche to the same extent as to River Vision.

2.5 Right to enter into a Partner Agreement with Third Parties. Subject to Roche's rights under Section 3, River Vision shall have the right to enter into a Partner Agreement, including but not limited to granting sublicenses to Partners under its rights granted under Section 2.1 and Section 2.2. Any rights granted to a Third Party under this Agreement shall be solely to the extent necessary to develop, commercialize, make, use, offer for sale, sell or import (and have others do the same) Compound and/or Product in the Field in the Territory. River Vision shall ensure that all of the applicable terms and conditions of this Agreement, including the obligations under the [***] Agreement, the [***] Agreement and the [***] Agreement, shall apply to the Partner under the Partner Agreement to the same extent as they apply to River Vision for all purposes. River Vision assumes full responsibility for the performance of all obligations and observance of all terms so imposed to the Partner under such Partner Agreement and shall itself account to Roche for all payments due under this Agreement. The Partner of River Vision shall have no right to further sub-license rights to develop and commercialise the Compound or Product to a Third Party, with the understanding that co-promotion or distribution or other marketing arrangements are permitted.

River Vision shall disclose a copy of the draft Partner Agreement to Roche, subject to redaction of financial terms. [***].

2.6 Know-How Transfer.

(a) Roche Know-How transfer. Promptly after the Effective Date, Roche will transfer the Roche Know-How listed in Appendix 3 to River Vision, with the exception of the Process Manufacture Know-How. The Process Manufacture Know-How will be transferred within [***] days after written request from River Vision.

(b) Technical Support. If River Vision has made the Process Manufacture Transfer Payment, then Roche will provide up to [***] man days of technical support free of charge in order to assist River Vision with the Process Manufacture Transfer to a CMO agreed between Roche and River Vision. This support shall be used in the [***] month period that starts with the receipt by Roche of the Process Manufacture Transfer Payment. Further technical support from Roche will be provided at Roche's discretion and, if such support is provided by Roche, charged at Roche's standard commercial rate applicable at that time.

(c) Follow-up Questions. Roche shall provide up to [***] hours for general questions and [***] hours for regulatory questions free of charge.

(d) No further obligation. Roche shall have no obligation to transfer any Know-How or to provide technical support other than expressly stated in this Section 2.6.

2.7 Alliance Manager. To facilitate communication between the parties, each party shall designate an Alliance Manager within thirty (30) days after the Effective Date. The Roche Alliance Manager and his/her counterpart at River Vision shall be the primary points of contact between the parties with respect to all matters arising under this Agreement. Each party may change its Alliance Manager from time to time in its sole discretion, effective upon notice to the other party of such change.

2.8 Freedom-to-Operate. River Vision hereby grants to Roche a non-exclusive, perpetual, worldwide, royalty-free license, with the right to sublicense, under the River Vision Patents, to operate, utilize or improve those IGF-1 R antibodies (but not including Compound or Product) developed and commercialized by Roche with its Affiliates and licensees, but only in Oncology.

2.9 Retained Rights. Roche shall retain the right for Roche and its Affiliates and licensees to use the Compound for internal pre-clinical purposes in and outside of the Field; provided that no studies requiring reporting to Regulatory Authorities in the Territory will be conducted in the Field. Except as permitted by this Agreement or any other agreement between the parties, Roche and its Affiliates and licensees will not use the Compound or Product for any other purpose, nor will Roche or any of its Affiliates or licensees practice any of the Patents or Know-How (including, without limitation, any Roche Intellectual Property) exclusively licensed or sub-licensed to River Vision hereunder within the scope of those licenses in the Field in the Territory.

3. ROCHE'S RIGHT OF FIRST OFFER.

3.1 Notice to Roche by River Vision. If River Vision, at any time during the Term but not earlier than availability of the data generated under the first of the River Vision Studies to be completed, intends to (i) enter into a Partner Agreement relating to the Compound and/or the Product or (ii) undergo a Change of Control or (iii) enter into Phase 3 Trial with the Compound without a Partner, then River Vision shall have the obligation to inform Roche in writing accordingly and give Roche access to the Data Room.

3.2 Process. Within [***] days following the receipt by Roche of such written notice, Roche shall review the Data Room ("***Review Period***"). If Roche is interested in taking the project back, then the parties shall have [***] days from the date of the expiry of the Review Period to exclusively negotiate the terms to regain the rights to the Compound and/or the Product (i.e. to take the license for the whole program back and ownership under the River Vision Patents and Know-How or, if transfer of ownership is not possible, a perpetual, exclusive license for the whole program) (the "***Negotiation Period***"). If (i) the parties, after good faith discussions in the Negotiation Period, cannot agree on the structure and terms of such agreement or (ii) Roche confirms

in writing to River Vision that it is not interested in regaining the rights to the Compound and/or the Product, then River Vision shall be free to enter into a Partner Agreement with a Third Party or to undergo a Change of Control and this Section 3 will have no further force or effect, subject to the limitations specified in Sections 2.5 and 18.4 with respect thereto. Notwithstanding the foregoing, if River Vision (1) does not enter into a Partner Agreement or does not undergo a Change of Control but continues the development and/or commercialisation of the Compound and/or Product and (2) at any time during the Term thereafter there is additional material clinical data available as compared to the clinical data previously reviewed by Roche in the Data Room, and (3) River Vision thereafter intends to enter into a Partner Agreement relating to the Compound and/or the Product or undergo a Change of Control, then Roche's Right of First Offer under this Section 3 shall apply one more time again. If (a) Roche does not regain its rights to the Compound and/or the Product if offered to Roche a second time under this Section 3.2 and (b) River Vision thereafter intends to enter into a Partner Agreement or to undergo a Change of Control, then Roche shall have a non-exclusive right under this Section 3.2 to negotiate the terms to regain the rights to the Compound and/or the Product.

4. DILIGENCE AND REPORTING

4.1 Diligence. River Vision shall use Commercially Reasonable Efforts to develop and commercialize the Compound and/or Product in the Field in the Territory.

4.2 Reporting.

(a) Prior to First Commercial Sale. During the Term up to First Commercial Sale of the Product, River Vision shall have the obligation to submit detailed annual reports to Roche summarizing development progress of the Product, including the Development Plan, pursuant to Section 5.1. The first such annual report shall be provided on the first anniversary of the Effective Date. Each subsequent annual report shall be provided on subsequent anniversaries of the Effective Date.

(b) After First Commercial Sale. From the First Commercial Sale of the Product during the Term, River Vision shall inform Roche in a detailed report regarding the commercialization of Products in the Field in the Territory by River Vision, its Affiliates and Partners. The first such annual report shall be provided on the first anniversary of the First Commercial Sale. Each subsequent annual report shall be provided on subsequent anniversaries of the First Commercial Sale.

5. DEVELOPMENT

5.1 Responsibility. River Vision, at its sole cost, shall use Commercially Reasonable Efforts to conduct the development of Compound and/or Product in the Field in the Territory.

5.2 Development Plan. River Vision will conduct (or have conducted) the development of the Compound and Product in the Field in the Territory in accordance with a written plan ("***Development Plan***"). River Vision shall send a then current version of the Development Plan to Roche at each anniversary of the Effective Date. If River Vision wishes to improve the manufacturing process of the Compound or the Product resulting in a change of the cell bank expressing the Compound, then River Vision shall provide written notice to Roche of the nature of such intended work [***].

5.3 Different Product. If, as a result of any permitted work performed pursuant to Section 5.2, River Vision uses a new master cell line to develop and subsequently commercializes a Compound and/or a Product as a new biological entity (in addition to a first Compound and/or Product), so that such Compound and/or Product qualifies for an independent period of data exclusivity based on it being a new biological entity under a separate regulatory process, then such Compound and/or Product shall be a separate Product for purposes of Section 9.

6. SUPPLY

6.1 Clinical Supply of Product.

(a) Responsibility. River Vision shall be solely and exclusively responsible at its own expense for the manufacture and supply of clinical supplies of the Product. River Vision shall supply at its own cost all clinical supply of Product during the Term, either by itself, or through a Third Party.

(b) Supply. Notwithstanding Section 6.1(a), Roche shall supply to River Vision Drug Product as specified in Appendix 4 purely for the purposes of conducting the River Vision Studies. Roche shall have no obligation to produce, process or test such Drug Product, except as explicitly stated in this Section 6 or on Appendix 4. The parties shall enter into a Quality Agreement within ninety (90) days of the Effective Date.

(c) Restrictions of Use. River Vision shall not administer to any patient Drug Product supplied by Roche that has an actual shelf age higher than the shelf age supported by the last real-time stability data within specification ("***Supported Shelf Age***"). In this context actual shelf age means the period of time between present date and the manufacturing date of the respective batch. Supported Shelf Age is stated in Appendix 4 and will be revised and communicated to River Vision in written form with each future stability report, and will become integral part of Appendix 4 together with the supportive stability report.

6.2 Commercial Supply of Product. River Vision shall be solely and exclusively responsible at its own expense for the commercial manufacture and commercial supply of Product for sale in the Territory, either by itself or through Third Parties.

7. REGULATORY

7.1 Responsibility. River Vision, at its sole cost, shall pursue all regulatory affairs related to Product in the Field in the Territory including the preparation and filing of applications for Regulatory Approval, as well as any or all governmental approvals required to develop, have developed, make, have made, use, have used, import, have imported sell and have sold Compound and/or Product. River Vision shall be responsible for pursuing, compiling and submitting all regulatory filing documentation, and for interacting with regulatory agencies, for Compound and Product in all countries in the Territory. River Vision shall own and file in their discretion all regulatory filings and Regulatory Approvals for the Compound and Product in all countries of the Territory. River Vision shall supply Roche with a copy of all material communications related to Compound and Product to or from the regulatory agencies.

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7.2 IND. River Vision shall establish a separate IND or equivalent under which to conduct their clinical trials of the Compound and Product in the Field in the Territory. River Vision shall submit draft protocols to Roche for review and approval as long as patients are still being treated in Roche trials sponsored or supported by Roche. River Vision and its Affiliates and Partners shall have the right to cross-reference any IND or other regulatory documentation of Roche or any of its Affiliates regarding Compound or Product.

7.3 Informed Consent forms. Any Informed Consent forms with patients under any River Vision study shall include the right to transfer samples, data and information to Roche.

7.4 Pharmacovigi lance Agreement. The parties agree that they shall execute a separate Pharmacovigi lance Agreement if deemed applicable prior to, but no later than, the date on which River Vision establishes either a separate IND or equivalent under which they intend to initiate their first clinical trial of the Compound or Product in the Field in the Territory.

8. COMMERCIALIZATION

River Vision, at its own expense, shall have sole responsibility and decision making authority for the marketing, commercialization, promotion, sale and distribution of Products in the Field in the Territory.

9. RIVER VISION PAYMENT OBLIGATIONS

9.1 License Fee. River Vision shall pay to Roche a one time, non-refundable, non-creditable payment of [***] CHF ([***] CHF) within [***] days after the Effective Date. Any non-royalty payments payable to Genentech under the Cabilly License Agreement shall be creditable in full against amounts payable to Roche hereunder.

9.2 Execution of a Partner Agreement. River Vision shall pay to Roche a one time, non-refundable, non-creditable payment in the amount of CHF [***] ([***] CHF) within [***] days after the execution of a Partner Agreement or a Change of Control.

9.3 Process Manufacture Transfer and Other Payments.

(a) River Vision shall make a one time, non-refundable, non-creditable payment in the amount of CHF [***] ([***] CHF) within [***] days after the date of the initiation of the Process Manufacture Know-How transfer (the "***Process Manufacture Transfer Payment***").

(b) River Vision shall make a one time, non-refundable, non-creditable payment in the amount of [***] ([***] CHF) within [***] days after the date on which [***].

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(c) If the payments under Sections 9.3(a) and (b) have not been made when River Vision enters into a Partner Agreement or undergoes a Change of Control, as applicable, such payments shall be due within [***] days after the effective date of the Partner Agreement or the Change of Control, as applicable.

9.4 Development Event Payments

(a) For the first Indication.

River Vision shall pay up to a total of CHF [***] (CHF [***]) in relation to the achievements of events with respect to each Product for the first Indication developed for the applicable Product. The development event payments under this Section 9.4(a) shall be paid for the first Indication on a Product-by-Product basis as follows:

Development Event	**Event Payment in [***] CHF**
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
Total	**[***]**

Each of the foregoing payments shall be paid no more than once for each Product.

(b) For the second and each subsequent Indication

River Vision shall pay up to a total of CHF [***] (CHF [***]) per Indication in relation to the achievements of events with respect to each Product for the second and each subsequent Indication developed for the applicable Product. The development event payments under this Section 9.4(b) shall be paid for the second and each subsequent Indication on a Product-by-Product basis as follows:

Development Event	**Event Payment in [***] CHF**
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
Total	**[***]**

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(c) Development Event Payments for the territory of Japan

In addition to payments due under paragraph (a) and (b) above, River Vision shall pay up to a total of CHF [***] (CHF [***]) in relation to the achievements of events with respect to each Product for the first Indication developed for the applicable Product. The development event payments under this Section 9.4(c) shall be paid for the first Indication on a Product-by-Product basis as follows:

Development Event	**Event Payment in [***] CHF**
[***]	[***]
[***]	[***]
Total	**[***]**

Each of the foregoing payments shall be paid no more than once for each Product.

In addition to payments due under paragraphs (a) and (b) above, River Vision shall pay up to a total of CHF [***] (CHF [***]) per Indication in relation to the achievements of events with respect to each Product for the second and each subsequent Indication developed for the applicable Product. The development event payments under this Section 9.4(c) shall be paid for the second and each subsequent Indication on a Product-by-Product basis as follows:

Development Event	**Event Payment in [***] CHF**
[***]	[***]
[***]	[***]
Total	**[***]**

If Chugai terminates the Chugai Agreement [***], and Japan is within the Territory under this Agreement, then all applicable payments under this Section 9.4(c) shall be due.

(d) Development Event Payments for the second Product and each subsequent Product

For the second Product and each subsequent Product, the development event payments payable to Roche under Sections 9.4(a), 9.4(b) and 9.4(c) shall be reduced by [***]%.

9.5 Sales Based Events

River Vision shall pay to Roche up to a total of CHF [***] (CHF [***]) based on aggregate Calendar Year Net Sales of a Product in the Territory:

Net Sales Threshold	**Payment [***] CHF**
Total Calendar Year Net Sales in the Territory of a Product exceed CHF [***] CHF	[***]
Total Calendar Year Net Sales in the Territory of a Product exceed CHF [***] CHF	[***]
Total Calendar Year Net Sales in the Territory of a Product exceed CHF [***] CHF	[***]
TOTAL	**[***]**

Each of the sales based event payments shall be paid no more than once, at first occurrence of the event for the Product in the Territory first reaching the respective Net Sales Threshold, irrespective of whether or not the previous sales based event payment was triggered by the same or by a different Product, and shall be non-refundable and non-creditable.

9.6 Royalties.

Royalties shall be payable by River Vision on Net Sales of Products on a Product-by-Product and country-by-country basis until the expiry of the Royalty Term. Thereafter, the licenses set forth in Section 2 shall be fully paid up and royalty-free for a Product in a country.

The following royalty rates shall apply to the respective tiers of aggregate Calendar Year Net Sales of a Product in the Territory, on an incremental basis, as follows:

Tier of Calendar Year Net Sales in million CHF	**Percent (%) of Net Sales**
[***]	9
[***]	[***]
[***]	12

For example, if Net Sales of a Product in the Territory, for a given Calendar Year, are CHF [***], then the royalty rate applicable on such Net Sales of such Product for that year shall be calculated as follows:

[***].

9.7 Credit of Royalty Payments

River Vision may credit [***] of the royalties payable to Genentech under the Cabilly License Agreement against the royalties payable to Roche under Section 9.6.

9.8 Third Party Payments

Roche shall be responsible at its sole expense for making any payments under the [***] Agreement, the [***] Agreement and the [***] Agreement.

River Vision shall be responsible for and pay or have paid any consideration owed to any Third Party in relation to Third Party intellectual property rights, except with respect to any payments owed under the [***] Agreement, the [***] Agreement and the [***] Agreement in accordance with the terms of such agreements. Such Third Party payments shall not be deductable against the amounts payable under this Agreement or refundable under this Agreement. [***].

10. GENERAL PAYMENT PROVISIONS

10.1 Accounting and reporting

(a) Timing of Payments.

(i) All payments made under Section 9.4 shall be non-refundable and non-creditable. River Vision shall inform Roche by written notice within [***] days after the occurrence of the respective event and the respective payment shall be made within [***] days after the occurrence of the respective event.

(ii) River Vision shall calculate royalties on Net Sales quarterly as of March 31, June 30, September 30 and December 31 (each being the last day of an "***Accounting Period***") and shall pay royalties on Net Sales within the [***] days after the end of each Accounting Period in which such Net Sales occur.

(b) Late Payment. Any payment under this Agreement that is not paid on or before the date such payment is due shall bear interest, to the extent permitted by applicable law, at [***] percentage points above the average one-month Euro Interbank Offered Rate (EURIBOR), as reported by Reuters from time to time, calculated on the number of days such payment is overdue.

(c) Currency of Payment. Royalties on Net Sales shall be paid by River Vision in Swiss Francs.

(d) Currency Conversion. When calculating the Sales for countries other than Switzerland, River Vision shall convert the amount of such sales in currencies other than Swiss Francs into Swiss Francs using for internal foreign currency translation River Vision's then current standard practices actually used on a consistent basis in preparing its audited financial statements.

10.2 Reporting. With each payment River Vision shall provide Roche in writing for the relevant Calendar Quarter on a Product-by-Product basis the following information:

a) Gross Sales on a country-by-country basis in local currencies;

b) Net Sales on a country-by-country basis in local currencies;

c) Net Sales on a country-by-country basis in Swiss Francs;

d) Total Net Sales in the Territory in Swiss Francs;

e) Total royalty payable in Swiss Francs; and

f) Exchange rates used for the conversion to Swiss Francs made under Section 10.1(d) and Section 10.2(c).

10.3 Taxes

Roche shall pay all sales, turnover, income, revenue, value added, and other taxes levied on account of any payments accruing or made to Roche under this Agreement.

If provision is made in law or regulation of any country for withholding of taxes of any type, levies or other charges with respect to any royalty or other amounts payable under this Agreement to Roche, then River Vision shall promptly pay such tax, levy or charge for and on behalf of Roche to the proper governmental authority, and shall promptly furnish Roche with receipt of payment. River Vision shall be entitled to deduct any such tax, levy or charge actually paid from royalty or other payment due to Roche or be promptly reimbursed by Roche if no further payments are due to Roche. Each party agrees to reasonably assist the other party in claiming exemption from such deductions or withholdings under double taxation or similar agreement or treaty from time to time in force and in minimizing the amount required to be so withheld or deducted.

10.4 Auditing

(a) Roche's Right to Audit

River Vision shall keep, and shall require its Affiliates and Partners to keep, full, true and accurate books of account containing all particulars that may be necessary for the purpose of calculating all royalties payable under this Agreement. Such books of accounts shall be kept at their principal place of business. At the expense of Roche, Roche has the right to engage Roche's then current worldwide independent public accountant to perform, on behalf of Roche an audit of such books and records of River Vision and its Affiliates and Partners, that are deemed necessary by the public accountant to report on Net Sales of Product for the period or periods requested by Roche and the correctness of any report or payments made under this Agreement.

Upon timely request and at least [***] working days' prior written notice from Roche, such audit shall be conducted in the countries specifically requested by Roche, during regular business hours in such a manner as to not unnecessarily interfere with River Vision's normal business activities, and shall be limited to results in the [***] calendar years prior to audit notification.

Such audit shall not be performed more frequently than once per Calendar Year nor more frequently than once with respect to records covering any specific period of time.

All information, data documents and abstracts herein referred to shall be used only for the purpose of verifying royalty statements, shall be treated as River Vision Confidential Information subject to the obligations of this Agreement and need neither be retained more than [***] year after completion of an audit hereof, if an audit has been requested; nor more than [***] years from the end of the calendar year to which each shall pertain; nor more than [***] year after the date of termination of this Agreement.

(b) Sharing of draft reports. The auditors shall share all draft reports with Roche and River Vision before the final document is issued; the auditors shall not interpret the agreement. The final report shall be shared by Roche and River Vision.

(c) Over-or Underpayment. If the audit is undisputed and reveals an overpayment, Roche shall reimburse River Vision for the amount of the overpayment within [***] days. If the audit is undisputed and reveals an underpayment, River Vision shall make up such underpayment with the next royalty payment or, if no further royalty payments are owed to Roche, River Vision shall reimburse Roche for the amount of the underpayment within [***] days. River Vision shall pay for the out-of-pocket audit costs if the underpayment of River Vision exceeds [***]% of the aggregate amount of royalty payments owed with regard to the royalty statements subject of the audit. Section 10.1(b) shall apply to this Section 10.4(c), interest to run from the date such audit is reported to the parties.

(d) Duration of Audit Rights. The failure of Roche to request verification of any royalty calculation within the period during which corresponding records must be maintained under this Section 10.4 will be deemed to be acceptance of the royalty payments and reports.

11. INTELLECTUAL PROPERTY

11.1 Ownership of Patent Rights. River Vision shall own all River Vision Inventions, Roche shall own all Roche Inventions, and River Vision and Roche shall jointly own all Joint Inventions. River Vision and Roche each shall require all of its employees, agents and consultants to assign all inventions related to Products made by them to Roche and River Vision, as the case may be. The determination of inventorship for Inventions worldwide shall be in accordance with US inventorship laws.

11.2 Patent prosecution and maintenance. Roche shall have the first right (but not the obligation) to prepare, file, prosecute and maintain all Roche Patents at Roche's sole expense. River Vision shall have the first right (but not the obligation) to prepare, file, prosecute and maintain all River Vision Patents at River Vision's sole expense. The party responsible for the filing, prosecution and maintenance of any Roche Patents or River Vision Patents (the "***Responsible Party***") shall provide the other party with a reasonable opportunity to review drafts of proposed patent applications with respect to Patents owned solely by the Responsible Party that claim the manufacture, use or sale of Compound or Product being developed or commercialized by either party, if appropriate, depending on the contents of the submission. The Responsible Party shall consider in good faith the requests and suggestions of the other party with respect to the content and strategies for such patent applications. For clarity, Roche is not obliged to and River Vision has no right request Roche to prepare, file, prosecute and maintain general claims of the Roche Patents going beyond the Compound and/or Product or any other IGF-1 R antibody. Notwithstanding anything in this Section 11 to the contrary, Roche's rights with respect to River Vision Patents for prosecution, defense, enforcement and otherwise under this Section 11 will extend only to Compound and/or Product in the Field, and further Roche will not seek to enforce any River Vision Patents without the consent of River Vision.

11.3 Assignment of Patents. If Roche is no longer interested in prosecuting or maintaining any of the Roche Patents, then Roche shall notify River Vision thereof and Roche shall assign such Roche Patents to River Vision (or license on an exclusive basis all claim scope to River Vision if any such assignment is not possible under applicable patent law), provided that River Vision shall bear the costs for such assignments and for all future costs. All Patent Rights so assigned from Roche to River Vision shall remain Roche Patents as defined in this Agreement. If River Vision is no longer interested inprosecuting or maintaining any of the River Vision Patents, then River Vision shall notify Roche thereof by at least [***] days prior written notice.

11.4 Prosecution of Joint Patent Rights. River Vision shall be the Responsible Party for preparing, filing, prosecuting or maintaining Joint Patents, with the parties' sharing equally the expense thereof. River Vision shall not discontinue prosecution or maintenance of Joint Patents without at least [***] days prior written notice to Roche. If River Vision decides to discontinue prosecution or maintenance of any Joint Patents, Roche shall have the option to continue to prosecute or maintain such Joint Patents, at Roche's sole expense.

11.5 Cooperation of the Parties. Each party agrees to cooperate in the preparation, filing and prosecution of any Patents under this Agreement and in the obtaining of any patent extensions, supplementary protection certificates and the like with respect to any such Patent. Such cooperation includes, but is not limited to: (a) executing all papers and instruments, or requiring its employees, agents or consultants, to execute such papers and instruments and to enable the Responsible Party to apply for and to prosecute and maintain patent applications in any country; and (b) promptly informing the Responsible Party of any matters coming to such party's attention that may affect the preparation, filing, prosecution or maintenance of any such patent applications; and (c) the Responsible Party regularly update the other party on the status of all Patents, including any dates for action required or due dates for payments. River Vision shall have the right using a form mutually agreed to by the parties to record its exclusive license under the Roche Patents in countries in the Territory.

11.6 Infringement by Third Parties.

(a) Infringement. Each party shall promptly provide written notice to the other party during the Term of any known infringement or suspected infringement by a Third Party of any Roche Patents, River Vision Patents (if any) or Joint Patents (if any), or of any invalidity or unenforceability assertion or challenge to any such patents, or of any unauthorized use or misappropriation of Roche Know-How, and shall provide the other party with all evidence in its possession supporting such infringement, assertion or challenge or unauthorized use or misappropriation. For clarity, any challenge amounting to a reexamination, interference or opposition will be addressed by Sections 11.2 through 11.5.

(b) Defense and Enforcement. Within a period of [***] days after either party provides or receives such written notice with respect to its Patents ("***Decision Period***"), the party that has the first right to enforce any such Patents as set forth on Schedule 11.6(b) (the "***First Party***") that are allegedly infringed, in its sole discretion, shall decide whether or not to initiate a suit or take other appropriate action with respect to any allegedly infringing activities in the Field (including without limitation defending any assertion or challenge) and shall notify the other party in writing of its decision in writing ("***Suit Notice***").

If the First Party for its Patents are allegedly infringed decides to bring a suit or take action with respect to any allegedly infringing activities in the Field and provides a respective Suit Notice, then such party may immediately commence such suit or take such action. If such party (i) does not in writing advise the other party within the Decision Period that it will commence suit or take action, or (ii) fails to commence suit or take action within a reasonable time after providing Suit Notice, then the other party shall thereafter have the right to commence suit or take action with respect to any allegedly infringing activities in the Field and shall provide written notice to the party whose Patents are allegedly infringed of any such suit commenced or action taken by the other party.

Upon written request, the party bringing suit or taking action ('Initiating Party') shall keep the other party informed of the status of any such suit or action and shall provide the other party with copies of all substantive documents and communications filed in such suit or action. The Initiating Party shall have the sole and exclusive right to control any such suit or action, including but not limited to selecting counsel for any such suit or action. If each of the parties elects to be an Initiating Party with respect to the same allegedly infringing activities within the Field, then the parties shall meet and agree on how to manage the resulting suits and actions (including with respect to the process set forth in Section 11.7). If River Vision is the Initiating Party with respect to the Compound Patent, upon Roche request, River Vision and Roche shall jointly agree in good faith on the strategy on how to bring suit or take action with respect to such Compound Patent, such discussions to be held in good faith, and failure to agree shall not jeopardize timing regarding any such suit or action.

The Initiating Party shall, except as provided below, pay all expenses of the suit or action, including, without limitation, the Initiating Party's attorneys' fees, damages and court costs.

If the Initiating Party believes it reasonably necessary, upon written request the other party shall join as a party to the suit or action, but shall be under no obligation to participate, except to the extent that such participation is required as the result of its being a named party to the suit or action. Alternatively, at the Initiating Party's request, the other party will bring the suit or action in the other party's name, if the Initiating Party reasonably believes that the Initiating Party does not have standing to bring the suit or action, and in such event, the Initiating Party will still control the suit or action as provided above. At the Initiating Party's written request, the other party shall offer reasonable assistance to the Initiating Party in connection therewith at no charge to the Initiating Party except for reimbursement of reasonable out-of-pocket expenses incurred by the other party in rendering such assistance. The other party shall have the right to participate and be represented in any such suit or action by its own counsel at its own expense.

The Initiating Party shall not settle, agree to a consent judgment or otherwise voluntarily dispose of the suit or action without the written consent of the other party, which consent shall not be unreasonably withheld or delayed; provided that if River Vision is the Initiating Party, any such consent from Roche is not required if River Vision grants a permitted sub-license under Sections 2.5 and 3.

Except as otherwise agreed by the parties in connection with a cost-sharing arrangement, any recovery realized as a result of litigation described in this Section 11.6 (whether by way of settlement or otherwise) will be first allocated to reimbursement of unreimbursed legal fees and expenses incurred by the Initiating Party(ies), then toward reimbursement of any unreimbursed legal fees and expenses of the other party if not an Initiating Party, and then the remainder will be shared between the parties by allocating (i) [***]% to River Vision and [***] to Roche for those Patents infringed where River Vision is the Initiating Party, (ii) [***]% to Roche and [***] to Roche for those Patents infringed where Roche is the Initiating Party, and (iii) if there are Patents infringed for which River Vision is the Initiating Party for one or more of those Patents and Roche is the Initiating Party for one or more of those Patents, [***].

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(c) Exclusion. For clarity, this Section 11.6 shall not apply to the [***] Agreement, the [***] Agreement and the [***] Agreement.

11.7 Hatch-Waxman. Notwithstanding anything herein to the contrary, should a party receive a certification for a Product pursuant to the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417, known as the Hatch-Waxman Act), as amended, or its equivalent in a country other than the US, then such party shall immediately provide the other party with a copy of such certification. The First Party for any such Patent shall have [***] days from date on which it receives or provides a copy of such certification to provide written notice to the other party ("***H-W Suit Notice***") whether the First Party will bring suit at its expense within a [***] day period from the date of such certification. Should such [***] day period expire without the First Party bringing suit or providing such H-W Suit Notice, then the other party shall be free to immediately bring suit with respect to such Patent as the Initiating Party.

11.8 Biosimilar or interchangeable biological products. Notwithstanding anything herein to the contrary, within [***] years after the approval of a Product which has been licensed in the US as a biological product under 42 USC 262(a), and as may be needed from time to time thereafter, the parties shall consult as to potential strategies with respect to unexpired US Patent Rights which cover the Product; such consultation shall occur at least [***] days before such [***] anniversary. Specifically, in anticipation of a receipt by the Product's reference product sponsor ("***Reference Product Sponsor***") of a biosimilar or interchangeable product application pursuant to the Biologics Price Competition and Innovation Act of 2009 (Public Law 111-148), the parties will discuss the Reference Product Sponsor's likely course of action with regard to each such US Patent Right in the procedural steps set forth under 42 USC §262(l), including a general plan for timely communication between the parties in light of the statutory response deadlines.

11.9 Patent Term Extensions. The parties shall use Commercially Reasonable Efforts to obtain all available patent term extensions, adjustments or restorations, or supplementary protection certificates ("***SPCs***", and together with patent term extensions, adjustments and restorations, "***Patent Term Extensions***"). Roche shall execute such authorizations and other documents and take such other actions as may be reasonably requested by River Vision to obtain such Patent Term Extensions, including without limitation designating River Vision as its agent for such purpose as provided in 35 U.S.C. Section 156. All filings for such Patent Term Extensions shall be made by Roche; provided, that in the event that Roche elects not to file for a Patent Term Extension, Roche shall (a) promptly inform River Vision of its intention not to file and (b) grant the right to file for such Patent Term Extension to River Vision as its agent, such acts to occur well in advance of any deadlines for applying for any such Patent Term Extensions for River Vision to act thereupon. Each party shall execute such authorizations and other documents and take such other actions as may be reasonably requested by the other party to obtain such extensions. The parties shall cooperate with each other in gaining patent term restorations, extensions and/or SPCs wherever applicable to such Roche Patents.

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12. TRADEMARKS AND LABELING

River Vision shall own all trademarks used on or in connection with Product in the Territory, and shall, at its sole cost, be responsible for procurement, maintenance, enforcement and defense of all trademarks used on or in connection with Product in the Territory.

If requested by Roche and to the extent permitted by applicable law, all packaging and labeling shall display that the Product has been "***licensed from Roche***".

13. REPRESENTATIONS AND WARRANTIES

13.1 Mutual representations and warranties. Each party represents and warrants to the other that, as of the Effective Date: (a) it is duly organized and validly existing under the laws of its jurisdiction of incorporation or formation, and has full corporate or other power and authority to enter into this Agreement and to carry out the provisions hereof; (b) it is duly authorized to execute and deliver this Agreement and to perform its obligations hereunder, and the person or persons executing this Agreement on its behalf has been duly authorized to do so by all requisite corporate or partnership action; and (c) this Agreement is legally binding upon it, enforceable in accordance with its terms, and does not conflict with any agreement, instrument or understanding, oral or written, to which it is a party or by which it may be bound, nor violate any material law or regulation of any court, governmental body or administrative or other agency having jurisdiction over it.

13.2 Roche representations and warranties. Roche represents and warrants to River Vision that, as of the Effective Date: (a) Roche has not received written notice from any Third Party claiming that the manufacture, use or sale of Compound or Product infringes any Patent of any Third Party; (b) Roche is not aware of any Patent that would be infringed by Compound in the Field in the Territory by River Vision; (c) Roche is not a party to any legal action, suit or proceeding relating to Compound or Product; (d) Roche has the full right, power and authority to grant all of the right, title and interest in the licenses, sub-licenses and other rights granted to River Vision under this Agreement; (e) the Roche Patents constitute all of the Patents owned or in-licensed by Roche or any of its Affiliates that are necessary to develop, commercialize, make, use, sell, offer for sale, and import Compound or Product (other than as disclosed by Roche to River Vision before the Effective Date); (f) Roche has Control of all the Roche Patents; and (g) the [***] Agreement, the [***] License Agreement and the [***] License Agreement are in full force and effect.

13.3 Limitations. Except as provided in Section 13.2, Roche makes no representation or warranty that all intellectual property rights necessary for River Vision to make, have made, use, sell, offer for sale and import the Compound or the Product in the Territory have been granted to River Vision under Section 2. Roche did not perform an exhaustive and final search for Third Party patents or an evaluation thereof for Compound and technologies relevant under this Agreement. Roche will not keep River Vision updated about further searches or analyses of Third Party patents nor will it keep River Vision updated about any further developments of any Third Party rights or steps taken or intended to be taken by Roche with regard to such Third Party rights.

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13.4 Disclaimer. Except as expressly set forth herein and elsewhere in this Agreement, THE INTELLECTUAL PROPERTY RIGHTS PROVIDED BY EACH PARTY HEREUNDER ARE PROVIDED "***AS IS***" AND EACH PARTY EXPRESSLY DISCLAIMS ANY AND ALL WARRANTIES OF ANY KIND, EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION THE WARRANTIES OF DESIGN, MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, NON-INFRINGEMENT OF THE INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES, OR ARISING FROM A COURSE OF DEALING, USAGE OR TRADE PRACTICES.

13.5 Debarment. River Vision represents and warrants that it has never been debarred under 21 U.S.C. §335a, disqualified under 21 C.F.R. §312.70 or §812.119, sanctioned by a Federal Health Care Program (as defined in 42 U.S.C §1320 a-7b(f)), including without limitation the federal Medicare or a state Medicaid program, or debarred, suspended, excluded or otherwise declared ineligible from any other similar Federal or state agency or program. In the event River Vision receives notice of debarment, suspension, sanction, exclusion, ineligibility or disqualification under the above-referenced statutes, River Vision shall immediately notify Roche in writing and Roche shall have the right, but not the obligation, to terminate this Agreement, effective, at Roche's option, immediately or at a specified future date, with the consequences set forth in Section 15.4(a).

14. CONFIDENTIALITY; PUBLICATION

14.1 Non-Use and Non-Disclosure. During the Term of this Agreement and for [***] years thereafter, a Receiving Party shall (i) treat Confidential Information provided by Disclosing Party as it would treat its own information of a similar nature, (ii) take all reasonable precautions not to disclose such Confidential Information to Third Parties, without the Disclosing Party's prior written consent, and (iii) not use such Confidential Information other than for fulfilling its obligations under this Agreement. For the purposes of this Section 14, Roche Know-How shall be considered Confidential Information of both parties.

14.2 Authorized disclosure. Each party may disclose Confidential Information of the other party as expressly permitted by this Agreement or if and to the extent such disclosure is reasonably necessary in the following instances:

(a) filing or prosecuting Patents as permitted by this Agreement;

(b) prosecuting or defending litigation as permitted by this Agreement;

(c) complying with applicable court orders or governmental regulations; and

(d) disclosure to (i) Affiliates, (ii) for River Vision, NRM and potential or actual subcontractors, Partners, assignees and Change of Control counterparties, (iii) Third Parties in connection with due diligence or similar investigations by such Third Parties, and (iv) disclosure to potential Third Party investors or financial institutions or advisors (including, without limitation, for River Vision, on behalf of NRM), provided, in each case, that any such Third Party agrees to be bound by obligations of confidentiality and non-use, such obligations of confidentiality to contain a confidentiality period of at least [***] years or [***] but not less than [***] years.

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Notwithstanding the foregoing, in the event a party is required to make a disclosure of the other party's Confidential Information pursuant to Sections 14.2(b) or 14.2(c), it will, except where impracticable, give reasonable advance notice to the other party of such disclosure and use efforts to secure confidential treatment of such information at least as diligently as such party would use to protect its own confidential information, but in no event less than reasonable efforts. In any event, the parties agree to take all reasonable action to avoid disclosure of Confidential Information hereunder. The parties will consult with each other on the provisions of this Agreement to be redacted in any filings made by the parties with the Securities and Exchange Commission (or any other relevant agency or body related to a regulated stock exchange) or as otherwise required by law.

14.3 Publications. River Vision shall have the right to publish any papers regarding results and other information regarding Compound and/or Product, including oral presentations and abstracts. River Vision shall provide Roche with a copy of any proposed papers at least [*** days prior to submission for publication so as to provide Roche with an opportunity to review drafts of the proposed papers. River Vision shall consider in good faith the requests and suggestions of Roche.

Roche shall have the right to publish (i) the results of past and ongoing studies and (ii) any particular work that must be disclosed by law. Roche shall provide River Vision with a copy of any proposed papers at least [***] days prior to submission for publication so as to provide River Vision with an opportunity to review drafts of the proposed papers. Roche shall consider in good faith the requests and suggestions of River Vision.

14.4 Use of name or trademarks. Neither party shall use the other party's or its Affiliates' names, with respect to Roche including but not limited to the compound code name "[*******]","[*******]" or "[*******]", or trademarks for publicity or advertising purposes, except with the prior written consent of the other party.

14.5 Publicity. It is understood that the parties intend to issue a joint press release announcing the execution of this Agreement at a mutually agreed upon time (the "***Initial Press Release***"). Thereafter both parties may desire or be required to issue subsequent press releases relating to the Agreement or activities hereunder. The parties agree to consult with each other reasonably and in good faith with respect to the text and timing of such subsequent press releases prior to the issuance thereof, provided that a party may not unreasonably withhold or delay consent to such subsequent releases, and that either party may issue such subsequent press releases as it determines, based on advice of counsel, are reasonably necessary to comply with laws or regulations or for appropriate market disclosure. In addition, following the Initial Press Release announcing this Agreement, either party shall be free to disclose, without the other party's prior written consent, the existence of this Agreement, the fact that River Vision has taken a license from Roche to the Compound and Product for development and commercialization in the Field, and those terms of the Agreement which have already been publicly disclosed in accordance herewith.

15. TERM

15.1 Term. The term of this Agreement shall commence on the Effective Date and, unless earlier terminated pursuant to Section 15.2, continue until the expiration of the Royalty Term (the "***Term***").

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15.2 Termination. Subject to Section 15.4:

(a) Breach. A party ("***Non-Breaching Party***") shall have the right to terminate this Agreement in its entirety in the event the other party ("***Breaching Party***") is in breach of any of its obligations under this Agreement. The non-Breaching Party shall provide written notice to the Breaching Party, which notice shall identify the breach. The Breaching Party shall have a period of ninety (90) days after such written notice is provided to cure such breach ("***Peremptory Notice Period***"). If such breach is not cured within the Peremptory Notice Period, this Agreement shall effectively terminate, unless there exists a bona fide dispute as to whether such breach occurred or such breach has been cured, whereupon such Peremptory Notice Period shall be tolled and shall not expire until such dispute is settled pursuant to Section 17, whereupon thereafter the Breaching Party may attempt to cure such breach if in the wrong. Non-payment by River Vision is considered a breach under this Agreement.

(b) Insolvency. A party shall have the right to terminate this Agreement, if the other party incurs an Insolvency Event; provided, however, in the case of any involuntary bankruptcy proceeding, such right to terminate shall only become effective if the party that incurs the Insolvency Event consents to the involuntary bankruptcy or such proceeding is not dismissed within ninety (90) days after the filing thereof.

(c) Challenging the Roche Patent Rights. If River Vision is challenging the validity of the Roche Patent Rights, then Roche shall have the right to terminate this Agreement in its entirety with immediate effect. Section 15.4(a) shall apply mutatis mutandis.

15.3 Termination by River Vision without a Cause. If River Vision wishes to terminate the Agreement, River Vision shall notify Roche in writing and Roche and River Vision shall discuss in good faith methods to avoid such termination. If however, the Parties cannot agree on a method to avoid such termination within thirty (30) days of such notice, and River Vision continues to wish to terminate this Agreement, then the following shall apply: River Vision shall have the right to terminate this Agreement in its entirety within six (6) months of such notice before First Commercial Sale of the Product or within nine (9) months of such notice after the First Commercial Sale of the Product. The effective date of termination under this Section 15.3 shall be the date six (6) months (or nine (9) months as the case may be) after River Vision provides such notice to Roche.

15.4 Consequences of Breach and Termination

(a) Breach by River Vision

(i) Both parties shall discuss in good faith and shall attempt to agree on the extent of damages caused by River Vision's breach of its obligations under this Agreement, and appropriate compensation for damages as may be applicable. Roche shall retain all its remedies as against River Vision in addition to those provided in this Agreement (including, without limitation, when clause (ii) below applies). Notwithstanding anything in this Section 15 to the contrary, if River Vision disputes the breach as specified in Section 15.2(a) and/or any remedy therefor, then in lieu of any of the remedies specified below in clause (ii) of this Section 15.4(a), the parties agree to have the ICC under Section 17 determine (1) whether any breach has occurred (and if any such breach is found to have occurred, subject to the subsequent cure period provided in Section 15.2(a)) and (2) an appropriate remedy in proportion to any such uncured breach. For clarity, Roche shall not be required to seek, before the ICC or otherwise, to terminate this Agreement upon any breach by River Vision.

(ii) If River Vision elects not to dispute the alleged breach and/or the remedy therefor as provided in clause (i) above, then the following shall apply:

(a) Roche shall notify River Vision its decision on whether or not it shall terminate this Agreement within ninety (90) days after the expiration of the Peremptory Notice Period. Such notice shall contain the information to which extent Roche wishes to continue the development and commercialization of the Compound and/or Product.

(b) Upon any termination by Roche for breach by River Vision, all rights and licenses granted by Roche to River Vision under this Agreement shall also terminate on the effective date of termination. River Vision shall, upon Roche's written request, to the extent River Vision has the right to do so, assign and transfer to Roche, [***] all regulatory filings and approvals, Product specific- trademarks, and all data, including clinical data, samples, materials and information, in River Vision's possession and Control related to Product necessary for the development and commercialization of the Product. Upon request of Roche, River Vision shall assign clinical trial agreements to the extent permitted.

(c) Roche shall, upon such transfer, have the right to disclose such filings, approvals and data to (i) governmental agencies to the extent required or desirable to secure government approval for the development, manufacturing or sale of Product, (ii) Third Parties acting on behalf of Roche, its Affiliates or licensees, to the extent reasonably necessary solely for the development, manufacture, or sale of Product, and (iii) Third Parties to the extent reasonably necessary to market Product.

(d) Roche shall have [***] solely for Roche, its Affiliates or licensees to develop, manufacture and have manufactured, use offer to sell, sell, promote, export and import the applicable Products in the Territory. Upon request of Roche, any license agreements between River Vision and a Third Party relating to Product shall be either assigned to Roche, or if this is not possible, sub-licensed to Roche to the extent permitted under the then prevailing conditions.

(b) Breach by Roche

(i) Both parties shall discuss in good faith and shall attempt to agree on the extent of damages caused by Roche's breach of its obligations under this Agreement, and appropriate compensation for damages as may be applicable. River Vision shall retain all its remedies as against Roche in addition to those provided in this Agreement (including, without limitation, when clause (ii) below applies). Notwithstanding anything in this Section 15 to the contrary, if Roche disputes the breach as specified in Section 15.2(a) and/or any remedy therefor, then in lieu of any of the remedies specified below in clause (ii) of this Section 15.4(b), the parties agree to have the ICC under Section 17 determine (1) whether any breach has occurred (and if any such breach is found to have occurred, subject to the subsequent cure period provided in Section 15.2(a)) and (2) an appropriate remedy in proportion to any such uncured breach. For clarity, River Vision shall not be required to seek, before the ICC or otherwise, to terminate this Agreement upon any breach by Roche.

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(ii) If Roche elects not to dispute the alleged breach or the remedy therefor as provided in clause (i) above, then the following shall apply:

(a) Upon any breach by Roche for which River Vision has the right to terminate this Agreement under Section 15.2, River Vision shall have the right to terminate this Agreement in accordance with Section 15.2, with the consequences set forth in Section 15.4(c). If River Vision does not practice its aforementioned right to terminate, then River Vision may retain the rights and licenses granted by Roche under this Agreement after the expiration of the Peremptory Notice Period and this Agreement shall not terminate but rather shall continue in full force and effect. River Vision shall notify Roche its decision on whether or not it shall terminate this Agreement within ninety (90) days after the expiration of the Peremptory Notice Period.

(c) Termination by River Vision without Cause

(i) Roche shall inform River Vision within thirty (30) days after the notice of termination under this Section 15.4(c) whether or not and to which extent Roche wishes to continue the development and commercialization of the Compound and/or Product.

(ii) Upon any termination by River Vision under this Section 15.4(c), all rights and licenses granted by Roche to River Vision under this Agreement shall terminate in their entirety.

(iii) River Vision shall, upon Roche's written request, to the extent it has the right to do so, assign to Roche, [***] all Product regulatory filings and approvals and Product-specific trademarks (including but not limited to data, including clinical data, samples, materials and information) in River Vision's possession and Control. If requested by Roche, River Vision shall assign clinical trial agreements to the extent permitted.

Roche shall have [***] solely for Roche, its Affiliates or licensees to develop, have developed, commercialize, have commercialized, make, have made, use, have used, sell, have sold, offer for sale, have offered for sale, import and have imported the applicable Products in the Territory.

Roche shall, upon such transfer, have the right to disclose such filings, approvals and data to (i) governmental agencies to the extent required or desirable to secure government approval for the development, manufacture or sale of Product; (ii) Third Parties acting on behalf of Roche, its Affiliates or licensees, to the extent reasonably necessary solely for the development, manufacture, or sale of Product, or (iii) Third Parties to the extent reasonably necessary to market Product.

Upon request of Roche, any agreements between River Vision and a Third Party relating to Product shall be either assigned to Roche, or if this is not possible, sub-licensed to Roche to the extent permitted under the then prevailing conditions.

15.5 Other Obligations

(a) Obligations Related to Ongoing Activities

(i) From the date of notice of termination until the effective date of termination, this Agreement shall remain in full force and effect

(ii) If Roche has provided notice to River Vision pursuant to Section 15.4(c)(i) that it does not wish to continue the development and commercialization of the Compound and/or Product, then River Vision (A) has the right to cancel all ongoing obligations and (B) shall complete all non-cancellable obligations at its own expense.

(iii) If Roche has provided notice to River Vision pursuant to Section 15.4(c) that Roche wishes to continue the development and/or commercialization of the Compound and/or Product, then, at Roche's request, River Vision shall [***] continue non-clinical activities ongoing as of the date of notice of termination (for clarity, the treatment of clinical trials is addressed below).

(iv) If Roche has provided notice to River Vision pursuant to Section 15.4(c) that Roche wishes to continue the development and/or commercialization of the Product, then, upon the request of Roche, River Vision shall complete [***], any clinical studies related to the Product that are being conducted under its IND (or equivalent) for the Product and are ongoing as of the notice of termination; provided, however, that Roche agrees [***] in completing such clinical studies and provided further that each of River Vision and Roche in their respective reasonable judgment has concluded that completing any such clinical studies does not present a unreasonable risk to patient safety.

(v) In any case, after the effective date of termination, River Vision shall not have any obligation to perform and/or complete any new activities or to make any payments for performing or completing any new activities under this Agreement, except as expressly stated in Section 15.5(a)(iii).

(b) Obligations Related to Manufacturing. If (i) Roche has provided notice to River Vision that Roche wishes to continue the development and/or commercialization of the Product, and (ii) Product is then being manufactured, then, upon the request of Roche, River Vision shall use Commercially Reasonable Efforts to manufacture and supply (or have manufactured or supplied, as the case may be) Product to Roche for a period which shall not exceed [***] months from the effective date of the termination of this Agreement at a price to be agreed by the parties in good faith. Roche shall use Commercially Reasonable Efforts to take over the manufacturing as soon as possible after the effective date of termination.

(c) Royalty and Payment Obligations

Expiration or termination of this Agreement (or any provision hereof) for any reason shall be without prejudice to any right that shall have accrued to the benefit of a party prior to such expiration or termination, including without limitation damages arising from any breach under this Agreement.

Termination of this Agreement by a party, for any reason, shall not release River Vision from any obligation to pay royalties or make any payments to Roche which are due and payable prior to the effective date of termination. Termination of this Agreement by a party, for any reason, will release River Vision from any obligation to pay royalties or make any payments to Roche which would otherwise become due or payable on or after the effective date of termination.

(d) Survival. Expiration or termination of this Agreement shall not relieve a party from any obligation that is expressly indicated to survive such expiration or termination. In addition to the termination consequences set forth in Section 15.4, the following provisions shall survive termination or expiration of this Agreement: 2.8 (Freedom-to-operate); 11. Intellectual Property; 14. Confidentiality/Publication; 16. Indemnification, 17. Dispute Resolution, Governing Law and Jurisdiction, and the following provisions of 18. General Provisions: 18.2, 18.3, 18.6, 18.7, 18.8, 18.10, 18.11 and 18.12.

16. INDEMNIFICATION

16.1 Roche indemnification. Roche hereby agrees to save, defend, indemnify and hold harmless River Vision and its officers, directors, employees, consultants and agents ("***River Vision Indemnitees***") from and against any and all losses, damages, liabilities, expenses and costs, including reasonable legal expense and attorneys' fees ("***Indemnified Losses***"), to which any such River Vision Indemnitee may become subject as a result of any claim, demand, action or other proceeding by any Third Party to the extent such Indemnified Losses arise out of the breach by Roche of any obligation, representation, warranty, covenant or agreement made by it under this Agreement, except to the extent such Indemnified Losses result from the negligence or willful misconduct of any River Vision Indemnitee (including without limitation any item subject to indemnification by River Vision under Section 16.2).

16.2 River Vision indemnification. River Vision hereby agrees to save, defend, indemnify and hold harmless Roche and its officers, directors, employees, consultants and agents ("***Roche Indemnitees***") from and against any and all Indemnified Losses, to which any such Roche Indemnitee may become subject as a result of any claim, demand, action or other proceeding by any Third Party to the extent such Indemnified Losses arise out of (i) the breach by River Vision of any representation, warranty, covenant or agreement made by it under this Agreement, or (ii) the development, manufacture, use, handling, storage, sale or other disposition of the Compound and/or any Product by River Vision or any of its Affiliates or Partners (including but not limited to (1) Product liability claims and (2) infringement of Third Party patents, other than those for this clause (2) Patents sub-licensed to River Vision by Roche under the [***] Agreement, the [***] Agreement or the [***] Agreement or any in-licensed Roche Patents provided that River Vision has complied with the applicable terms of this Agreement), except to the extent such Indemnified Losses result from the negligence or willful misconduct of any Roche Indemnitee (including without limitation any item subject to indemnification by Roche under Section 16.1).

16.3 Control of defense. In the event an River Vision Indemnitee or Roche Indemnitee (as the case may be) seeks indemnification under Section 16.1 or 16.2, it shall inform the other party (the "***Indemnifying Party***") of a claim as soon as reasonably practicable after it receives notice of the claim, shall permit the Indemnifying Party to assume direction and control of the defense of the claim (including the right to settle the claim solely for monetary consideration), and shall cooperate as requested (at the expense of the Indemnifying Party) in the defense of the claim, provided that the Indemnifying Party shall not settle any such claim without the prior written consent of any affected Roche Indemnitee or River Vision Indemnitee (as the case may be), if such settlement contains any admission of fault of such River Vision Indemnitee or Roche Indemnitee (as the case may be).

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17. DISPUTE RESOLUTION, GOVERNING LAW AND JURISDICTION

17.1 Dispute resolution. Any dispute arising under or relating to the parties rights and obligations under this Agreement will be referred to the Chief Executive Officer of River Vision or his designee and the Head of Roche Partnering of Roche with authority to resolve such dispute, for resolution. In the event the two individuals referred to in the preceding sentence are unable to resolve such dispute within [***] days of such dispute being referred to the officers, then, upon the written request of either party to the other party, the dispute shall be addressed as provided in Section 17.2.

17.2 Governing law and jurisdiction.

This Agreement shall be governed by and construed in accordance with the laws of Switzerland, without reference to its conflict of laws principles and shall not be governed by the United Nations Convention of International Contracts on the Sale of Goods (the Vienna Convention).

If a dispute cannot be resolved in application of Section 17.1, then such dispute shall be finally settled under the rules of arbitration of the International Chamber of Commerce ("***ICC***") by three arbitrators.

Each party shall nominate one arbitrator. Should the claimant fail to appoint an arbitrator in the request for arbitration within [***] days of being requested to do so, or if the respondent should fail to appoint an arbitrator in its answer to the request for arbitration within [***] days of being requested to do so, the other party shall request the ICC court to make such appointment.

The arbitrators nominated by the parties shall, within [***] days from the appointment of the arbitrator nominated in the answer to the request for arbitration, and after consultation with the parties, agree and appoint a third arbitrator, who will act as a chairman of the arbitral tribunal. Should such procedure not result in an appointment within the [***] day time limit, either party shall be free to request the ICC court to appoint the third arbitrator.

Where there is more than one claimant and/or more than one respondent, the multiple claimants or respondents shall jointly appoint one arbitrator. In other respects the provisions of this Section 17.1 shall apply.

If any party-appointed arbitrator or the third arbitrator resigns or ceases to be able to act, a replacement shall be appointed in accordance with the arrangements provided for in this Section 17.1.

Basel, Switzerland, shall be the seat of the arbitration.

The language of the arbitration shall be English. Documents submitted in the arbitration (the originals of which are not in English) shall be submitted together with an English translation.

This arbitration agreement does not preclude either party seeking conservatory or interim measures from any court of competent jurisdiction including, without limitation, the courts having jurisdiction by reason of either party's domicile. Conservatory or interim measures sought by either party in any one or more jurisdictions shall not preclude the arbitral tribunal granting conservatory or interim measures. Conservatory or interim measures sought by either party before the arbitral tribunal shall not preclude any court of competent jurisdiction granting conservatory or interim measures.

In the event that any issue shall arise which is not clearly provided for in this arbitration agreement the matter shall be resolved in accordance with the ICC arbitration rules.

*****Certain Confidential Information Omitted**

18. GENERAL PROVISIONS

18.1 No implied licenses. No right or license under any Patents or Know-How is granted or shall be granted by implication. All such rights or licenses are or shall be granted only as expressly provided in the terms of this Agreement. Each party hereby expressly reserves the right to practice, and to grant licenses under, the Patents and Know-How Controlled by such party for any and all purposes other than as expressly provided herein or for the specific purposes for which the other party has been granted an exclusive license under this Agreement.

18.2 Relationship between the parties. The parties' relationship, as established by this Agreement, is solely that of independent contractors. This Agreement does not create any partnership, joint venture or similar business relationship between the parties. Neither party is a legal representative of the other party and neither party can assume or create any obligation, representation, warranty or guarantee, express or implied, on behalf of the other party for any purpose whatsoever.

18.3 Non-waiver. The failure of a party to insist upon strict performance of any provision of this Agreement or to exercise any right arising out of this Agreement shall neither impair that provision or right nor constitute a waiver of that provision or right, in whole or in part, in that instance or in any other instance. Any waiver by a party of a particular provision or right shall be in writing, shall be as to a particular matter and, if applicable, for a particular period of time and shall be signed by such party.

18.4 Assignment. Neither party shall have the right to assign the present Agreement or any part thereof to any Third Party other than Affiliates without the prior written approval of the other Party, such approval not to be unreasonably withheld or delayed.

18.5 Change of Control. River Vision shall not have the right to undergo a Change of Control without the prior written approval of Roche, such approval not to be unreasonably withheld or delayed. For purposes of this Agreement, "***Change of Control***" shall mean, with respect to River Vision, (i) a merger, reorganization or consolidation involving River Vision in which the members of River Vision, immediately prior to the merger, reorganization or consolidation, would not, immediately after the merger, reorganization or consolidation, beneficially own (directly or indirectly) membership interests representing in the aggregate more than fifty percent (50%) of the combined voting power of the entity issuing cash or securities in the merger, reorganization or consolidation (or of its ultimate parent entity, if any), or (ii) a person or entity becomes the beneficial owner of more than fifty percent (50%) of the voting securities of River Vision, other than directly from River Vision; however, "Change of Control" will not include any transaction effected for equity or debt financing purposes pursuant to which River Vision receives cash therefor, provided River Vision does not grant any sublicense of the rights granted to River Vision by Roche in Section 2.1(a) as part of such transaction. For purposes of this Section 18.4 and the last sentence of Section 2.5, River Vision shall have the right to provide the identity of the counterparty to the proposed Partner Agreement or Change of Control, and Roche shall indicate within [***] business days if Roche approves such proposed transaction (and if Roche fails to reply in such [***]-day period, then such approval will be deemed given).

*****Certain Confidential Information Omitted**

18.6 No Third Party beneficiaries. This Agreement is neither expressly nor impliedly made for the benefit of any party other than those executing it.

18.7 Severability. If, for any reason, any part of this Agreement is adjudicated invalid, unenforceable or illegal by a court of competent jurisdiction, then such adjudication shall not, to the extent feasible, affect or impair, in whole or in part, the validity, enforceability or legality of any remaining portions of this Agreement. All remaining portions shall remain in full force and effect as if the original Agreement had been executed without the invalidated, unenforceable or illegal part.

18.8 Notices. Any notice to be given under this Agreement must be in writing and delivered either in person, by any method of mail (postage prepaid) requiring return receipt, or by overnight courier or facsimile confirmed thereafter by any of the foregoing, to the party to be notified at its address(es) given below, or at any address such party has previously designated by prior written notice to the other. Notice shall be deemed sufficiently given for all purposes upon the earliest of: (a) the date of actual receipt; (b) if mailed, [***] days after the date of postmark; or (c) if delivered by overnight courier, the next business day the overnight courier regularly makes deliveries.

If to River Vision, notices must be addressed to:

River Vision, LLC
Narrow River Management
One Rockefeller Plaza. Ste. 1204
New York, NY 10020 U.S.A.
Attention: David Madden, Principal
Facsimile: [***]

If to Roche, notices must be addressed to:

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110, USA
Attention: Corporate Secretary
Facsimile: [***]

And:

F.Hoffmann-La Roche Ltd
Grenzacherstrasse 124
CH-4070 Basel
Switzerland
Attention: Legal Department
Facsimile: [***]

In the event of a change of notice address, recipient or both, a party shall provide the other party written notice pursuant to this Section 18.8 setting forth the new address and/or recipient, as appropriate.

*****Certain Confidential Information Omitted**

18.9 Force majeure. Except for the obligation to make payment when due, each party shall be excused from liability for the failure or delay in performance of any obligation under this Agreement by reason of any event beyond such party's reasonable control including but not limited to Acts of God, fire, flood, explosion, earthquake, or other natural forces, war, civil unrest, acts of terrorism, accident, destruction or other casualty, any lack or failure of transportation facilities, any lack or failure of supply of raw materials, any strike or labor disturbance, or any other event similar to those enumerated above. Such excuse from liability shall be effective only to the extent and duration of the event(s) causing the failure or delay in performance and provided that the party has not caused such event(s) to occur. Notice of a party's failure or delay in performance due to force majeure must be given to the other party within [***] days after its occurrence. All delivery dates under this Agreement that have been affected by force majeure shall be tolled for the duration of such force majeure. In no event shall any party be required to prevent or settle any labor disturbance or dispute.

18.10 Interpretation. All references to days in this Agreement shall mean calendar days, unless otherwise specified. This Agreement has been prepared in the English language and the English language shall control its interpretation. In addition, all notices required or permitted to be given hereunder, and all written, electronic, oral or other communications between the parties regarding this Agreement shall be in the English language. All headings in this Agreement are for convenience only and shall not affect the meaning of any provision hereof. "Herein," "hereby," "hereunder," "hereof" and other equivalent words refer to this Agreement as an entirety and not solely to the particular portion of this Agreement in which any such word is used. All definitions set forth herein shall be deemed applicable whether the words defined are used herein in the singular or the plural. Each party has had the opportunity to consult with counsel in connection with the review, drafting and negotiation of this Agreement. Accordingly, the rule of construction that any ambiguity in this Agreement shall be construed against the drafting party shall not apply.

18.11 Binding Effect. This Agreement shall inure to the benefit of and be binding upon the parties, their Affiliates, and their respective successors and assigns.

18.12 Counterparts. This Agreement may be executed in two or more counterparts, each of which shall be deemed an original document, and all of which, together with this writing, shall be deemed one instrument.

[Remainder of this page intentionally left blank.]

*****Certain Confidential Information Omitted**

IN WITNESS WHEREOF, the parties have executed this LICENSE AGREEMENT as of the date first above written.

F. HOFFMANN-LA ROCHE LTD

By: /s/ Andrew Jefferson
Name: Andrew Jefferson
Title: Global Licensing Director

Date: 23/6/11

F. HOFFMANN-LA ROCHE LTD

By: /s/ Frank J. D'Angelo
Name: Frank J. D'Angelo
Title: V.P.

Date:

By: /s/ Dr. Melanie Frey Wick
Name: Dr. Melanie Frey Wick
Title: Legal Counsel

Date: June 23, 2011

RIVER VISION LLC

By: **NARROW RIVER MANAGEMENT, LP**

MANAGING MEMBER

By: /s/ D. Madden
Name: D. Madden
Title: Principal

Date:

Appendix 1

Compound

teprotumumab is a human IgG1 antibody binding to IGFIR [***]

[Remainder of this page intentionally left blank.]

Appendix 2

Roche Patents

[***]

*****Certain Confidential Information Omitted**

Appendix 3

Roche Know-How:

[***]

*****Certain Confidential Information Omitted**

Appendix 4

River Vision Studies:

[***]

Supply of Drug Product and Supported Shelf Life under Sections 6.1(b) and 6.1(c):

River Vision will send a written order to Roche to ship Drug Product with no less than [***] months lead time from the delivery date.

The order shall contain: (a) the order number, (b) quantity of Drug Product vials, (c) invoicing address and (d) delivery date. Roche shall deliver Drug Product according to Table I EXW (Incoterms 2000) to the delivery address named by River Vision. The delivery address for the material shall be communicated to Roche no fewer than [***] days prior to the agreed delivery date.

With each shipment of Drug Product, Roche will send the packing list, the Certificate of Analysis for the batches included in the shipment, the current Material Safety Data Sheet and a pro forma invoice. In addition, Roche will provide River Vision with the documents listed in Table II. Roche guarantees that it has manufactured Product in conformity with the Product specifications, all applicable laws and regulations, and in accordance with cGMP.

[***]

Appendix 5

Redacted copy of [***] Agreement

See attached.

[Remainder of this page intentionally left blank.]

Appendix 6

Redacted copy of [***] Agreement

See attached.

[Remainder of this page intentionally left blank.]

Appendix 7

Redacted copy of [***] Agreement

See attached.

[Remainder of this page intentionally left blank.]

Schedule 11.6(b)

Patents and First Parties

[***]

[Remainder of this page intentionally left blank.]

Amendment No 1 to License Agreement

THIS AMENDMENT NO 1. TO LICENSE AGREEMENT *("**Amendment**")* is entered into as of the 19th of November, 2012 ("**Effective Date**") by and among:

F. HOFFMANN-LA ROCHE LTD, a corporation organized and existing under the laws of Switzerland, with its principal office at Grenzacherstrasse 124, CH-4070 Basel, Switzerland *("**Roche Basel**")* and Hoffmann-La Roche Inc., a corporation organized and existing under the laws of New Jersey, with its principle office at 340 Kingsland Street, Nutley, New Jersey 07110, U.S.A. *("**Roche Nutley**";* Roche Basel and Roche Nutley together referred to as *"**Roche**")*

and

RIVER VISION LLC, a limited liability company organized and existing under the laws of Delaware, with its principal office at One Rockefeller Plaza, New York NY, 10020, U.S.A. *("**River Vision**").*

WHEREAS, River Vision and Roche wish to amend the agreement to as follows:

I. Section 2.4 shall be deleted and replaced by the following

"**2.4. Sub-Contractors**. River Vision has the right to sub-contract the work performed under this Agreement. Any sub-contract agreement shall include the right to disclose (i) a copy of the Agreement and confidential information to Roche and (ii) the right to assign the agreement to Roche, including the right to transfer of the ownership of data, information and results arising therefrom to Roche to the same extent as to River Vision.

II. Section 2.5 shall be deleted and replace by the following:

"**2.5 Right to enter into a Partner Agreement with Third Parties**. Subject to Roche's rights under Section 3, River Vision shall have the right to enter into a Partner Agreement, including but not limited to granting sublicenses to Partners under its rights granted under Section 2.1 and Section 2.2. Any rights granted to a Partner under this Agreement shall be solely to the extent necessary to develop, commercialize, make, use, offer for sale, sell or import (and have others do the same) Compound and/or Product in the Field in the Territory. River Vision shall ensure that all of the applicable terms and conditions of this Agreement, including the obligations under the [***] Agreement, the [***] Agreement and the [***] Agreement, shall apply to the Partner under the Partner Agreement to the same extent as they apply to River Vision for all purposes. River Vision assumes full responsibility for the performance of all obligations and observance of all terms so imposed to the Partner under such Partner Agreement and shall itself account to Roche for all payments due under this Agreement. The Partner of River Vision shall have no right to further sub-license rights to develop and commercialise the Compound or Product to a Third Party, with the understanding that co-promotion or distribution or other marketing arrangements are permitted.

Any sublicenses granted by River Vision to a Partner under the [***] Agreement, the [***] Agreement and the [***] Agreement shall be subject to prior approval of Roche. For clarity, River Vision is free to sub-contract any rights under such agreements.

River Vision shall disclose a copy of the draft Partner Agreement to Roche, subject to redaction of financial terms.

*****Certain Confidential Information Omitted**

III. Section 18.4 of the Agreement shall be deleted and replaced by the following:

"**Section 18.4. Assignment**. Neither party shall have the right to assign the present Agreement or any part thereof to any Third Party other than (I) Affiliates or (11) in connection with a Change of Control as contemplated by Section 18.5, without the prior written approval of the other Party, such approval not to be unreasonably withheld or delayed.'

IV. Section 18. 5 of the Agreement shall be deleted and replaced by the following:

"**Section 18.5. Change of Control**. Subject to Roche's right of first offer under Section 3 hereof, River Vision shall have the right to undergo a Change of Control. For purposes of this Agreement, "Change of Control shall mean, with respect to River Vision, (i) a merger, reorganization or consolidation involving River Vision in which the members of River Vision, immediately prior to the merger, reorganization or consolidation, would not, Immediately after the merger, reorganization or consolidation, beneficially own (directly or Indirectly) membership interests representing in the aggregate more than fifty percent (50%) of *the* combined voting power of the entity Issuing cash or securities in the merger, reorganization or consolidation (or of Its ultimate parent entity, If any), or (ii) a person or entity becomes the beneficial owner of more than fifty percent (50%) of the voting securities of River Vision, other than directly from River Vision; however, "Change of Control" will not Include any transaction effected for equity or debt financing purposes pursuant to which River Vision receives cash therefor, provided River Vision does not grant any sublicense of the rights granted to River Vision by Roche as part of such transaction.'

V. Capitalized terms shall have the same meaning as defined in the Agreement.

VI. Except as expressly stated herein, no other changes are made to tie Agreement and all other terms and conditions of the Agreement remain in full force and effect

VII. This Amendment enters into effect on the Effective Date.

[REMAINDER OF THIS PAGE INTENTIONALLY LEFT BLANK.]

IN WITNESS WHEREOF, the parties have executed this **AMENDMENT NO. 1 TO THE LICENSE AGREEMENT** as of the date first above written.

F. HOFFMANN-LA ROCHE LTD

By: /s/ Christophe Carissimo
Name: Christophe Carissimo
Title: Global Licensing Director

Date: Nov 19, 2012

HOFFMANN-LA ROCHE INC.

By: /s/ Joseph S. McCracken
Name: Joseph S. McCracken
Title: Vice President

Date: November 19, 2012

By: /s/ Dr. Melanie Frey Wiek
Name: Dr. Melanie Frey Wiek
Title: Legal Counsel

Date: November 19, 2012

RIVER VISION LLC

BY: **NARROW RIVER MANAGEMENT, LP**

MANAGING MEMBER

By: /s/ D. Madden
Name: D. Madden
Title: Principal

Date: 11/19/2012

THIS AMENDMENT NO. 2 TO LICENSE AGREEMENT ("***Amendment***") is entered into as of the 1st of February 2013 ("Effective Date") by and among:

F.HOFFMANN-LA ROCHE LTD, a corporation organized and existing under the laws of Switzerland, with its principal office at Grenzacherstrasse 124, CH-4070 Basel, Switzerland ("***Roche Basel***") and **Hoffmann-La Roche Inc.**, a corporation organized and existing under the laws of New Jersey, with its principle office at 340 Kingsland Street, Nutley, New Jersey 07110, U.S.A. ("***Roche Nutley***"; Roche Basel and Roche Nutley together referred to as "***Roche***")

and

RIVER VISION DEVELOPMENT CORP., a corporation organized and existing under the laws of Delaware, with its principal office at One Rockefeller Plaza, New York NY, 10020, U.S.A.

WHEREAS, River Vision Development Corp. is successor in interest to River Vision LLC and River Vision Development Corp. and Roche wish to amend the agreement to as follows:

I. The table "II. Material" in Process, Manufacturing Know how on page 61 of Appendix 3 shall be amended by the addition of the following after the existing table under the titles

[***]

*****Certain Confidential Information Omitted**

II. Capitalized terms shall have the same meaning as defined in the Agreement.

III. Except as expressly stated herein, no other changes are made to the Agreement and all other terms and conditions of the Agreement remain in full force and effect.

IV. This Amendment enters into effect on the Effective Date.

[REMAINDER OF THIS PAGE INTENTIONALLY LEFT BLANK.]

IN WITNESS WHEREOF, the parties have executed this **AMENDMENT NO. 2 TO THE AGREEMENT** as of the date first above written.

F. HOFFMANN-LA ROCHE LTD

By: /s/ Christoph Sarry
Name: Dr. Christoph Sarry
Title: Global Alliance Director

Date: 14/02/2013

By: /s/ Melanie Frey Wick
Name: Dr. Melanie Frey Wick
Title: Legal Counsel

Date: February 14, 2013

HOFFMANN-LA ROCHE INC.

By: /s/ Joseph S. McCracken
Name: Joseph S. McCracken
Title: Vice President

Date: 21-Feb-2013

Apprv'd As To Form LAW DEPT.

By /s/ MDM

RIVER VISION DEVELOPMENT CORP.

By: /s/ D Madden
Name: D Madden
Title: Chief Executive Officer

Date: 5 February 2013

THIS AMENDMENT NO. 3 TO LICENSE AGREEMENT ("***Amendment***") is entered into as of the 1st of February 2013 ("Effective Date") by and among:

F. HOFFMANN-LA ROCHE LTD, a corporation organized and existing under the laws of Switzerland, with its principal office at Grenzacherstrasse 124, CH-4070 Basel, Switzerland ("***Roche Basel***") and **Hoffmann-La Roche Inc.**, a corporation organized and existing under the laws of New Jersey, with its principle office at 340 Kingsland Street, Nutley, New Jersey 07110, U.S.A. ("***Roche Nutley***"; Roche Basel and Roche Nutley together referred to as "***Roche***")

and

RIVER VISION DEVELOPMENT CORP., a limited liability company organized and existing under the laws of Delaware, with its principal office at One Rockefeller Plaza, Suite 1204, New York, NY, 10020, U.S.A. ("***RV***").

WHEREAS, River Vision and Roche wish to amend the agreement as follows:

I. The table "II. Material" in Process, Manufacturing Know how on page 61 of Appendix 3 shall be amended by the addition of the following table after the existing table under the titles

[***]

*****Certain Confidential Information Omitted**

[***]

IN WITNESS WHEREOF, the parties have executed this **AMENDMENT NO**. 3 TO THE AGREEMENT as of the date first above written.

F. HOFFMANN-LA ROCHE LTD

By: /s/ Christophe Carissimo
Name: Christophe Carissimo
Title: Global Head Transaction Excellence

Date: May 31, 2013

By: /s/ Melanie Frey Wick
Name: Dr. Melanie Frey Wick
Title:

Date: May 31, 2013

HOFFMANN-LA ROCHE INC.

By: /s/ John P. Parise
Name: John P. Parise
Title: Authorized Signatory

Date: June 4, 2013

Apprv'd As To Form LAW DEPT.

By /s/ MM

RIVER VISION DEVELOPMENT CORP.

By: /s/ D Madden
Name: D Madden
Title: CEO

Date: 6/11/13

*****Certain Confidential Information Omitted**

THIS AMENDMENT NO. 4 TO LICENSE AGREEMENT ("***Amendment***") is entered into as of the 21st of October 2013 ("Effective Date") by and among:

F. HOFFMANN-LA ROCHE LTD, a corporation organized and existing under the laws of Switzerland, with its principal office at Grenzacherstrasse 124, CH-4070 Basel, Switzerland ("***Roche Basel***") and **Hoffmann-La Roche Inc.**, a corporation organized and existing under the laws of New Jersey, with its principle office at 340 Kingsland Street, Nutley, New Jersey 07110, U.S.A. ("***Roche Nutley***"; Roche Basel and Roche Nutley together referred to as "***Roche***")

and

RIVER VISION DEVELOPMENT CORP., a limited liability company organized and existing under the laws of Delaware, with its principal office at One Rockefeller Plaza, Suite 1204, New York NY, 10020, U.S.A. ("***River Vision***").

WHEREAS, River Vision and Roche wish to amend the agreement as follows:

I. The table "II. Material" in Process, Manufacturing Know how on page 61 of Appendix 3 shall be amended by the addition of the following after the existing table under the titles

[***]

II. Capitalized terms shall have the same meaning as defined in the Agreement.

III. Except as expressly stated herein, no other changes are made to the Agreement and all other terms and conditions of the Agreement remain in full force and effect.

IV. This Amendment enters into effect on the Effective Date.

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*****Certain Confidential Information Omitted**

IN WITNESS WHEREOF, the parties have executed this **AMENDMENT NO. 4 TO THE AGREEMENT** as of the date first above written.

F. HOFFMANN-LA ROCHE LTD

By: /s/ Vikas Kabra
Name: Vikas Kabra
Title: Head of Transaction Excellence

Date: _____

By: /s/ Melanie Frey Wick
Name: Dr. Melanie Frey Wick
Title: Legal Counsel

Date: July 16, 2014

HOFFMANN-LA ROCHE INC.

By: /s/ John P. Parise
Name: John P. Parise
Title: Authorized Signatory

Date: _____

RIVER VISION DEVELOPMENT CORP.

By: /s/ D Madden
Name: D Madden
Title: CEO

Date: Oct/18/13

Apprv'd As To Form LAW DEPT.

By /s/ GB

Amendment No 5 to License Agreement

THIS AMENDMENT No 5. to License Agreement ("**Amendment**") is entered into as of the 11th of November 2013 ("Effective Date") by and among:

F. HOFFMANN-LA ROCHE LTD, a corporation organized and existing under the laws of Switzerland, with its principal office at Grenzacherstrasse 124, CH-4070 Basel, Switzerland *("**Roche Basel**")* and Hoffmann-La Roche Inc., a corporation organized and existing under the laws of New Jersey, with its principle office at 340 Kingsland Street, Nutley, New Jersey 07110, U.S.A. *("**Roche Nutley**";* Roche Basel and Roche Nutley together referred to as *"**Roche**")*

and

RIVER VISION LLC, a limited liability company organized and existing under the laws of Delaware, with its principal office at One Rockefeller Plaza, New York NY, 10020, U.S.A. *("**River Vision**").*

WHEREAS, River Vision and Roche wish to amend the agreement to as follows:

I. The table "II. Material" in Process, Manufacturing Know how on page 61 of Appendix 3 was amended in Amendment No. 2 and Amendment No. 4 with lines as follows:

Amendment No. 2
[***]

Amendment No. 4
[***]

Remarks of the Amendments No. 2 and No. 4 for the test material as mentioned above will be completely replaced by the following remark:

*****Certain Confidential Information Omitted**

[***]

II. Capitalized terms shall have the same meaning as defined in the Agreement.

III. Except as expressly stated herein, no other changes are made to the Agreement and all other terms and conditions of the Agreement remain in full force and effect.

IV. This Amendment enters into effect on the Effective Date.

[REMAINDER OF THIS PAGE INTENTIONALLY LEFT BLANK.]

IN WITNESS WHEREOF, the parties have executed this **AMENDMENT NO. 1 TO THE LICENSE AGREEMENT** as of the date first above written.

F. HOFFMANN-LA ROCHE LTD

By: /s/ Christophe Carissimo
Name: Christophe Carissimo
Title: Global Head Transaction Excellence

Date: Nov 14, 2013

By: /s/ Dr. Melanie Frey Wiek
Name: Dr. Melanie Frey Wiek
Title: Legal Counsel

Date: November 14, 2013

HOFFMANN-LA ROCHE INC.

By: /s/ John Parise
Name: John Parise
Title: Authorized Signatory

Date: November 20, 2013

RIVER VISION LLC

By: /s/ D. Madden
Name: D. Madden
Title: CEO

Date: 12 November 2013

THIS AMENDMENT NO. 6 TO LICENSE AGREEMENT ("***Amendment***") is entered into as of the 18th December 2014 ("Effective Date") by and among:

F. HOFFMANN-LA ROCHE LTD, a corporation organized and existing under the laws of Switzerland, with its principal office at Grenzacherstrasse 124, CH-4070 Basel, Switzerland ("***Roche Basel***") and **Hoffmann-La Roche Inc.**, a corporation organized and existing under the laws of New Jersey, with its principle office and place of business at 150 Clove Road, 8th Floor, Little Falls, New Jersey 07424, U.S.A. ("***Roche Little Fall***"; Roche Basel and Roche Little Falls together referred to as "***Roche***")

and

RIVER VISION DEVELOPMENT CORP., a limited liability company organized and existing under the laws of Delaware, with its principal office at One Rockefeller Plaza, New York NY, 10020, U.S.A. ("***River Vision***").

WHEREAS, River Vision and Roche wish to amend the agreement as follows:

I. The table "II. Material" in Process, Manufacturing Know how on page 61 of Appendix 3 shall be amended by the addition of the following after the existing table

[***]

*****Certain Confidential Information Omitted**

II. Capitalized terms shall have the same meaning as defined in the Agreement.

III. Except as expressly stated herein, no other changes are made to the Agreement and all other terms and conditions of the Agreement remain in full force and effect.

IV. This Amendment enters into effect on the Effective Date.

[REMAINDER OF THIS PAGE INTENTIONALLY LEFT BLANK.]

IN WITNESS WHEREOF, the parties have executed this **AMENDMENT NO. 6 TO THE AGREEMENT** as of the date first above written.

F. HOFFMANN-LA ROCHE LTD

By: /s/ Timothy Steven
Name: Timothy Steven
Title: Global Alliance Director

Date: 8th Jan 2015

By: /s/ Melanie Frey Wick
Name: Dr. Melanie Frey Wick
Title: Legal Counsel

Date: 8th January 2015

HOFFMANN-LA ROCHE INC.

By: /s/ John P. Parise
Name: John P. Parise
Title: Authorized Signatory

Date: Jan 13, 2015

Apprv'd As To Form LAW DEPT.

By /s/

RIVER VISION DEVELOPMENT CORP.

By: /s/ D Madden
Name: D Madden
Title: CEO

Date: 12/17/14

Amendment No. 7 to the License Agreement

This Amendment No. 7 to the License Agreement ("Amendment") is entered into as of the 24th of June 2015 ("Effective Date") by and among:

F. Hoffmann-La Roche Ltd., a corporation organized and existing under the laws of Switzerland, with its principal office at Grenzacherstrasse 124, CH-4070 Basel, Switzerland ("Roche Basel") and Hoffmann-La Roche Inc., a corporation organized and existing under the laws of the State of New Jersey, with its principal office and place of business at 150 Clove Road, 8th Floor, Little Falls, NJ 07424, USA ("Roche Little Falls"; Roche Little Falls and Roche Basel together referred to as "Roche").

And

River Vision Development Corp, a corporation organized and existing under the laws of Delaware, with its principal office at One Rockefeller Plaza, Suite 1204, New York, NY 10020, USA ("River Vision").

Whereas, Roche and River Vision wish to amend the agreement as follows:

I. The Table (II. Material in Process, Manufacturing Know-How on page 61 of Appendix 3 shall be amended as follows:

[***]

II. Capitalized terms used herein shall have the same meaning as defined in the Agreement.

*****Certain Confidential Information Omitted**

III. Except as previously stated herein, no other changes are made to the Agreement and all other terms and conditions of the Agreement remain in effect.

IV. This Amendment enters into effect on the Effective Date.

In witness whereof, the parties have executed this Amendment No. 7 to the Agreement as of the date first above written.

F. Hoffmann-La Roche Ltd

By: /s/ Tim Steven
Name: Tim Steven
Title: Alliance Director

Date: 21st July 2015

By: /s/ Melanie Frey Wick
Name: Dr. Melanie Frey Wick
Title:

Date:

Hoffmann-La Roche Inc.

By: /s/ David P. McDede
Name: David P. McDede
Title: VP Treasurer

Date: 21 July 2015

River Vision Development Corp.

By: /s/ D Madden
Name: D Madden
Title: CEO

Date: 6/26/15

Apprv'd As To Form LAW DEPT.

By /s/ MM

Amendment No. 8 to the License Agreement

This Amendment No. 8 to the License Agreement ("Amendment") is entered into as of the 13th of November 2015 ("Effective Date") by and among:

F. Hoffmann-La Roche Ltd., a corporation organized and existing under the laws of Switzerland, with its principal office at Grenzacherstrasse 124, CH-4070 Basel, Switzerland ("Roche Basel") and Hoffmann-La Roche Inc., a corporation organized and existing under the laws of the State of New Jersey, with its principal office and place of business at 150 Clove Road, 8th Floor, Little Falls, NJ 07424, USA ("Roche Little Falls"; Roche Little Falls and Roche Basel together referred to as "Roche").

And

River Vision Development Corp, a corporation organized and existing under the laws of Delaware, with its principal office at One Rockefeller Plaza, Suite 1204, New York, NY 10020, USA ("River Vision").

Whereas, Roche and River Vision wish to amend the agreement as follows:

I. The Table (II. Material in Process, Manufacturing Know-How on page 61 of Appendix 3 shall be amended as follows:

[***]

II. Capitalized terms used herein shall have the same meaning as defined in the Agreement.

III. Except as previously stated herein, no other changes to the Agreement and all other terms and conditions of the Agreement remain in effect.

*****Certain Confidential Information Omitted**

IV. This Amendment enters into effect on the Effective Date.

In witness whereof, the parties have executed this Amendment No. 8 to the Agreement as of the date first above written.

F. Hoffmann-La Roche Ltd

By: /s/ Urs Schleuniger
Name: Dr. Urs Schleuniger
Title: Head Chugai and Basel Alliance & Asset Management

Date: 19 November 2015

By: /s/ Melanie Frey Wick
Name: Dr. Melanie Frey Wick
Title: Legal Counsel

Hoffmann-La Roche Inc.

By: /s/ John P. Parise
Name: John P. Parise
Title: Authorized Signatory

Date: Nov. 21, 2015

River Vision Development Corp.

By: /s/ D Madden
Name: D Madden
Title: CEO

Date: 24 November 2015

Amendment No. 9 to the License Agreement

This Amendment No. 9 to the License Agreement ("Amendment") is entered into as of the 21st of October, 2016 ("Effective Date") by and among

F. Hoffmann-La Roche Ltd, a corporation organized and existing under the laws of Switzerland, with its principal office at Grenzacherstrasse 124, CH-4070 Basel, Switzerland ("Roche Basel") and Hoffmann-La Roche Inc., a corporation organized and existing under the laws of the State of New Jersey, with its principal office and place of business at 150 Clove Road, Suite 8, Little Falls, NJ 07424, USA ("Roche Little Falls"; Roche Little Falls and Roche Basel together referred to as "Roche").

And

River Vision Development Corp, a corporation organized and existing under the laws of Delaware, with its principal office at One Rockefeller Plaza, Suite 1204, New York, NY 10020, USA ("River Vision").

WHEREAS, Roche and River Vision wish to amend the agreement as follows:

I. Section 11.6 shall be deleted and replaces by the following

"11.6 Infringement by Third Parties.

(a) Infringement. Each party shall promptly provide written notice to the other party during the Term of any known infringement or suspected infringement by a Third Party of any Roche Patents, River Vision Patents (if any) or Joint Patents (if any), or of any invalidity or unenforceability assertion or challenge to any such patents, or of any unauthorized use or misappropriation of Roche Know-How, and shall provide the other party with all evidence in its possession supporting such infringement, assertion or challenge or unauthorized use or misappropriation. For clarity, any challenge amounting to a reexamination, interference or opposition will be addressed by Sections 11.2 through 11.5.

(b) Defense and Enforcement. Within a period of [***] days ("Decision Period") after either party (i) provides or receives such written notice with respect to its Patents and (ii) such notice relates to the (a) Compound and/or Product in the Field or (b) an IGF-1R antibody of a third party in the Field ("Affected Patents"), the party that has the first right to enforce any such Affected Patents as set forth on Schedule 11.6(b) (the "First Party") that are allegedly infringed, in its sole discretion, shall decide whether or not to initiate a suit or take other appropriate action with respect to any allegedly infringing activities in the Field (including without limitation defending any assertion or challenge) and shall notify the other party in writing of its decision in writing ("Suit Notice").

*****Certain Confidential Information Omitted**

If the First Party for its Affected Patents are allegedly infringed decides to bring a suit or take action with respect to any allegedly infringing activities in the Field and provides a respective Suit Notice, then such party may immediately commence such suit or take such action. If such party (i) does not in writing advise the other party within the Decision Period that it will commence suit or take action, or (ii) fails to commence suit or take action within a reasonable time after providing Suit Notice, then the other party shall thereafter have the right to commence suit or take action with respect to any allegedly infringing activities in the Field and shall provide written notice to the party whose Affected Patents are allegedly infringed of any such suit commenced or action taken by the other party.

Upon written request, the party bringing suit or taking action ("Initiating Party") shall keep the other party informed of the status of any such suit or action and shall provide the other party with copies of all substantive documents and communications filed in such suit or action. The Initiating Party shall have the sole and exclusive right to control any such suit or action, including but not limited to selecting counsel for any such suit or action. If each of the parties elects to be an Initiating Party with respect to the same allegedly infringing activities within the Field, then the parties shall meet and agree on how to manage the resulting suits and actions (including with respect to the process set forth in Section 11.7). If River Vision is the Initiating Party with respect to the Compound Patent, upon Roche request, River Vision and Roche shall jointly agree in good faith on the strategy on how to bring suit or take action with respect to such Compound Patent, such discussions to be held in good faith, and failure to agree shall not jeopardize timing regarding any such suit or action.

The Initiating Party shall, except as provided below, pay all expenses of the suit or action, including, without limitation, the Initiating Party's attorneys' fees, damages and court costs. If the Initiating Party believes it reasonably necessary, upon written request the other party shall join as a party to the suit or action, but shall be under no obligation to participate, except to the extent that such participation is required as the result of its being a named party to the suit or action. Alternatively, at the Initiating Party's request, the other party will bring the suit or action in the other party's name, if the Initiating Party reasonably believes that the Initiating Party does not have standing to bring the suit or action, and in such event, the Initiating Party will still control the suit or action as provided above. At the Initiating Party's written request, the other party shall offer reasonable assistance to the Initiating Party in connection therewith at no charge to the Initiating Party except for reimbursement of reasonable out-of-pocket expenses incurred by the other party in rendering such assistance. The other party shall have the right to participate and be represented in any such suit or action by its own counsel at its own expense.

The Initiating Party shall not settle, agree to a consent judgment or otherwise voluntarily dispose of the suit or action without the written consent of the other party, which consent shall not be unreasonably withheld or delayed; provided that if River Vision is the Initiating Party, any such consent from Roche is not required if River Vision grants a permitted sub-license under Sections 2.5 and 3.

Except as otherwise agreed by the parties in connection with a cost-sharing arrangement, any recovery realized as a result of litigation described in this Section 11.6 (whether by way of settlement or otherwise) will be first allocated to reimbursement of unreimbursed legal fees and expenses incurred by the Initiating Party(ies), then toward reimbursement of any unreimbursed legal fees and expenses of the other party if not an Initiating Party, and then the remainder will be shared between the parties by allocating (i) [***]% to River Vision

and [***] to Roche for those Affected Patents infringed where River Vision is the Initiating Party, (ii) [***]% to Roche and [***] to Roche for those Affected Patents infringed where Roche is the Initiating Party, and (iii) if there are Affected Patents infringed for which River Vision is the Initiating Party for one or more of those Affected Patents and Roche is the Initiating Party for one or more of those Patents[***].

(c) Exclusion. For clarity, this Section 11.6 shall not apply to the [***] Agreement, the [***] Agreement and the [***] Agreement.

II. Appendix 1 of the Agreement shall be deleted and replaced by Appendix 1 attached to this Amendment No 9.

III. Appendix 2 of the Agreement shall be deleted and replaced by Appendix 2 attached to this Amendment No. 9.

IV.In case the validity of any patent family member of the Roche Patents summarized under [***] in Appendix 2 is challenged by a Third Party, Roche shall have the right to decide at its own discretion how to defend such patent family member or about further steps to be taken with respect to (including the decision to abandon) such patent family member of the Roche Patents summarized under [***]. Roche shall inform River Vision accordingly.

V. Capitalized terms used herein shall have the same meaning as defined in the Agreement.

VI. Except as previously stated herein, no other changes to the Agreement and all other terms and conditions of the Agreement remain in effect.

VII. This Amendment No. 9 enters into effect on the Effective Date.

Remainder of this page intentionally left blank

In witness whereof, the parties have executed this Amendment No. 9 to the Agreement as of the date first above written.

F. Hoffmann-La Roche Ltd

By: /s/ Timothy Steven
Name: Timothy Steven
Title: Global Alliance Director

Date: 9th May 2017

By: /s/ Melanie Wick
Name: Melanie Wick
Title: Legal Counsel

Hoffmann-La Roche Inc.

By: /s/ John Parise
Name: John Parise
Title: Assistant Secretary

Date: May 9, 2017

River Vision Development Corp.

By: /s/ D Madden
Name: D Madden
Title: CEO

Date: May / 5 / 2017

Appendix 1

Compound

teprotumumab is a human IgG1 antibody binding to IGFIR [***]

*****Certain Confidential Information Omitted**

Appendix 2

Roche Patents

[***]

[Remainder of this page intentionally left blank.]

[Remainder of this page intentionally left blank.]

CERTAIN CONFIDENTIAL INFORMATION CONTAINED IN THIS DOCUMENT, MARKED BY [***], HAS BEEN OMITTED BECAUSE HORIZON THERAPEUTICS PLC HAS DETERMINED THE INFORMATION (I) IS NOT MATERIAL AND (II) WOULD LIKELY CAUSE COMPETITIVE HARM TO HORIZON THERAPEUTICS PLC IF PUBLICLY DISCLOSED.

AMENDMENT NO. 2 TO COMMERCIAL SUPPLY AGREEMENT

This Amendment No. 2 (the "**Second Amendment**") to the Commercial Supply Agreement by and between Horizon Pharma Ireland Limited ("**Customer**") and AGC Biologics A/S, formerly known as CMC Biologics A/S ("**AGC**") is dated as of December 18, 2019 (the "**Second Amendment Effective Date**").

RECITALS

AGC and Customer are Parties to the Commercial Supply Agreement effective as of February 14, 2018 (the "**Agreement**"). AGC and Customer wish to amend certain pricing provisions of the Agreement to reflect volume discounts due to Customer's increased demand for Product.

AGREEMENT

1. Appendix Two of the Agreement is deleted in its entirety and replaced with the attached Appendix Two to this Amendment No. 2.

2. No Other Amendment; Confirmation. Except as expressly amended, modified and supplemented by this Amendment No. 2, the provisions of the Agreement, including the provisions Appendix Two, shall remain in full force and effect. Unless otherwise defined in this Amendment No. 2, all capitalized terms used but not defined in this Amendment No. 2 shall have the meaning set forth in the Agreement. Each Party acknowledges that it has read this Amendment No. 2, understands the changes affecting the Agreement and agrees to be bound by the terms of the Agreement as modified by this Amendment No. 2. The Parties further acknowledge and agree that the Agreement, as amended, embodies the complete and exclusive understanding among the Parties and supersedes and merges all related prior proposals and understandings whether oral or written.

IN WITNESS WHEREOF, the Parties have executed this Amendment **effective as of the Second Amendment Effective Date**.

HORIZON PHARMA IRELAND LIMITED

By /s/ Alan Mac Neice

Print Name Alan Mac Neice

Title Director

duly authorized

AGC BIOLOGICS A/S, formerly known as CMC Biologics A/S

By /s/ Patricio Massera

Print Name Patricio Massera

Title CEO

duly authorized

APPENDIX TWO

[***]

[***] = CERTAIN CONFIDENTIAL INFORMATION OMITTED

Amendment No. 2
to Commercial Supply Agreement
BETWEEN
CAMBREX PROFARMACO MILANO, and HORIZON PHARMA IRELAND LIMITED

Background:

This Amendment No. 2 ("**Amendment No. 2**") is made by and between Cambrex Profarmaco Milano Srl, Via E. Curiel, 34, 20067 Paullo (MI), Italy ("**Cambrex**") and Horizon Pharma Ireland Limited with its registered office at Connaught House, 1st Floor, 1 Burlington Road, Dublin 4, Ireland ("**Horizon**").

WHEREAS Cambrex and Raptor Pharmaceuticals Inc. entered into an API Supply Agreement dated November 3, 2010 (the "**Agreement**"), as amended on April 9, 2013.

WHEREAS the Agreement was assigned by way of mutual consent to Horizon on 10 May 2017.

Cambrex and Horizon now wish to amend the Agreement to replace the Purchasing Specifications Exhibit (Exhibit 1.13) to the Agreement. The effective date of this Amendment No. 2 is January 17, 2018 (the "**Effective Date**"). Cambrex and Horizon, as used herein, may be referred to, collectively, as "Parties" and individually as a "Party".

NOW THEREFORE in consideration of the premises hereof and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged by the Parties, the Parties agree to amend the Agreement as follows:

ARTICLE 1 AMENDMENT TO EXHIBIT 1.13

1.1 Specifications for Purchasing. Horizon and Cambrex hereby replace the existing Exhibit 1.13 with the Exhibit 1.13 attached here as Exhibit A.

ARTICLE 2 MISCELLANEOUS

2.1 No Other Modifications. The "Background" section of this document is incorporated into the Agreement. Except as expressly amended by this Amendment No. 2, the terms and conditions of the Agreement shall remain in full force and effect.

2.2 Counterparts. This Amendment No. 2 may be executed in two or more counterparts, each of which shall be deemed an original and all of which together shall constitute one instrument.

2.3 Entire Agreement. The Agreement, as amended hereby, together with all other Amendments, constitute the full, complete, final and integrated agreement between the parties related to the subject matter hereof and thereof and supersede all previous written or oral negotiations, commitments, agreements, transactions or understandings concerning the subject matter hereof.

(Signatures on next page)

IN WITNESS WHEREOF, the Parties hereto have executed this Amendment No. 2 as of the date first set forth above.

Agreed and Accepted:

Horizon Pharma Ireland Limited	**Cambrex Profarmaco Milano**
By: */s/ Paul Condon*	By: */s/ Aldo Magnini*
Printed Name: Paul Condon	Printed Name: Aldo Magnini
Title: Director	Title: Managing Director
Date: 7th January 2018	Date: January 17, 2018

Omitted Schedule:

Exhibit A – Replacement Exhibit 1.13

Exhibit 10.80

CERTAIN CONFIDENTIAL INFORMATION CONTAINED IN THIS DOCUMENT, MARKED BY [***], HAS BEEN OMITTED BECAUSE HORIZON THERAPEUTICS PLC HAS DETERMINED THE INFORMATION (I) IS NOT MATERIAL AND (II) WOULD LIKELY CAUSE COMPETITIVE HARM TO HORIZON THERAPEUTICS PLC IF PUBLICLY DISCLOSED.

AMENDMENT TO THE SUPPLY AGREEMENT BETWEEN CREALTA Pharmaceuticals LLC AND NOF CORPORATION

THIS AMENDMENT ("**Amendment**") is entered into effective this 30 November, 2018, ("**Effective Date**") by and among Horizon Pharma Rheumatology LLC (formerly known as CREALTA Pharmaceuticals LLC), an Delaware company, with its principal place of business located at 150 South Saunders Road, Lake Forest, IL 60045, USA ("**Horizon US**"), Horizon Pharma Ireland Limited, an Irish company, with its principal place of business located at Connaught House, 1st Floor, 1 Burlington Road, Dublin D04 C5Y6, Ireland ("**Horizon Ireland**") and NOF CORPORATION, a Japanese Corporation with its principal place of business located at 20-3, Ebisu 4-chome, Shibuya-ku, Tokyo 150-6019 Japan ("**NOF**").

WHEREAS, Horizon US and NOF entered into a SUPPLY AGREEMENT effective 3 August, 2015 ("**Agreement**"); and

WHEREAS, the parties now desire to amend the Agreement pursuant to Section 9.4 of the Agreement thereof to assign all of its rights, duties and obligations in the Agreement from Horizon US to an affiliate company of Horizon US, Horizon Ireland and to update section 3.3 of the Agreement;

NOW, THEREFORE, for good and valuable consideration, and intending to be legally bound, the parties hereby agree as follows:

1. Assignment and Assumption. Horizon US hereby transfers and assigns to Horizon Ireland, and Horizon Ireland hereby acquires from Horizon US all of Horizon US's rights, and interests in and to the Agreement, and Horizon Ireland hereby assumes and agrees to perform all obligations, duties, liabilities and commitments of Horizon US under the Agreement.

2. All references to CREALTA of the Agreement shall be replaced with HORIZON Ireland.

3. The following sentence in Section 3.3 of the Agreement shall be deleted in its entirety:

   "*Delivery shall be* [***] *(Incoterms 2000) or to such other location as may be directed by CREALTA in the applicable Firm Order*"

   and replaced with:

   "*Delivery shall be* [***] *(Incoterms 2010) or to such other location as may be directed by HORIZON Ireland in the applicable Firm Order*".

4. The following sentence shall be added as Section 3.9 of the Agreement:

   "3.9 *Performance of this Agreement by NOF's Subsidiary. NOF may have NOF EUROPE GmbH, NOF's subsidiary company, duly organized under the laws of Germany, and having its principal office at Mainzer Landstrasse 46, 60325, Frankfurt am Main Germany ("NEG') perform this Agreement on behalf of NOF,*

[***] = CERTAIN CONFIDENTIAL INFORMATION OMITTED

/s/ J.M.

*provided, however, that NOF shall impose all the same applicable obligations as those imposed on NOF under this Agreement on NEG. NOF shall be responsible for any performance of all obligations under this Agreement by NEG.***"**

5. Contact details in Section 9.3 of the Agreement shall be replaced with:

If to HORIZON Ireland, addressed to:

Horizon Pharma Ireland Limited
Connaught House, 1st Floor
1 Burlington Road
Dublin D04 C5Y6, Ireland
Att: Legal Department
Fax:

If to NOF, addressed to:

NOF Europe GmbH
Mainzer Landstralle 46
60325 Frankfurt am Main
Germany
Att:
Fax:

6. Any capitalized terms used herein and not defined herein are as defined in the Agreement.

7. All other terms and conditions in the Agreement shall remain unchanged and in full force and effect during the term thereof.

IN WITNESS WHEREOF, the parties to this Amendment indicate their agreement effective as of the date set forth at the beginning of this Amendment by signing below.

[SIGNATURE PAGE TO FOLLOW]

/s/ J.M.

Horizon Pharma Rheumatology LLC

By: */s/ Paul Hoelscher*
(Signed)

Name: Paul Hoelscher
(Typed)

Title: Executive Vice President, Chief Financial Officer

NOF CORPORATION

By: */s/ Tsuneharu Miyazaki*
(Signed)

Name: Tsuneharu Miyazaki
(Typed)

Title: Operating Officer, General manager DDS Development Division

Horizon Pharma Ireland Limited

By: */s/ Alan Mac Neice*
(Signed)

Name: Alan Mac Neice
(Typed)

Title: Director

Exhibit 21.1

Subsidiaries of Horizon Therapeutics Public Limited Company:

NAME:	JURISDICTION OF INCORPORATION:
Andromeda Biotech Limited	Israel
Horizon Medicines LLC	Delaware
Horizon Ophthalmology, Inc	Delaware
Horizon Orphan Holdings LLC	Delaware
Horizon Orphan LLC	Delaware
Horizon Pharma Aon Limited	Ireland
Horizon Pharma Dó Limited	Ireland
Horizon Pharma Israel Holding Corp. Ltd	Israel
Horizon Pharma Rheumatology LLC	Delaware
Horizon Pharma Trí Limited	Ireland
Horizon Therapeutics Capital Limited	Ireland
Horizon Therapeutics Finance Limited	Ireland
Horizon Therapeutics Finance S.à.r.l	Luxembourg
Horizon Therapeutics GmbH	Germany
Horizon Therapeutics Holdings Limited	Ireland
Horizon Therapeutics Investment Limited	Bermuda
Horizon Therapeutics Ireland DAC	Ireland
Horizon Therapeutics, LLC	Delaware
Horizon Therapeutics Schweiz GmbH	Switzerland
Horizon Therapeutics Services LLC	Delaware
Horizon Therapeutics Treasury DAC	Ireland
Horizon Therapeutics USA, Inc.	Delaware
Hyperion Therapeutics Ireland Holding Limited	Ireland
Hyperion Therapeutics Ireland Operating Limited	Ireland
HZNP Canada Limited	Canada
HZNP Finance Limited	Bermuda
HZNP Limited	Ireland
HZNP USA LLC	Delaware

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-3 (No. 333-230054) and Form S-8 (No. 333-198865, 333-203933, 333-211118, 333-220316, 333-222516, 333-224866 and 333-231183) of Horizon Therapeutics plc of our report dated February 26, 2020 relating to the financial statements, financial statement schedule and the effectiveness of internal control over financial reporting, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP
Chicago, Illinois
February 26, 2020

Exhibit 31.1

Certification of Principal Executive Officer

I, Timothy Walbert, certify that:

1. I have reviewed this annual report on Form 10-K of Horizon Therapeutics PLC (the "registrant");

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c. Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 26, 2020

/s/ Timothy Walbert
Timothy Walbert
Chairman, President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

Certification of Principal Financial Officer

I, Paul W. Hoelscher, certify that:

1. I have reviewed this annual report on Form 10-K of Horizon Therapeutics PLC (the "registrant");

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

    a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

    b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

    c. Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

    d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

    a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

    b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 26, 2020

/s/ Paul W. Hoelscher
Paul W. Hoelscher
Executive Vice President, Chief Financial Officer
(Principal Financial Officer)

Exhibit 32.1

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. Section 1350), I, Timothy Walbert, President, Chief Executive Officer and Chairman of the Board of Horizon Therapeutics PLC (the "Company"), certify to the best of my knowledge that:

1. the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2019 (the "Report"), to which this Certification is attached as Exhibit 32.1, fully complies with the requirements of Section 13(a) or 15(d) of the Exchange Act; and

2. the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 26, 2020

/s/ Timothy Walbert
Timothy Walbert
Chairman, President and Chief Executive Officer
(Principal Executive Officer)

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of the Company under the Securities Act of 1933, as amended, or the Exchange Act (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.

Exhibit 32.2

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. Section 1350), I, Paul W. Hoelscher, Executive Vice President and Chief Financial Officer of Horizon Therapeutics PLC (the "Company"), certify to the best of my knowledge that:

1. the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2019 (the "Report"), to which this Certification is attached as Exhibit 32.2, fully complies with the requirements of Section 13(a) or 15(d) of the Exchange Act; and

2. the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 26, 2020

/s/ Paul W. Hoelscher
Paul W. Hoelscher
Executive Vice President, Chief Financial Officer
(Principal Financial Officer)

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of the Company under the Securities Act of 1933, as amended, or the Exchange Act (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.

Patented Medicines (continued)

Excessive Prices

Order re excessive prices

83 (1) Where the Board finds that a patentee of an invention pertaining to a medicine is selling the medicine in any market in Canada at a price that, in the Board's opinion, is excessive, the Board may, by order, direct the patentee to cause the maximum price at which the patentee sells the medicine in that market to be reduced to such level as the Board considers not to be excessive and as is specified in the order.

Idem

(2) Subject to subsection (4), where the Board finds that a patentee of an invention pertaining to a medicine has, while a patentee, sold the medicine in any market in Canada at a price that, in the Board's opinion, was excessive, the Board may, by order, direct the patentee to do any one or more of the following things as will, in the Board's opinion, offset the amount of the excess revenues estimated by it to have been derived by the patentee from the sale of the medicine at an excessive price:

(a) reduce the price at which the patentee sells the medicine in any market in Canada, to such extent and for such period as is specified in the order;

(b) reduce the price at which the patentee sells one other medicine to which a patented invention of the patentee pertains in any market in Canada, to such extent and for such period as is specified in the order; or

(c) pay to Her Majesty in right of Canada an amount specified in the order.

Idem

(3) Subject to subsection (4), where the Board finds that a former patentee of an invention pertaining to a medicine had, while a patentee, sold the medicine in any market in Canada at a price that, in the Board's opinion, was excessive, the Board may, by order, direct the former patentee to do any one or more of the following things as will, in the Board's opinion, offset the amount of the excess revenues estimated by it to have been derived by the former patentee from the sale of the medicine at an excessive price:

(a) reduce the price at which the former patentee sells a medicine to which a patented invention of the former patentee pertains in any market in Canada, to such extent and for such period as is specified in the order; or

(b) pay to Her Majesty in right of Canada an amount specified in the order.

Where policy to sell at excessive price

(4) Where the Board, having regard to the extent and duration of the sales of the medicine at an excessive price, is of the opinion that the patentee or former patentee has engaged in a policy of selling the medicine at an excessive price, the Board may, by order, in lieu of any order it may make under subsection (2) or (3), as the case may be, direct the patentee or former patentee to do any one or more of the things referred to in that subsection as will, in the Board's opinion, offset not more than twice the amount of the excess revenues estimated by it to have been derived by the patentee or former patentee from the sale of the medicine at an excessive price.

Excess revenues

(5) In estimating the amount of excess revenues under subsection (2), (3) or (4), the Board shall not consider any revenues derived by a patentee or former patentee before December 20, 1991 or any revenues derived by a former patentee after the former patentee ceased to be entitled to the benefit of the patent or to exercise any rights in relation to the patent.

Right to hearing

(6) Before the Board makes an order under this section, it shall provide the patentee or former patentee with a reasonable opportunity to be heard.

Limitation period

(7) No order may be made under this section in respect of a former patentee who, more than three years before the day on which the proceedings in the matter commenced, ceased to be entitled to the benefit of the patent or to exercise any rights in relation to the patent.

1993, c. 2, s. 7; 1994, c. 26, s. 54(F).

Compliance

84 (1) A patentee or former patentee who is required by any order made under section 83 to reduce the price of a medicine shall commence compliance with the order within one month after the date of the order or within such greater period after that date as the Board determines is practical and reasonable, having regard to the circumstances of the patentee or former patentee.

Idem

(2) A patentee or former patentee who is directed by any order made under section 83 to pay an amount to Her Majesty shall pay that amount within one month after the date of the order or within such greater period after that date as the Board determines is practical and reasonable, having regard to the circumstances of the patentee or former patentee.

Debt due to Her Majesty

(3) An amount payable by a patentee or former patentee to Her Majesty under any order made under section 83 constitutes a debt due to Her Majesty and may be recovered in any court of competent jurisdiction.

1993, c. 2, s. 7.

Factors to be considered

85 (1) In determining under section 83 whether a medicine is being or has been sold at an excessive price in any market in Canada, the Board shall take into consideration the following factors, to the extent that information on the factors is available to the Board:

(a) the prices at which the medicine has been sold in the relevant market;

(b) the prices at which other medicines in the same therapeutic class have been sold in the relevant market;

(c) the prices at which the medicine and other medicines in the same therapeutic class have been sold in countries other than Canada;

(d) changes in the Consumer Price Index; and

(e) such other factors as may be specified in any regulations made for the purposes of this subsection.

Additional factors

(2) Where, after taking into consideration the factors referred to in subsection (1), the Board is unable to determine whether the medicine is being or has been sold in any market in Canada at an excessive price, the Board may take into consideration the following factors:

(a) the costs of making and marketing the medicine; and

(b) such other factors as may be specified in any regulations made for the purposes of this subsection or as are, in the opinion of the Board, relevant in the circumstances.

Research costs

(3) In determining under section 83 whether a medicine is being or has been sold in any market in Canada at an excessive price, the Board shall not take into consideration research costs other than the Canadian portion of the world costs related to the research that led to the invention pertaining to that medicine or to the development and commercialization of that invention, calculated in proportion to the ratio of sales by the patentee in Canada of that medicine to total world sales.

1993, c. 2, s. 7.

Hearings to be public

86 (1) A hearing under section 83 shall be held in public unless the Board is satisfied on representations made by the person to whom the hearing relates that specific, direct and substantial harm would be caused to the person by the disclosure of information or documents at a public hearing, in which case the hearing or any part thereof may, at the discretion of the Board, be held in private.

Notice of hearing to certain persons

(2) The Board shall give notice to the Minister of Industry or such other Minister as may be designated by the regulations and to provincial ministers of the Crown responsible for health of any hearing under section 83, and each of them is entitled to appear and make representations to the Board with respect to the matter being heard.

1993, c. 2, s. 7; 1995, c. 1, s. 62.

Information, etc., privileged

87 (1) Subject to subsection (2), any information or document provided to the Board under section 80, 81 or 82 or in any proceeding under section 83 is privileged, and no person who has obtained the information or document pursuant to this Act shall, without the authorization of the person who provided the information or document, knowingly disclose the information or document or allow it to be disclosed unless it has been disclosed at a public hearing under section 83.

Disclosure, etc.

(2) Any information or document referred to in subsection (1)

(a) may be disclosed by the Board to any person engaged in the administration of this Act under the direction of the Board, to the Minister of Industry or such other Minister as may be designated by the regulations and to the provincial ministers of the Crown responsible for health and their officials for use only for the purpose of making representations referred to in subsection 86(2); and

(b) may be used by the Board for the purpose of the report referred to in section 100.

1993, c. 2, s. 7; 1995, c. 1, s. 62.

Sales and Expense Information

Sales and expense information, etc., to be provided

88 (1) A patentee of an invention pertaining to a medicine shall, as required by and in accordance with the regulations, or as the Board may, by order, require, provide the Board with such information and documents as the regulations or the order may specify respecting

(a) the identity of the licensees in Canada of the patentee;

(b) the revenue of the patentee, and details of the source of the revenue, whether direct or indirect, from sales of medicine in Canada; and

(c) the expenditures made by the patentee in Canada on research and development relating to medicine.

Additional information, etc.

(2) Where the Board believes on reasonable grounds that any person has information or documents pertaining to the value of sales of medicine in Canada by a patentee or the expenditures made by a patentee in Canada on research and development relating to medicine, the Board may, by order, require the person to provide the Board with any of the information or documents that are specified in the order, or with copies thereof.

Compliance with order

(3) A person in respect of whom an order is made under subsection (1) or (2) shall comply with the order within such time as is specified in the order or as the Board may allow.

Information, etc., privileged

(4) Subject to section 89, any information or document provided to the Board under subsection (1) or (2) is privileged, and no person who has obtained the information or document pursuant to this Act shall, without the authorization of the person who provided the information or document, knowingly disclose the information or allow it to be disclosed, except for the purposes of the administration of this Act.

1993, c. 2, s. 7.

Date modified:

2020-10-01

The Value of Intangibles

Aswath Damodaran

Start with the obvious… Intangible assets are worth a lot and accountants don't do a good job in assessing their value

- Leonard Nakamura of the Federal Reserve Bank of Philadelphia provided three different measures of the magnitude of intangible assets in today's economy – an accounting estimate of the value of the investments in R&D, software, brand development and other intangibles; the wages and salaries paid to the researchers, technicians and other creative workers who generate these intangible assets; and the improvement in operating margins that he attributes to improvements to intangible factors. With all three approaches, he estimated the investments in intangible assets to be in excess of $ 1 trillion in 2000 and the capitalized value of these intangible assets to be in excess of $ 6 trillion in the same year.
- Baruch Lev has argued persuasively that the way in which accountants deal with intangibles is neither conservative nor informative. Expensing R&D, for instance, does understate earnings for high growth companies but it overstates earnings for low growth firms. In a paper with Paul Zarowin, he presents evidence that earnings at U.S. firms have become less correlated with stock prices and he attributes this phenomenon to the failure to accounting for intangible assets.

So, what are intangible assets?

- The loosest and broadest definition of an intangible asset is that it is an asset that we can neither see nor feel. Using that definition, though, we can come up with a broad range of intangible assets including:
  - Franchises, copyrights and trademarks
  - Patents
  - Brand names
- To this list, we can add on what we consider the invisible assets including
  - Top-notch management
  - Loyal and well-trained workforce
  - Technological know-how

And do we do them justice in valuation?

- Critics of valuation analysts, in particular, and quantitative valuation models, in general, argue that we miss intangible assets because we are so focused on the bottom line - earnings and cash flows.
- Implicit in this criticism is the belief that if accountants do not show intangible assets on the balance sheet, we will miss these assets when we are doing valuation.

The Solutions offered by Critics

- Premium approach: Add a premium to the values that we arrive at for companies with substantial intangible assets. The magnitude of the premium is usually subjective and left to the analyst to estimate for individual companies.
- Book Value approach: Force accountants to come up with reasonable values for intangible assets and show them as assets on the balance sheet.

Dangers of Ad-hoc approaches

- Double counting: For assets that already generate a portion of the earnings and the cash flows, adding a premium on to the value will be double counting value.
- Rules of thumb: Even when we are not double counting, there is a danger with using subjective rules of thumb to estimate the value of uncounted assets. For instance, technological prowess cannot add 20% to the value of a company. It has to be valued in each case, and may we worth 5% sometimes and 50% at other times.

Categorizing Intangibles

	Independent and Cash flow generating intangibles	*Not independent and cash flow generating to the firm*	*No cash flows now but potential for cashflows in future*
Examples	Copyrights, trademarks, licenses, franchises, professional practices (medical, dental)	Brand names, Quality and Morale of work force, Technological expertise, Corporate reputation	Undeveloped patents, operating or financial flexibility (to expand into new products/markets or abandon existing ones)
Valuation approach	Estimate expected cashflows from the product or service and discount back at appropriate discount rate.	• Compare DCF value of firm with intangible with firm without (if you can find one) • Assume that all excess returns of firm are due to intangible. • Compare multiples at which firm trades to sector averages.	Option valuation • Value the undeveloped patent as an option to develop the underlying product. • Value expansion options as call options • Value abandonment options as put options.
Challenges	• Life is usually finite and terminal value may be small. • Cashflows and value may be person dependent (for professional practices)	With multiple intangibles (brand name and reputation for service), it becomes difficult to break down individual components.	• Need exclusivity. • Difficult to replicate and arbitrage (making option pricing models dicey)

I. Valuing independent and cash flow producing intangible assets: Valuing a copyright

- Assume that John Wiley has been approached by another publisher who is interested in buying the copyright to this book (Damodaran on Valuation). To estimate the value of the copyright, we will make the following assumption.
  - The book is expected to generate $150,000 in after-tax cash flows for the next three years and $100,000 a year for the following two years. These are the cash flows after author royalties, promotional expenses and production costs.
  - About 40% of these cash flows are from large organizations that make bulk orders and are considered predictable and stable. The cost of capital applied to these cash flows is 7%.
  - The remaining 60% of the cash flows are to the general public and this segment of the cash flows is considered much more volatile. The cost of capital applied to these cash flows is 10%.

Valuing Damodaran on Valuation

Year	*Stable Cashflows*	*Present value @ 7%*	*Volatile Cashflows*	*Present value @ 10%*
1	$60,000	$56,075	$90,000	$81,818
2	$60,000	$52,406	$90,000	$74,380
3	$60,000	$48,978	$90,000	$67,618
4	$40,000	$30,516	$60,000	$40,981
5	$40,000	$28,519	$60,000	$37,255
		$216,494		$302,053

Franchise Value

- *Brand Name Value*: The franchise might have a brand name value that enables the franchisee to charge higher prices and attract more customers than an otherwise similar business. Thus, an investor may be willing to pay a significant up-front fee to acquire a McDonald's franchise, in order to take advantage of the brand name value associated with the company. This brand name value is augmented by the fact that the franchisor often provides the advertising for the product.
- *Product/Service Expertise*: In some cases, a franchise has value because the franchisor provides expertise on the product or service that is being sold. For instance, a McDonald's franchisee will have access to the standard equipment that McDonald's uses as well as the product ingredients (the special sauce on the Big Mac).
- *Legal Monopolies*: Sometimes, a franchise may have value because the franchisee is given the exclusive right to provide a service. For instance, a company may pay a large fee for the right to operate concession stands in a baseball stadium, knowing that they will face no competition within the stadium. In a milder variant of this, multiple franchises are sometimes sold but the number of franchises is kept limited to insure that the franchisees earn excess returns. New York City, for example, sells cab medallions that are a pre-requisite for operating a yellow cab in the city. They also have tight restrictions on non-medallion owners offering the same service. Consequently, a market where cab medallions are bought and sold exists.

Businesses with personal components

- Some businesses have a personal component to them, and their value can be linked to this personal component. A doctor's practice or a highly rated restaurant are good examples. While these businesses may be very profitable, a significant portion of the profits may be attributed to the person running the business (the doctor or the chef).
- When paying for these businesses, you will have to value them on the assumption that this key person will leave after the sale. The resulting lower value will create a key person discount.
- This may allow for a negotiation process where the key person agrees to stay on to allow for a transition period.

II. Firm-wide intangible assets- Ways of valuing

- Capital Invested: We can estimate the book value of an asset by looking at what a firm has invested in that asset over time. With brand name, for instance, this would require looking at advertising expenditures over time, capitalizing these expenses and looking at the balance that remains unamortized of these expenses today.
- Discounted Cash Flow Valuation: We can discount the expected incremental cash flows generated by the intangible asset in question to the firm. This will require separating out the portion of the aggregate cash flows of a firm that can be attributed to brand name or technological expertise and discounting back these cash flows at a reasonable discount rate.
- Relative Valuation: One way to isolate the effect of an intangible asset such as brand name is compare how the market values the firm (with the intangible) with how it values otherwise similar companies without the intangible asset. The difference can be attributed to the intangible asset.

a. Valuing Coca Cola's brand name: Capital Invested approach

Year	Total Selling and Advertising	Brand Name Related Expense	Amortization this year	Unamortized Expense
1980	$1,121	$561	$22.43	$0.00
1981	$1,189	$594	$23.77	$23.77
1982	$1,221	$610	$24.41	$48.83
1983	$1,376	$688	$27.52	$82.56
1984	$1,543	$771	$30.85	$123.41
1985	$1,579	$789	$31.57	$157.87
1986	$1,631	$815	$32.61	$195.68
1987	$1,777	$888	$35.53	$248.73
1988	$2,025	$1,013	$40.51	$324.05
1989	$2,232	$1,116	$44.64	$401.76
1990	$2,717	$1,359	$54.35	$543.47
1991	$3,069	$1,535	$61.39	$675.25
1992	$3,499	$1,750	$69.99	$839.84
1993	$3,797	$1,898	$75.93	$987.13
1994	$4,198	$2,099	$83.96	$1,175.44
1995	$4,657	$2,329	$93.15	$1,397.20
1996	$5,347	$2,673	$106.93	$1,710.93
1997	$5,235	$2,617	$104.69	$1,779.79
1998	$5,523	$2,761	$110.45	$1,988.16
1999	$6,543	$3,271	$130.85	$2,486.21
2000	$5,701	$2,850	$114.01	$2,280.27
2001	$4,099	$2,050	$81.99	$1,721.72
2002	$4,667	$2,334	$93.35	$2,053.63
2003	$4,992	$2,496	$99.84	$2,296.32
2004	$5,431	$2,715	$108.61	$2,606.72
			$1,703.35	$26,148.75

Valuing Coca Cola's Brand Name

- If we just accumulate the advertising expenses over time, assuming that 50% is attributable to building up brand name, we get a value of $ 26 billion.
- If we adjust the expenses for inflation, the value that we obtain for the brand name value is close to 50%.
- The two key problems with this approach are
  - Estimating the proportion of advertising that can be attributed to brand name building
  - Estimating the life of brand name as an asset

b. Valuing Coca Cola's brand name: Generic comparison

	Coca Cola	*With Cott Margins*
Current Revenues =	$21,962.00	$21,962.00
Length of high-growth period	10	10
Reinvestment Rate =	50%	50%
Operating Margin (after-tax)	15.57%	5.28%
Sales/Capital (Turnover ratio)	1.34	1.34
Return on capital (after-tax)	20.84%	7.06%
Growth rate during period (g) =	10.42%	3.53%
Cost of Capital during period =	7.65%	7.65%
Stable Growth Period		
Growth rate in steady state =	4.00%	4.00%
Return on capital =	7.65%	7.65%
Reinvestment Rate =	52.28%	52.28%
Cost of Capital =	7.65%	7.65%
Value of Firm =	**$79,611.25**	**$15,371.24**

Value of brand name = $79, 611 million - $15,371 million = $ 64,240 million

c. Valuing Coca Cola's brand name: Relative Valuation

	Coca Cola	*Cott*
Market value of Equity	$98,160	$949
Debt	$7,178	$345
Cash	$6,707	$27
Enterprise Value	$98,631	$1,267
Sales	$21,962	$1,646
EBITDA	$7,760	$186
Capital Invested	$16,406	$775
EV Multiples		
EV/Sales	4.49	0.77
EV/EBITDA	12.71	6.81
EV/Capital Invested	6.01	1.63

Value of brand name = 16,406 (6.01 – 1.63) = $71,821 million

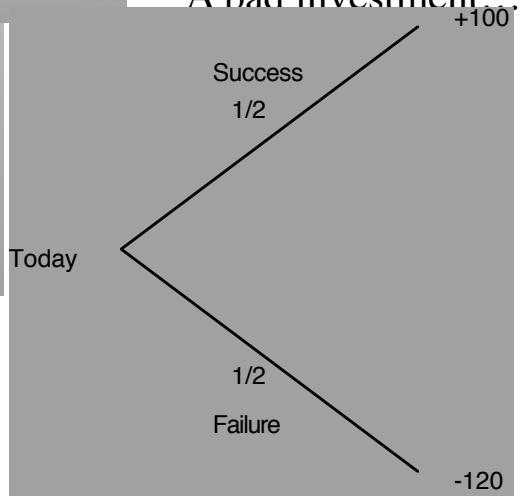
III. Valuing intangible assets that do not generate cash flows now but might in the future….

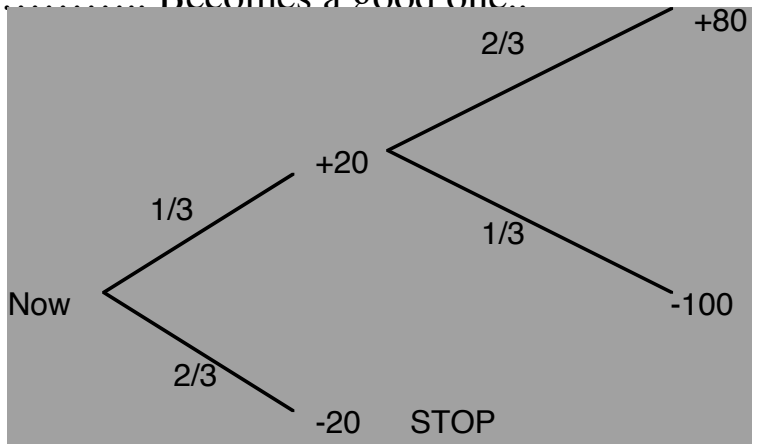
- The most difficult intangible assets to value are those that have the potential to create cash flows in the future but do not right now. Examples would include:
  - Undeveloped patents
  - Undeveloped natural resource options
  - Flexibility to expand into new markets and businesses in the future
  - Flexibility to abandon investments, if they turn out to be losers.
- While these assets are difficult to value on a discounted cash flow valuation basis and often impossible to evaluate on a relative basis, they do have option characteristics and are best valued using option pricing models.

A Real Option Premium

- In the last few years, there are some who have argued that discounted cashflow valuations under valued some companies and that a real option premium should be tacked on to DCF valuations. To understanding its moorings, compare the two trees below:

A bad investment..... Becomes a good one..





1. Learn at relatively low cost
2. Make better decisions based on learning

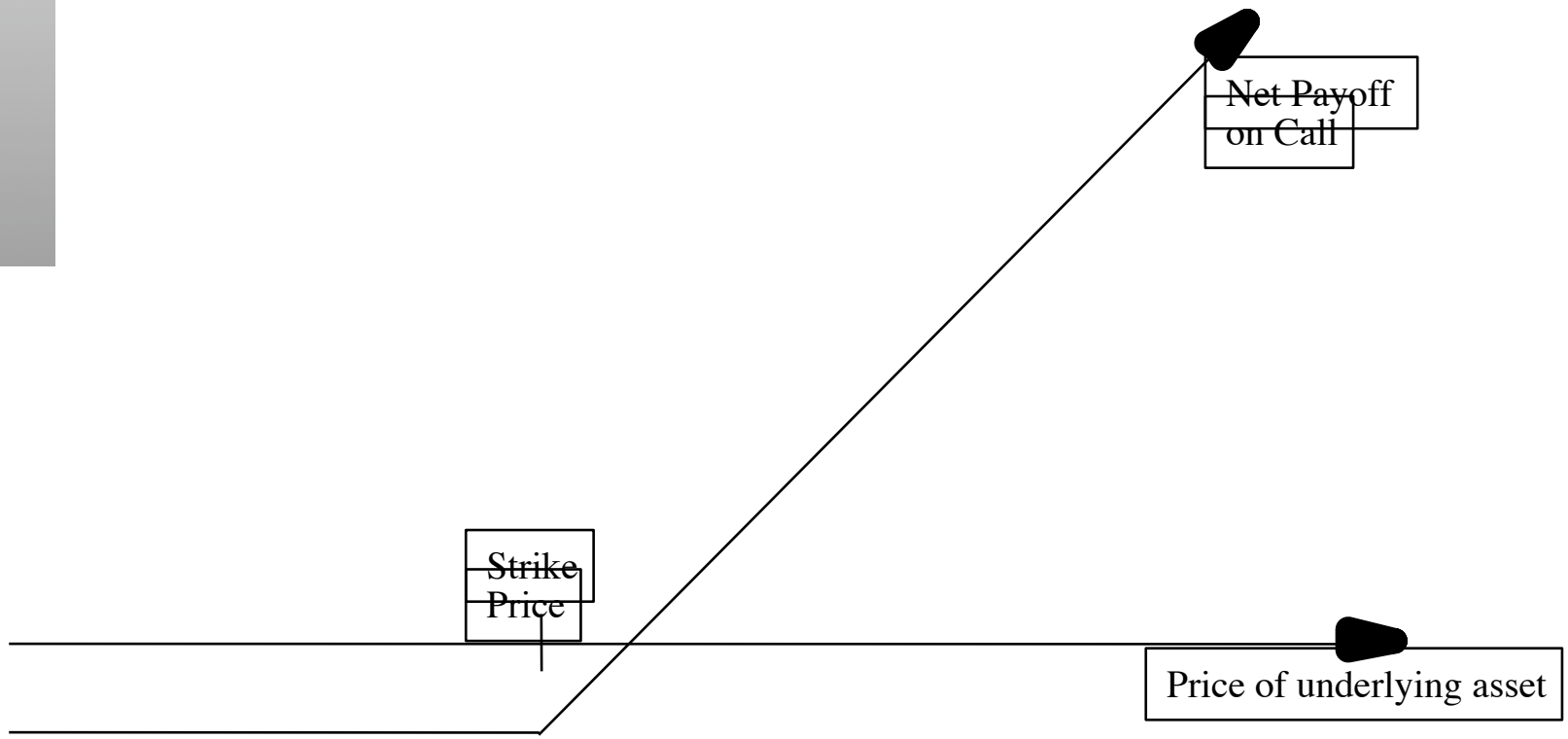
Three Basic Questions

- When is there a real option embedded in a decision or an asset?
- When does that real option have significant economic value?
- Can that value be estimated using an option pricing model?

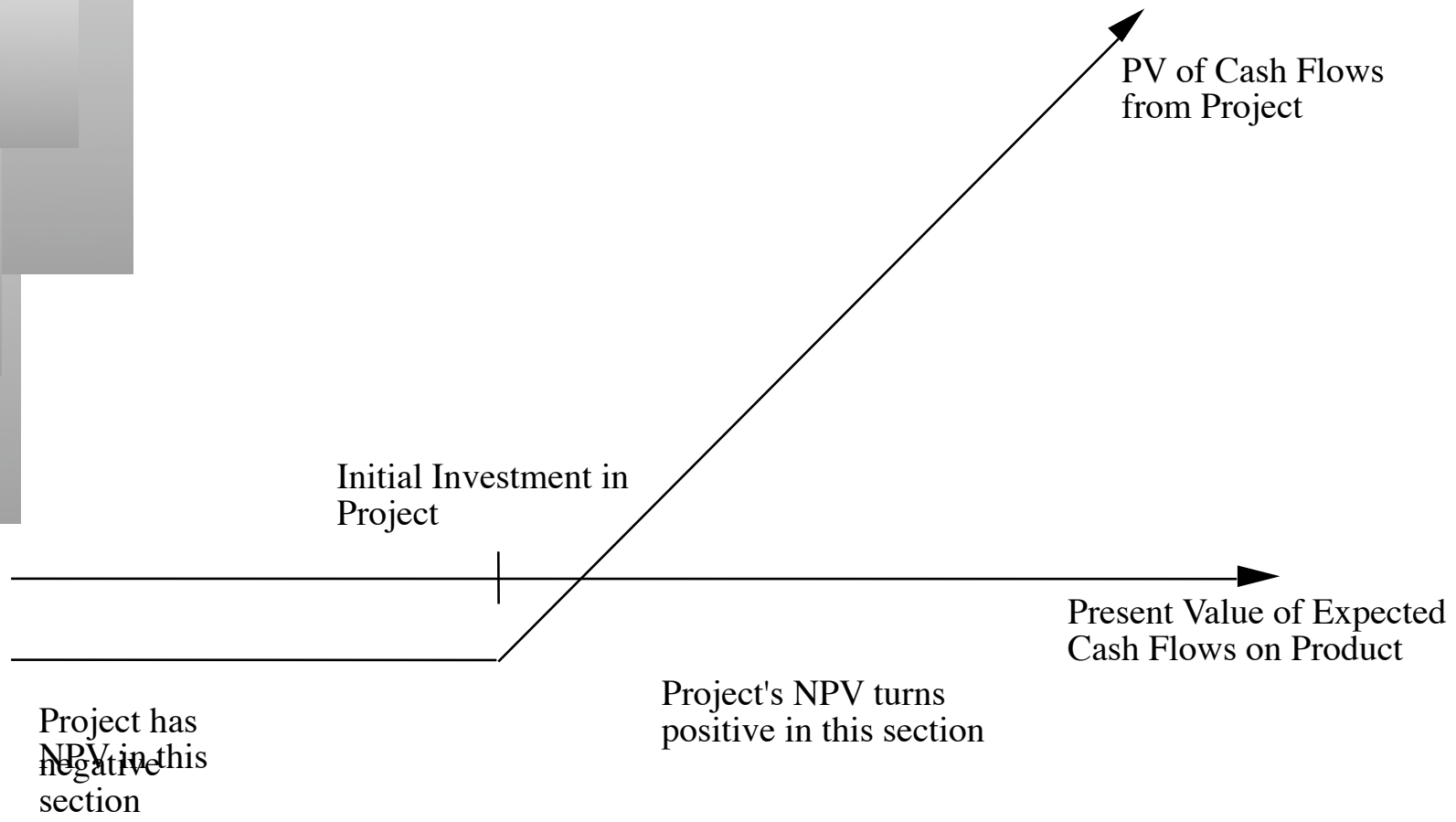
When is there an option embedded in an action?

- An option provides the holder with the **right** to buy or sell a specified quantity of an underlying asset at a fixed price (called a strike price or an exercise price) at or before the expiration date of the option.
- There has to be a clearly defined underlying asset whose value changes over time in unpredictable ways.
- The payoffs on this asset (real option) have to be contingent on an specified event occurring within a finite period.

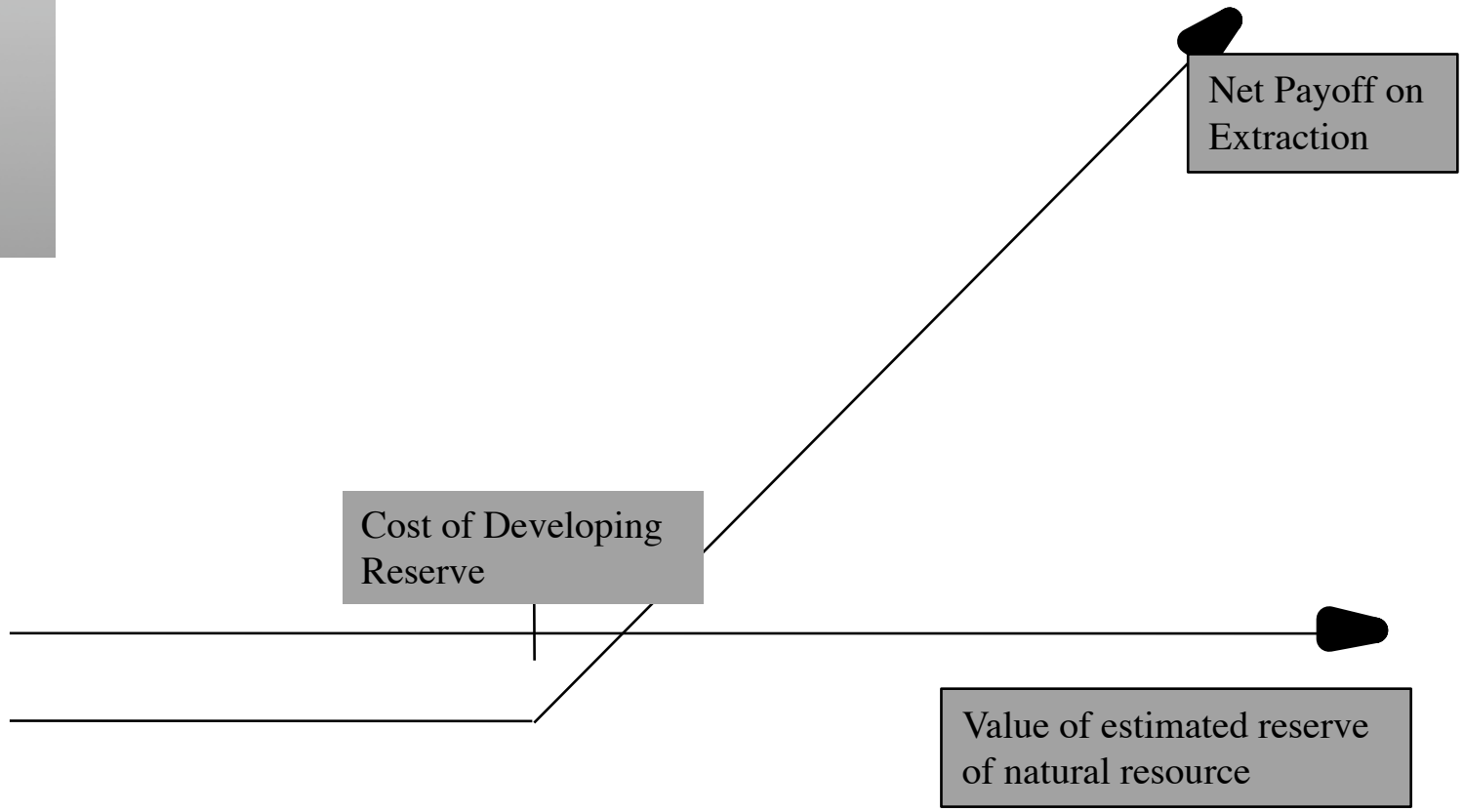
Payoff Diagram on a Call



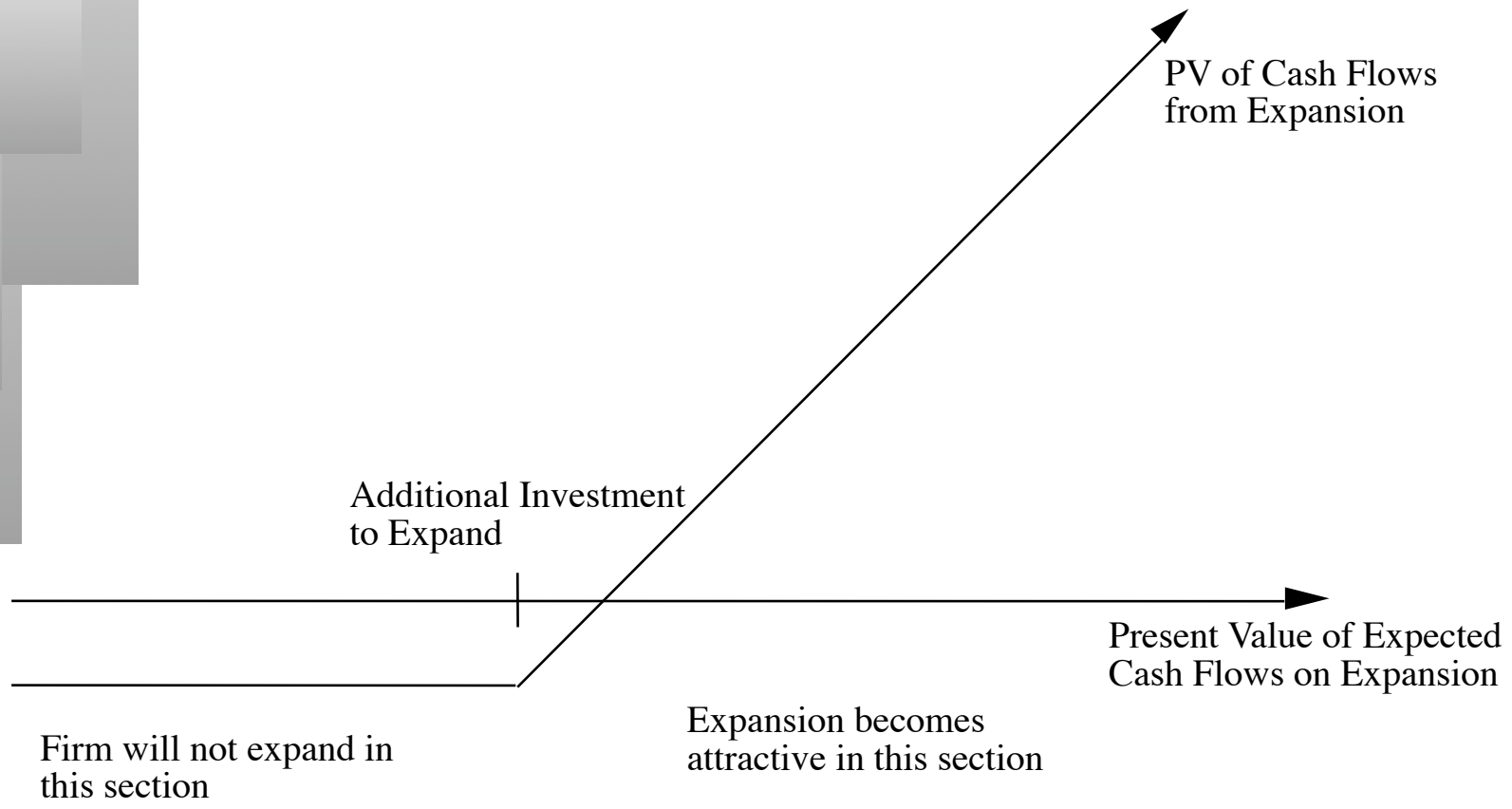
Example 1: Product Patent as an Option



Example 2: Undeveloped Oil Reserve as an option



Example 3: Expansion of existing project as an option



When does the option have significant economic value?

- For an option to have significant economic value, there has to be a restriction on competition in the event of the contingency. In a perfectly competitive product market, no contingency, no matter how positive, will generate positive net present value.
- At the limit, real options are most valuable when you have exclusivity - you and only you can take advantage of the contingency. They become less valuable as the barriers to competition become less steep.

Exclusivity: Putting Real Options to the Test

- Product Options: Patent on a drug
  - Patents restrict competitors from developing similar products
  - Patents do not restrict competitors from developing other products to treat the same disease.
- Natural Resource options: An undeveloped oil reserve or gold mine.
  - Natural resource reserves are limited.
  - It takes time and resources to develop new reserves
- Growth Options: Expansion into a new product or market
  - Barriers may range from strong (exclusive licenses granted by the government - as in telecom businesses) to weaker (brand name, knowledge of the market) to weakest (first mover).

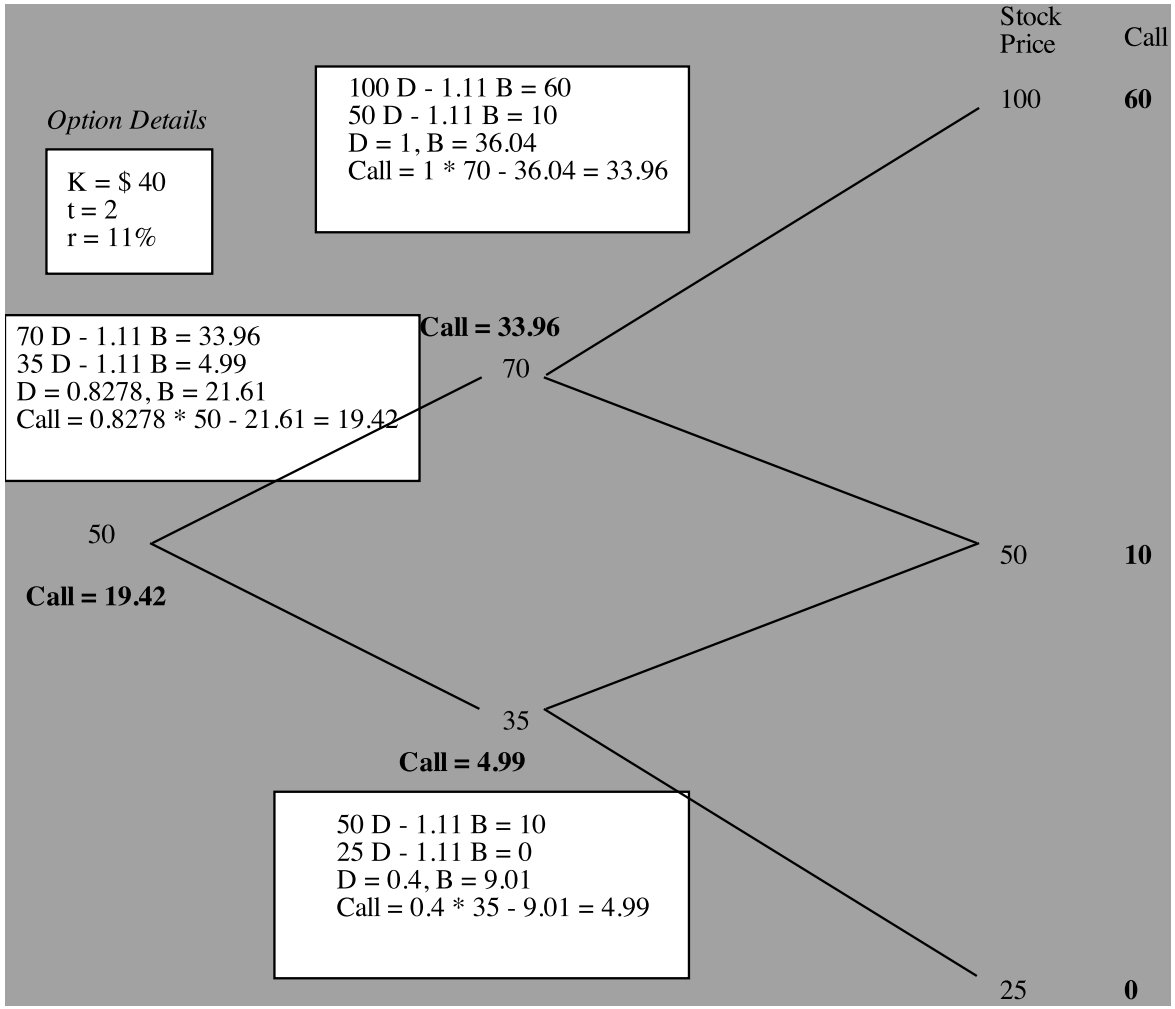
Determinants of option value

- Variables Relating to Underlying Asset
  - Value of Underlying Asset; as this value increases, the right to buy at a fixed price (calls) will become more valuable and the right to sell at a fixed price (puts) will become less valuable.
  - Variance in that value; as the variance increases, both calls and puts will become more valuable because all options have limited downside and depend upon price volatility for upside.
  - Expected dividends on the asset, which are likely to reduce the price appreciation component of the asset, reducing the value of calls and increasing the value of puts.
- Variables Relating to Option
  - Strike Price of Options; the right to buy (sell) at a fixed price becomes more (less) valuable at a lower price.
  - Life of the Option; both calls and puts benefit from a longer life.
- Level of Interest Rates; as rates increase, the right to buy (sell) at a fixed price in the future becomes more (less) valuable.

The Building Blocks for Option Pricing Models: Arbitrage and Replication

- The objective in creating a replicating portfolio is to use a combination of riskfree borrowing/lending and the underlying asset to create the same cashflows as the option being valued.
  - Call = Borrowing + Buying Δ of the Underlying Stock
  - Put = Selling Short Δ on Underlying Asset + Lending
  - The number of shares bought or sold is called the **option delta**.
- The principles of arbitrage then apply, and the value of the option has to be equal to the value of the replicating portfolio.

The Binomial Option Pricing Model



The Limiting Distributions….

- As the time interval is shortened, the limiting distribution, as t -> 0, can take one of two forms.
  - If as t -> 0, **price changes become smaller**, the limiting distribution is the normal distribution and the **price process is a continuous one**.
  - If as t->0, **price changes remain large**, the limiting distribution is the poisson distribution, i.e., a **distribution that allows for price jumps**.
- **The Black-Scholes model** applies when the **limiting distribution is the normal distribution** , and explicitly assumes that the price process is continuous and that there are no jumps in asset prices.

The Black Scholes Model

Value of call = $S\, N(d_1) - K\, e^{-rt}\, N(d_2)$

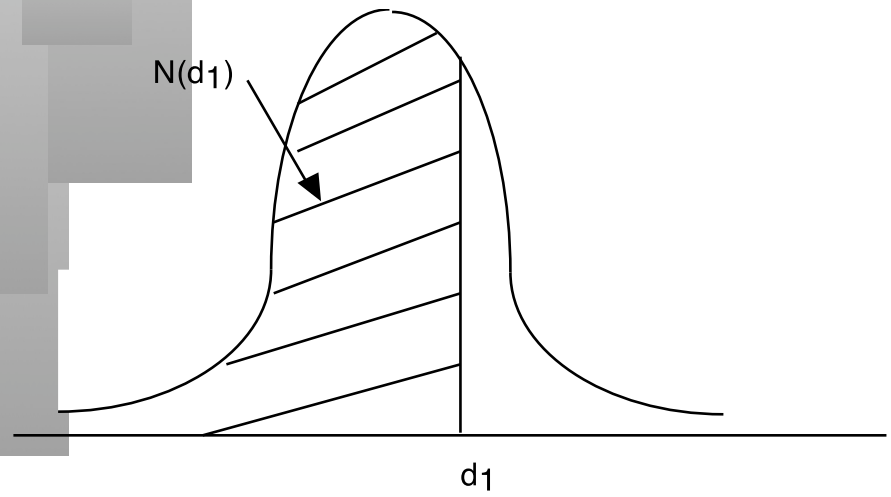
where,

$$d_1 = \frac{\ln\left(\frac{S}{K}\right) + \left(r + \frac{\sigma^2}{2}\right) t}{\sigma \sqrt{t}}$$

- $d_2 = d_1 - \sigma \sqrt{t}$

- The replicating portfolio is embedded in the Black-Scholes model. To replicate this call, you would need to
  - Buy N(d1) shares of stock; N(d1) is called the option delta
  - Borrow $K\, e^{-rt}\, N(d_2)$

The Normal Distribution



d	N(d)	d	N(d)	d	N(d)
-3.00	0.0013	-1.00	0.1587	1.05	0.8531
-2.95	0.0016	-0.95	0.1711	1.10	0.8643
-2.90	0.0019	-0.90	0.1841	1.15	0.8749
-2.85	0.0022	-0.85	0.1977	1.20	0.8849
-2.80	0.0026	-0.80	0.2119	1.25	0.8944
-2.75	0.0030	-0.75	0.2266	1.30	0.9032
-2.70	0.0035	-0.70	0.2420	1.35	0.9115
-2.65	0.0040	-0.65	0.2578	1.40	0.9192
-2.60	0.0047	-0.60	0.2743	1.45	0.9265
-2.55	0.0054	-0.55	0.2912	1.50	0.9332
-2.50	0.0062	-0.50	0.3085	1.55	0.9394
-2.45	0.0071	-0.45	0.3264	1.60	0.9452
-2.40	0.0082	-0.40	0.3446	1.65	0.9505
-2.35	0.0094	-0.35	0.3632	1.70	0.9554
-2.30	0.0107	-0.30	0.3821	1.75	0.9599
-2.25	0.0122	-0.25	0.4013	1.80	0.9641
-2.20	0.0139	-0.20	0.4207	1.85	0.9678
-2.15	0.0158	-0.15	0.4404	1.90	0.9713
-2.10	0.0179	-0.10	0.4602	1.95	0.9744
-2.05	0.0202	-0.05	0.4801	2.00	0.9772
-2.00	0.0228	0.00	0.5000	2.05	0.9798
-1.95	0.0256	0.05	0.5199	2.10	0.9821
-1.90	0.0287	0.10	0.5398	2.15	0.9842
-1.85	0.0322	0.15	0.5596	2.20	0.9861
-1.80	0.0359	0.20	0.5793	2.25	0.9878
-1.75	0.0401	0.25	0.5987	2.30	0.9893
-1.70	0.0446	0.30	0.6179	2.35	0.9906
-1.65	0.0495	0.35	0.6368	2.40	0.9918
-1.60	0.0548	0.40	0.6554	2.45	0.9929
-1.55	0.0606	0.45	0.6736	2.50	0.9938
-1.50	0.0668	0.50	0.6915	2.55	0.9946
-1.45	0.0735	0.55	0.7088	2.60	0.9953
-1.40	0.0808	0.60	0.7257	2.65	0.9960
-1.35	0.0885	0.65	0.7422	2.70	0.9965
-1.30	0.0968	0.70	0.7580	2.75	0.9970
-1.25	0.1056	0.75	0.7734	2.80	0.9974
-1.20	0.1151	0.80	0.7881	2.85	0.9978
-1.15	0.1251	0.85	0.8023	2.90	0.9981
-1.10	0.1357	0.90	0.8159	2.95	0.9984
-1.05	0.1469	0.95	0.8289	3.00	0.9987
-1.00	0.1587	1.00	0.8413		

When can you use option pricing models to value real options?

- The notion of a replicating portfolio that drives option pricing models makes them most suited for valuing real options where
  - The underlying asset is traded - this yield not only observable prices and volatility as inputs to option pricing models but allows for the possibility of creating replicating portfolios
  - An active marketplace exists for the option itself.
  - The cost of exercising the option is known with some degree of certainty.
- When option pricing models are used to value real assets, we have to accept the fact that
  - The value estimates that emerge will be far more imprecise.
  - The value can deviate much more dramatically from market price because of the difficulty of arbitrage.

Valuing a Product Patent as an option: Avonex

- Biogen, a bio-technology firm, has a patent on Avonex, a drug to treat multiple sclerosis, for the next 17 years, and it plans to produce and sell the drug by itself. The key inputs on the drug are as follows:

  PV of Cash Flows from Introducing the Drug Now = S = $ 3.422 billion

  PV of Cost of Developing Drug for Commercial Use = K = $ 2.875 billion

  Patent Life = t = 17 years Riskless Rate = r = 6.7% (17-year T.Bond rate)

  Variance in Expected Present Values = σ^2 = 0.224 (Industry average firm variance for bio-tech firms)

  Expected Cost of Delay = y = 1/17 = 5.89%

  d1 = 1.1362 N(d1) = 0.8720

  d2 = -0.8512 N(d2) = 0.2076

Call Value= $3,422 \exp^{(-0.0589)(17)} (0.8720) - 2,875 (\exp^{(-0.067)(17)} (0.2076) = \$ 907$ million

Valuing an Oil Reserve

- Consider an offshore oil property with an estimated oil reserve of 50 million barrels of oil, where the cost of developing the reserve is $ 600 million today.
- The firm has the rights to exploit this reserve for the next twenty years and the marginal value per barrel of oil is $12 per barrel currently (Price per barrel - marginal cost per barrel). There is a 2 year lag between the decision to exploit the reserve and oil extraction.
- Once developed, the net production revenue each year will be 5% of the value of the reserves.
- The riskless rate is 8% and the variance in ln(oil prices) is 0.03.

Valuing an oil reserve as a real option

- Current Value of the asset = S = Value of the developed reserve discounted back the length of the development lag at the dividend yield = \$12 * 50 / $(1.05)^2$ = \$ 544.22
- (If development is started today, the oil will not be available for sale until two years from now. The estimated opportunity cost of this delay is the lost production revenue over the delay period. Hence, the discounting of the reserve back at the dividend yield)
- Exercise Price = Present Value of development cost = \$12 * 50 = \$600 million
- Time to expiration on the option = 20 years
- Variance in the value of the underlying asset = 0.03
- Riskless rate =8%
- Dividend Yield = Net production revenue / Value of reserve = 5%

Valuing the Option

- Based upon these inputs, the Black-Scholes model provides the following value for the call:

  d1 = 1.0359 N(d1) = 0.8498

  d2 = 0.2613 N(d2) = 0.6030

- Call Value= 544 .22 $\exp^{(-0.05)(20)}$ (0.8498) -600 ($\exp^{(-0.08)(20)}$ (0.6030)= $ 97.08 million
- This oil reserve, though not viable at current prices, still is a valuable property because of its potential to create value if oil prices go up.
- Extending this concept, the value of an oil company can be written as the sum of three values:

Value of oil company = Value of developed reserves (DCF valuation)

+ Value of undeveloped reserves (Valued as option)

An Example of an Expansion Option

- Ambev is considering introducing a soft drink to the U.S. market. The drink will initially be introduced only in the metropolitan areas of the U.S. and the cost of this "limited introduction" is $ 500 million.
- A financial analysis of the cash flows from this investment suggests that the present value of the cash flows from this investment to Ambev will be only $ 400 million. Thus, by itself, the new investment has a **negative NPV of $ 100 million**.
- If the initial introduction works out well, Ambev **could go ahead with a full-scale introduction to the entire market** with **an additional investment of $ 1 billion** any time over the next 5 years. While the current expectation is that the cash flows from having this investment is only $ 750 million, there is considerable uncertainty about both the potential for the drink, leading to significant variance in this estimate.

Valuing the Expansion Option

- Value of the Underlying Asset (S) = PV of Cash Flows from Expansion to entire U.S. market, if done now =$ 750 Million
- Strike Price (K) = Cost of Expansion into entire U.S market = $ 1000 Million
- We estimate the standard deviation in the estimate of the project value by using the annualized standard deviation in firm value of publicly traded firms in the beverage markets, which is approximately 34.25%.
  - Standard Deviation in Underlying Asset's Value = 34.25%
- Time to expiration = Period for which expansion option applies = 5 years

Call Value= $ 234 Million

Multicenter Study Nephron Clin Pract. 2010;114(1):c12-8. doi: 10.1159/000245065.

Epub 2009 Oct 9.

Report of a Brazilian multicenter study on nephropathic cystinosis

Maria Helena Vaisbich [1], Vera H Koch

Affiliations

PMID: 19816039 DOI: 10.1159/000245065

Abstract

Introduction: The Brazilian Multicenter Nephropathic Study Group, founded in 1999, is currently composed of 16 pediatric nephrology units, which are coordinated by the Pediatric Nephrology Unit of Instituto da Criança--HCFMUSP. This Study Group intends to better know our patients, their special characteristics and facilitates the treatment.

Objective: To present an update on the demographics of the ongoing study participants with interest on renal function status, response to therapy, and extra-renal complications.

Methods: Patient recruitment to the study is based on informed consent and has been supported by the Brazilian Society of Nephrology, by the creation of an electronic homepage and by the participation in medical meetings and publications in medical periodicals. Our study protocol involves the initial and follow-up questionnaire, the measurement of intraleukocyte cystine content, initiation

and follow-up therapy with cysteamine, and clinical patient follow-up based on a protocol of subsidiary exams.

Results: We identified 102 patients (42 females) with nephropathic cystinosis in Brazil since 1999. Forty-six children are followed at the Instituto da Criança/SP, 15 at the Hospital Pequeno Príncipe/PR, 12 at the UNICAMP/SP, 10 at the Unidade de Transplante Renal - HCFMUSP/SP and 3 at the Santa Casa/SP; the remaining patients are followed at the Instituto da Criança and at their respective doctors' offices in different nephrology services in Brazil. Of these patients, 23/102 (22.5%) have normal renal function, 19/102 (18.6%) are in chronic renal failure with conservative treatment, 26/102 are on dialysis (18 on peritoneal dialysis and 8 on hemodialysis), and 34/102 received a renal transplant. The extra-renal involvement diagnosed was: hypothyroidism in 63 patients, diabetes mellitus in 8 patients, muscular involvement in 7 patients, a compromised central nervous system in 5 patients, hepatic complications in 5 patients, and deglutition dysfunction in 2 patients. During this period, 10/102 patients died. Cysteamine has been used by 81/102 patients (20 children started the therapy under 2 years of age). Growth parameters were improved by cysteamine, mainly in the youngest patients. We used recombinant growth hormone in 15 patients with persistent low growth velocity and stature z score under 2.5%. We could also observe a delay in appearance of extra-renal complications in patients receiving cysteamine.

Conclusion: Our study demonstrates the importance of a multi-center study for recruitment, diagnosis and management of rare diseases. This study promotes access to the adequate treatment with profound impact on the quality of life.

Related information

Cited in Books
MedGen
PubChem Compound
PubChem Compound (MeSH Keyword)
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LinkOut – more resources

Full Text Sources

S. Karger AG, Basel, Switzerland

Medical

Genetic Alliance

MedlinePlus Health Information

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EVENTO

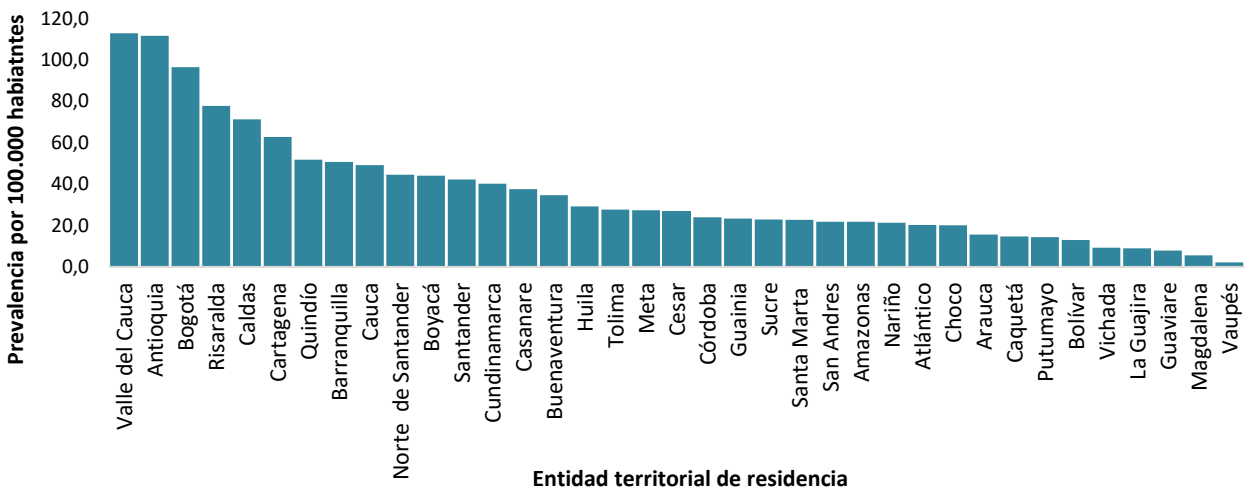
ENFERMEDADES HUÉRFANAS-RARAS

Colombia, periodo epidemiológico XIII, 2019

31.213

Casos notificados desde 2016 hasta periodo epidemiológico XIII de 2019

¿Cómo se **comporta** el evento?



Prevalencia de enfermedades huérfanas - raras, según entidad territorial de residencia, Colombia, 2016 hasta periodo epidemiológico XIII de 2019

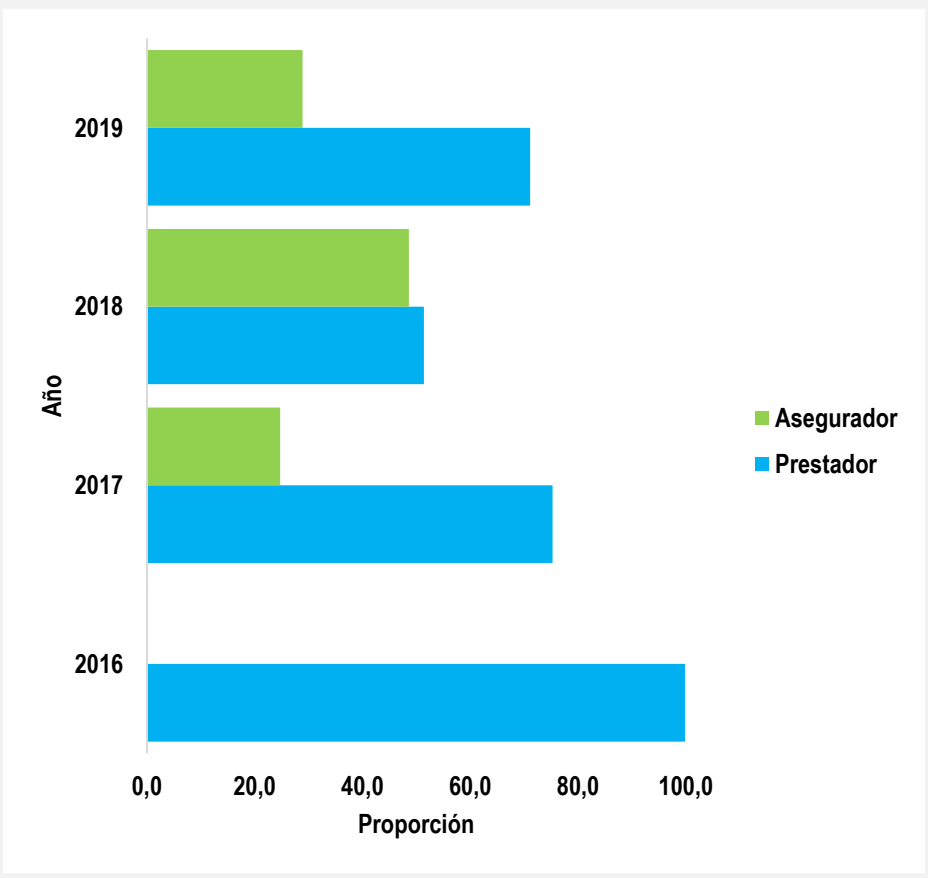
Año	Casos	Incidencia
2016	3151	6,5
2017	4189	8,5
2018	5085	10,2
2019	5514	10,9

Incidencia de enfermedades huérfanas - raras, según entidad territorial de residencia, Colombia, hasta periodo epidemiológico XIII 2016-2019
Tasa por 100.000 habitantes

Prevalencia por 100.000 habitantes
Colombia, hasta PE XIII de 2019

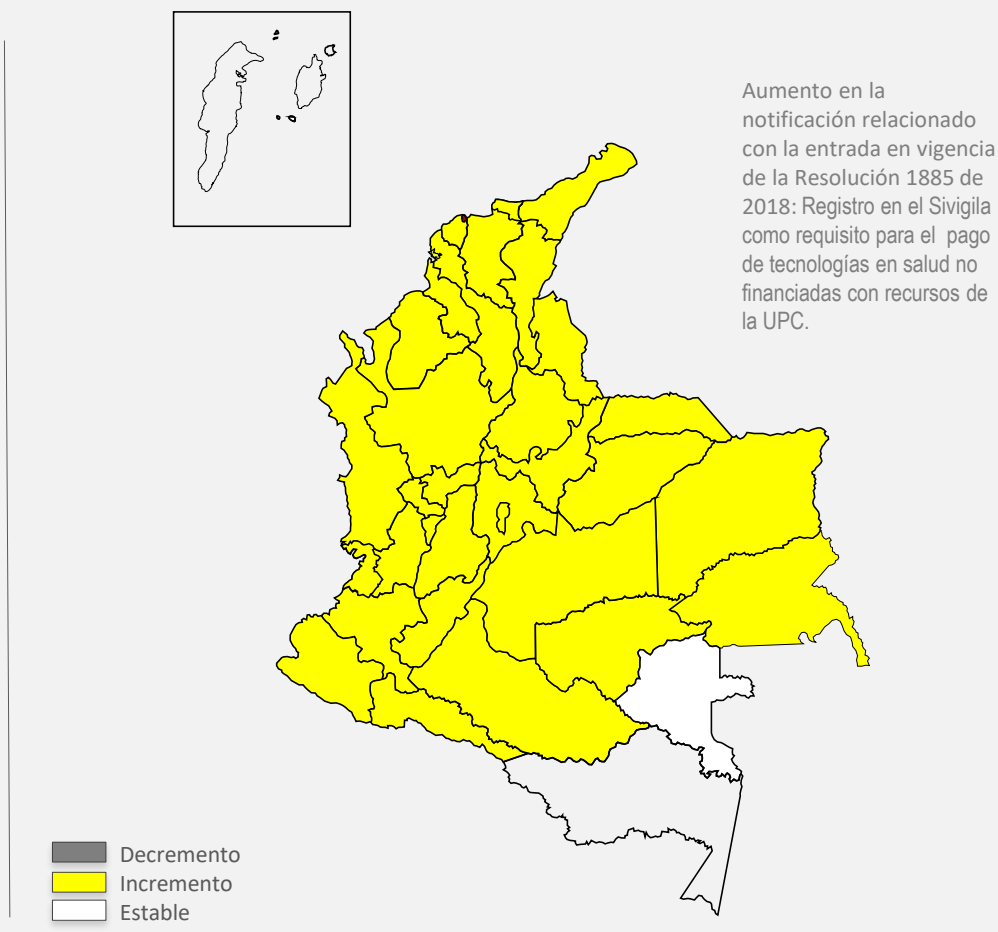
62,3

Entidad **notificadora**



Proporción de notificación por entidad notificadora, enfermedades huérfanas - raras, Colombia, 2016 hasta periodo epidemiológico XIII de 2019

Comportamientos **inusuales**



Aumento en la notificación relacionado con la entrada en vigencia de la Resolución 1885 de 2018: Registro en el Sivigila como requisito para el pago de tecnologías en salud no financiadas con recursos de la UPC.

Comportamiento inusuales, enfermedades huérfanas - raras, Colombia, 2016 hasta periodo epidemiológico XIII de 2019

¿Quiénes son los **afectados?**

Prevalencia por 100.000 habitantes

Mujeres — **69,9** — **17.434** casos

Hombres — **54,6** — **13.297** casos

Indígena — **9,9** — **118** casos

Afrocolombianos — **9,0** — **425** casos

Porcentajes

Confirmado por laboratorio — **43,5** — **13.580** casos

Hospitalizados — **16,6** — **5.168** casos

Menores de 5 años — **12,6** — **3.924** casos

Mayores de 65 años — **11,0** — **3.428** casos

Proporción de notificación por régimen de seguridad en salud, Colombia, 2016 hasta periodo epidemiológico XIII de 2019

Información notificada semanalmente por las entidades territoriales (ET) al Instituto Nacional de Salud (INS) a través del Sistema de vigilancia en salud pública (Sivigila). Información sujeta a cambios relacionados con ajuste de casos por las ET o las Empresas Administradores de Planes de Beneficios (EAPB).

INFORME DE
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ENFERMEDADES HUÉRFANAS-RARAS

Colombia, periodo epidemiológico XIII, 2019

31.213

Casos notificados desde 2016 hasta periodo epidemiológico XIII de 2019

Ficha técnica

Este informe corresponde a la información de SIVIGILA a periodo XIII de 2019.

Los datos fueron recolectados por los médicos especialistas de las Unidades Primerias Generadoras de Datos (UPGD) y Unidades Informadoras (UI); la información fue digitada y notificada en el aplicativo Sivigila para su reporte semanal al INS.

El plan de análisis incluyó la descripción de los casos en persona, tiempo y lugar, análisis de tendencia y medidas de ocurrencia.

Los comportamiento inusuales se definieron mediante la metodología de Poisson.

Las proporciones fueron calculadas con base en el total de casos notificados en el periodo.

Los denominadores para el calculo de las prevalencias fueron las proyecciones DANE de la población a mitad de periodo (2017).

Se anexa la tabla que incluye la proporción de notificación de todas las enfermedades huérfanas en el periodo de análisis.

Nidia Esperanza González Toloza
ngonzalezt@ins.gov.co
Grupo de Enfermedades No Transmisibles
Dirección de Vigilancia y Análisis del Riesgo en Salud Publica

Instituto Nacional de Salud
Correo electrónico:
contactenos@ins.gov.co
Teléfono: (1) 220 77 00
Ext. 1405 - 1431
Bogotá, COLOMBIA
www.ins.gov.co
Línea gratuita nacional:
01 8000 113 400

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ENFERMEDADES HUÉRFANAS-RARAS

Colombia, periodo epidemiológico XIII, 2019

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Casos notificados desde 2016 hasta periodo epidemiológico XIII de 2019

ANEXO 1. Proporción de notificación de enfermedades huérfanas - raras, Colombia, 2016 hasta periodo epidemiológico XIII de 2019

No.	Enfermedad Huérfana - Rara	Casos	%
1	Esclerosis Multiple	2558	8,20
2	Sindrome de Guillain-Barre	1522	4,88
3	Enfermedad de Von Willebrand	1291	4,14
4	Deficit congenito del factor VIII	1219	3,91
5	Drepanocitosis	885	2,84
6	Displasia broncopulmonar	724	2,32
7	Enfermedad de Crohn	670	2,15
8	Cirrosis biliar primaria	626	2,01
9	Fibrosis quistica	608	1,95
10	Esclerosis lateral amiotrofica	607	1,94
11	Hepatitis cronica autoinmune	599	1,92
12	Miastenia grave	573	1,84
13	Reumatismo psoriasico	524	1,68
14	Esclerosis sistemica cutanea limitada	505	1,62
15	Enfermedad de Devic	498	1,60
16	Esclerosis sistemica cutanea difusa	433	1,39
17	Distonia no especificada	418	1,34
18	Hipogamaglobulinemia inespecifica	393	1,26
19	Acromegalia	385	1,23
20	Angioedema hereditario	351	1,12
21	Esclerosis multiple - ictiosis - deficiencia del factor VIII	346	1,11
22	Artritis juvenil idiopatica de inicio sistemico	338	1,08
23	Microtia	301	0,96
24	Deficit congenito del factor IX	301	0,96
25	Sindrome de Turner	300	0,96
26	Fibrosis pulmonar idiopatica	300	0,96
27	Hiperplasia suprarrenal congenita	280	0,90
28	Polineuropatia desmielinizante inflamatoria cronica	260	0,83
29	Hipertension arterial pulmonar idiopatica	227	0,73
30	Distonia focal	212	0,68
31	Neurofibromatosis	208	0,67
32	Dermatomiositis	187	0,60
33	Atresia biliar	186	0,60
34	Enfermedad de Fabry	184	0,59
35	Mucopolisacaridosis tipo 4	180	0,58
36	Otras Acromegalias No especificadas	180	0,58
37	Hemoglobinuria paroxistica nocturna	177	0,57
38	Inmunodeficiencia primaria no especificada	164	0,53
39	Osteogenesis imperfecta	159	0,51
40	Sindrome hemolitico uremico atipico	153	0,49
41	Enfermedad de Wegener	148	0,47
42	Estatura baja por anomalia cualitativa de hormona de crecimiento	147	0,47
43	Enfermedad mixta del tejido conectivo	147	0,47
44	Gastrosquisis	144	0,46
45	Poliartritis factor reumatoide negativo	142	0,45
46	Enfermedad de Huntington	142	0,45
47	Poliartritis factor reumatoide positivo	141	0,45
48	Hipertensión Pulmonar Tromboembólica Crónica	137	0,44
49	Vasculitis	134	0,43
50	Porfiria aguda intermitente	131	0,42
51	Purpura de Henoch-Schoenlein	128	0,41
52	Enfermedad de Gaucher	127	0,41
53	Penfigo vulgar	120	0,38
54	Hipertension arterial pulmonar idiopatica y/o familiar	118	0,38
55	Distrofia muscular no especificada	116	0,37
56	Distrofia muscular tipo Duchenne	115	0,37
57	Enfermedad de Still del adulto	113	0,36
58	Atrofia optica	101	0,32
59	Sindrome del injerto contra huesped	96	0,31
60	Enfermedad de Behçet	92	0,29
61	Enfermedad de Hirschsprung	87	0,28
62	Sindrome de West	84	0,27
63	Polimiositis	79	0,25
64	Aplasia medular idiopatica	79	0,25
65	Beta-talasemia	76	0,24
66	Enfermedad de Takayasu	75	0,24
67	Sindrome de intestino corto	73	0,23
68	Enfermedad de Cushing	72	0,23
69	Deficit congenito del factor VII	71	0,23
70	Anemia de Fanconi	71	0,23
71	Otras alteraciones cromosomicas no especificadas	70	0,22
72	Acondroplasia	69	0,22
73	Sindrome CREST	68	0,22
74	Enfermedad de Gaucher tipo 1	66	0,21
75	Artritis relacionada con entesitis	65	0,21
76	Craneosinostosis - hidrocefalia - malformacion de Chiari I - sinostosis radioulnar	65	0,21
77	Deficit congenito del factor XI	62	0,20
78	Distrofia muscular congenita	61	0,20
79	Sindrome de Marfan	61	0,20
80	Inmunodeficiencia comun variable	60	0,19
81	Histiocitosis de celulas de Langerhans	59	0,19
82	Polidactilia en espejo - segmentacion vertebral anomalias de los miembros	59	0,19
83	Siringomielia	59	0,19
84	Esclerosis tuberosa	58	0,19
85	Lipodistrofia no especificada	58	0,19
86	Sindrome de Marinesco-Sjogren	55	0,18
87	Enfermedad de las neuronas motoras patron Madras	55	0,18
88	Queratoconjuntivitis atopica	54	0,17
89	Mucopolisacaridosis tipo 2	53	0,17
90	Inmunodeficiencia por deficit selectivo de anticuerpos anti-polisacaridos	51	0,16
91	Encefalopatia epileptica infantil temprana	51	0,16
92	Sindrome de Prader-Willi	50	0,16
93	Sindrome de Rett	49	0,16
94	Sindrome de Moebius	49	0,16
95	Monosomia 22q11	47	0,15
96	Estenosis pulmonar valvular	46	0,15
97	Sindrome de Noonan	46	0,15
98	Trastorno del metabolismo de los aminoacidos no especificado	45	0,14
99	Hipoglucemia hiperinsulinemica persistente de la infancia	43	0,14
100	Esferocitosis hereditaria	43	0,14

No.	Enfermedad Huérfana - Rara	Casos	%
101	Sarcoidosis	42	0,13
102	Hipospadias - hipertelorismo - coloboma y sordera	42	0,13
103	Disquinesia ciliar primaria	42	0,13
104	Penfigo foliaceo	42	0,13
105	Hipercolesterolemia familiar homocigota	41	0,13
106	Sindrome de aspiracion de meconio	40	0,13
107	Mucopolisacaridosis tipo 6	39	0,12
108	Malformacion de Ebstein	39	0,12
109	Mucopolisacaridosis no especificada	38	0,12
110	Sindactilia no especificada	37	0,12
111	Enfermedades hematologicas no especificadas	37	0,12
112	Sindrome de Evans	37	0,12
113	Enfermedad de Pompe	37	0,12
114	Agenesia de cuerpo calloso - neuropatia	36	0,12
115	Distrofia muscular de Duchenne y Becker	36	0,12
116	Epilepsia mioclonica de la infancia	36	0,12
117	Retraso mental ligado al cromosoma X no especificado	35	0,11
118	Atrofia muscular espinal proximal de tipo 1	35	0,11
119	Hiperglicinemia no cetosica	35	0,11
120	Paralisis supranuclear progresiva	34	0,11
121	Sindrome de Lennox-Gastaut	34	0,11
122	Apnea de la prematuridad (AOP)	33	0,11
123	Sindrome Klippel Trenaunay Weber	32	0,10
124	Colangitis esclerosante	32	0,10
125	Sindrome de Angelman	32	0,10
126	Anemia hemolitica debido a deficit de piruvato quinasa de los globulos rojos	31	0,10
127	Ictiosis atresia biliar	31	0,10
128	Hipogamaglobulinemia de la infancia (transitoria)	31	0,10
129	Artrogriposis no especificado	30	0,10
130	Sindrome Klippel Trenaunay Servelle	30	0,10
131	Mastocitosis	30	0,10
132	Fibrosis pulmonar - inmunodeficiencia - disgenesia gonadal	30	0,10
133	Otras ataxias hereditarias no especificadas	30	0,10
134	Acalasia primaria	30	0,10
135	Raquitismo Hipofosfatemico Familiar Ligado al Cromosoma X	29	0,09
136	Enfermedad de Von Willebrand adquirida	29	0,09
137	Deficit congenito del factor XIII	29	0,09
138	Deficit congenito del factor V	29	0,09
139	Amiloidosis secundaria	29	0,09
140	Sindrome de Goldenhar	29	0,09
141	Distonias mixtas	28	0,09
142	Lipomatosis encefalocraneocutanea	27	0,09
143	Porfiria hepatica cronica	27	0,09
144	Ataxia de Friedreich	27	0,09
145	Atrofia muscular espinal proximal de tipo 2	27	0,09
146	Artrogriposis multiple congenita - cara de silbido	26	0,08
147	Mielofibrosis con metaplasia mielocitoide	26	0,08
148	Miopatia con inclusiones reductoras	25	0,08
149	Demencia frontotemporal	25	0,08
150	Gastroenteritis eosinofilica	25	0,08
151	Leucodistrofia no especificada	25	0,08
152	Sindrome de Williams	25	0,08
153	Trisomia 18	25	0,08
154	Sindrome de Alport	25	0,08
155	Sindrome de Alagille	25	0,08
156	Disautonomia familiar	24	0,08
157	Malformacion linfatica	24	0,08
158	Mucolipidosis no especificada	24	0,08
159	Paraplejia espastica no especificada	24	0,08
160	Bajo peso al nacer - enanismo -disgammaglobulinemia	22	0,07
161	Trastornos del ciclo de la urea	22	0,07
162	Otras ataxias espinocerebelosas no especificadas	22	0,07
163	Sindrome de Pierre Robin aislado	22	0,07
164	Distrofia miotonica de Steinert	22	0,07
165	Enfermedad de Wilson	22	0,07
166	Ictiosis no especificada	21	0,07
167	Albinismo oculo-cutaneo	21	0,07
168	Linfedema congenito	21	0,07
169	Epidermolisis ampollosa distrofica	21	0,07
170	Sindrome de Bartter	21	0,07
171	Telangiectasia epileptica	21	0,07
172	Deficiencia selectiva de IgA	21	0,07
173	Homocistinuria clasica por deficit de cistationina betasintasa	21	0,07
174	Diabetes insipida nefrogenica	21	0,07
175	Fibrosis pulmonar - hiperplasia hepatica - hipoplasia de medula osea	20	0,06
176	Delecion 22q13	20	0,06
177	Esclerosis lateral primaria	20	0,06
178	Enfermedad mitocondrial no especificada	20	0,06
179	3MC Sindrome de Deficiencia COLEC11	20	0,06
180	Sindrome de Tourette	19	0,06
181	Sindrome de Cornelia de Lange	19	0,06
182	Sindrome H	19	0,06
183	Agammaglobulinemia ligada a X	19	0,06
184	Atrofia muscular espinal proximal de tipo 3	19	0,06
185	Retraso mental ligado al cromosoma X - macrocefalia - macroorquidismo	19	0,06
186	Adrenoleucodistrofia ligado al cromosoma X	19	0,06
187	Sindrome de Cushing dependiente de ACTH	19	0,06
188	Hernia diafragmatica	19	0,06
189	Mastocitosis cutanea	19	0,06
190	Polineuropatia amiloide familiar	18	0,06
191	Sindrome de Silver-Russell	18	0,06
192	Sindrome de Churg-Strauss	18	0,06
193	Hipofosfatasia	18	0,06
194	Epidermolisis ampollosa hereditaria	18	0,06
195	Diabetes neonatal - grupo hipotiroidismo congenito - glaucoma congenito - fibrosis hepatica - riñones	18	0,06
196	Sindrome de Budd-Chiari	18	0,06
197	Sindrome nefrotico idiopatico sensible a esteroides	18	0,06
198	Mucopolisacaridosis tipo 3	18	0,06
199	Urticaria solar	17	0,05
200	Glucogenosis tipo 1	17	0,05

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INFORME DE
EVENTO

ENFERMEDADES HUÉRFANAS-RARAS

Colombia, periodo epidemiológico XIII, 2019

31.213

Casos notificados desde 2016 hasta periodo epidemiológico XIII de 2019

ANEXO 1. Proporción de notificación de enfermedades huérfanas - raras, Colombia, 2016 hasta periodo epidemiológico XIII de 2019

No.	Enfermedad Huérfana - Rara	Casos	%
201	Pneumonia intersticial aguda	17	0,05
202	Trastornos hormonales no especificados	17	0,05
203	Atresia de intestino delgado	17	0,05
204	Atrofia muscular espinal proximal	17	0,05
205	Poliquistosis renal autosomica y recesiva	17	0,05
206	Displasia esqueletica no especificada	17	0,05
207	Protoporfiria eritropoyetica	17	0,05
208	Neuropatia optica hereditaria de Leber	17	0,05
209	Atresia duodenal	17	0,05
210	Craniosinostosis - malformacion de Dandy-Walker - hidrocefalia	17	0,05
211	Epidermolisis ampollosa epidermolitica	16	0,05
212	Deficit congenito de fibrinogeno	16	0,05
213	Sindrome de Sotos	16	0,05
214	Neuropatia axonal motora aguda	16	0,05
215	Onfalocele	16	0,05
216	Atresia tricuspide	15	0,05
217	Porfiria eritropoyetica congenita	15	0,05
218	Osteopetrosis - hipogammaglobulinemia	15	0,05
219	Sindrome de Beckwith-Wiedemann	15	0,05
220	Cistinosis	15	0,05
221	Periarteritis nodosa	15	0,05
222	Holoprosencefalia	15	0,05
223	Agenesia de cuerpo calloso microcefalia talla baja	15	0,05
224	Enfermedad de Moya-Moya	15	0,05
225	Ataxia cerebelosa autosomica recesiva	14	0,04
226	Plagiocefalia aislada	14	0,04
227	CAMPS (CARD14 psoriasis mediada)	14	0,04
228	Derivados mullerianos - linfangiectasia - polidactilia	14	0,04
229	Atrofia multisistemica	14	0,04
230	Sindrome de Pierre Robin - anomalia faciodigital	14	0,04
231	Microcefalia - polimicrogiria- agenesia del cuerpo calloso	14	0,04
232	Trisomia 13	14	0,04
233	Microcefalia - deficit intelectual - anomalias falangicas y neurologicas	14	0,04
234	Enfermedad de Alzheimer autosomica dominante de aparicion temprana	14	0,04
235	Neuropatia axonal aguda motora y sensitiva	14	0,04
236	Distrofia muscular de cinturas	14	0,04
237	Deficit de enzima ramificante del glucogeno	13	0,04
238	Microcefalia miocardiopatia	13	0,04
239	Policondritis atrofiante	13	0,04
240	Pityriasis rubra pilaris	13	0,04
241	Microftalmia - atrofia cerebral	13	0,04
242	Distonia-parkinsonismo de inicio rapido	13	0,04
243	Microcefalia - anomalias digitales - deficit intelectual	13	0,04
244	Ataxia telangiectasia	13	0,04
245	Trombocitopenia - sindrome de Pierre Robin	13	0,04
246	Osteocondromas multiples	12	0,04
247	Arteritis de celulas gigantes	12	0,04
248	Sindrome miastenico de Lambert-Eaton	12	0,04
249	Sindrome de Wiskott-Aldrich	12	0,04
250	Hemangiomatosis neonatal difusa	12	0,04
251	Microcefalia epilepsia retraso mental cardiopatia	12	0,04
252	Anemia hemolitica por deficit de glutation reductasa	12	0,04
253	Fenilcetonuria	12	0,04
254	Paralisis periodica no especificada	12	0,04
255	Sindrome de Wolf-Hirschhorn	12	0,04
256	Acromegalia cutis gyrata	12	0,04
257	Enfermedad de Castleman	12	0,04
258	Sindrome de Cushing	12	0,04
259	Macrocefalia - talla baja - paraplejia	12	0,04
260	Ateroesclerosis- sordera - diabetes - epilepsia - nefropatia	12	0,04
261	Hiperplasia regenerativa nodular	11	0,04
262	Monosomia 5p	11	0,04
263	Sindromes hipereosinofilicos	11	0,04
264	Deficit combinado de los factores V y VIII	11	0,04
265	Microcefalia hipoplasia pontocerebelosa disquinesia	11	0,04
266	Enfermedad de Blackfan-Diamond	11	0,04
267	Sindrome de Sjögren-Larsson	11	0,04
268	Otras atrofias musculares espinales no especificadas	11	0,04
269	Enfermedad de Niemann-Pick tipo C	11	0,04
270	Enfermedad granulomatosa cronica	11	0,04
271	Trastornos del metabolismo de los acidos grasos	11	0,04
272	Displasia acromesomelica tipo Hunter - Thompson	10	0,03
273	Sindrome de Ehlers-Danlos tipo hiperlaxitud – TIPO III	10	0,03
274	Ictiosis lamelar	10	0,03
275	Atresia de coanas	10	0,03
276	Sindrome de Kabuki make up	10	0,03
277	Enfermedad de Buerger	10	0,03
278	Paralisis supranuclear progresiva - sindrome corticobasal	10	0,03
279	Sindrome de Poland	10	0,03
280	Sindrome de Aicardi	10	0,03
281	Desordenes lisosomales no especificados	10	0,03
282	Sindrome de Apert	10	0,03
283	Sindrome de Leigh	10	0,03
284	Lipofuscinosis neuronal ceroidea juvenil	10	0,03
285	Cataratas-glaucoma	10	0,03
286	Trastorno inmunoneurologico ligado al cromosoma X	10	0,03
287	Demencia frontotemporal y parkinsonismo ligado al cromosoma 17	10	0,03
288	Autismo mancha en vino de Oporto	10	0,03
289	Enfermedad de Creutzfeldt-Jakob	10	0,03
290	Sindrome de Ehlers-Danlos tipo clasico – TIPO I Y II	10	0,03
291	Pancreatitis cronica hereditaria	10	0,03
292	Sindrome de Joubert	10	0,03
293	Histiocitosis azul marino	10	0,03
294	Sindrome de Ehlers-Danlos de tipo vascular	10	0,03
295	AD-HIES (Sindrome de Hiper IgE) Sindrome Job	10	0,03
296	Enfermedad de Darier	9	0,03
297	Hipercolesterolemia debido a deficiencia de colesterol 7-alfa-hidroxilasa	9	0,03
298	Neuropatia motriz multifocal con bloqueo de conduccion	9	0,03
299	Sindrome de Sturge Weber	9	0,03
300	Sindrome triple A	9	0,03

No.	Enfermedad Huérfana - Rara	Casos	%
301	Sindrome de Gorlin	9	0,03
302	Poliposis adenomatosa familiar	9	0,03
303	Sindromes miastenicos congenitos	9	0,03
304	VACTERL hidrocefalia	9	0,03
305	Macroglobulinemia de Waldenström	9	0,03
306	Agenesia renal bilateral	9	0,03
307	Epidermolisis ampollar adquirida	9	0,03
308	Sindrome de Rubinstein-Taybi	9	0,03
309	Otros trastornos del metabolismo de los carbohidratos no especificados	9	0,03
310	Coartacion atipica de aorta	9	0,03
311	Glucogenosis tipo 2	9	0,03
312	Agamaglobulinemia (XLA)- Deficiencia BTK	9	0,03
313	Sindrome CHARGE	9	0,03
314	Deficiencia de C1 inhibidor	8	0,03
315	Mastocitosis sistemica	8	0,03
316	Deficiencia de anticuerpos especificos (normal igG y celulas B)	8	0,03
317	Linfangioleiomiomatosis	8	0,03
318	Aniridia	8	0,03
319	Pseudomixoma peritoneal	8	0,03
320	Sindrome hipereosinofilico idiopatico	8	0,03
321	Desprendimiento de retina regmatogeno autosomico dominante	8	0,03
322	Sindrome de Gorham Stout	8	0,03
323	Enfermedad de Pelizaeus-Merzbacher	8	0,03
324	Encondromatosis	8	0,03
325	Lipofuscinosis neuronal ceroide tardia infantil	8	0,03
326	Distrofia facioescapulohumeral	8	0,03
327	Acondroplasia severa - retraso del desarrollo - acantosis nigricans	8	0,03
328	Sindrome de Coffin Siris	8	0,03
329	Sindrome de microdelecion 2q37	8	0,03
330	Inmunodeficiencia combinada severa ligado a deficit de adenosina desaminasa	8	0,03
331	Enfermedad de Rendu-Osler-Weber	8	0,03
332	Eritrodermia congenita ictiosiforme ampollosa	8	0,03
333	Sindrome de Bardet-Biedl	8	0,03
334	Displasia ectodermica no especificada	8	0,03
335	Ataxia espinocerebelosa autosomica dominante	8	0,03
336	Distrofia muscular congenita tipo 1A	8	0,03
337	Distrofia muscular de Emery Dreifuss	8	0,03
338	Agammaglobulinemia - microcefalia - craneosinostosis - dermatitis severa	8	0,03
339	Sindrome de microdelecion 15q24	8	0,03
340	Penfigoide bulloso	8	0,03
341	Leucodistrofia - paraplejia espastica - distonia	7	0,02
342	Incontinentia pigmenti	7	0,02
343	Sindrome de Gitelman	7	0,02
344	Angioedema adquirido	7	0,02
345	Deficit congenito del factor II	7	0,02
346	Galactosemia	7	0,02
347	Porfiria cutanea tarda (PCT)	7	0,02
348	Enfermedad de Caroli	7	0,02
349	Retraso mental y del crecimiento - disostosis mandibulo facial - microcefalia - fisura palatina	7	0,02
350	Osteocraneoestenosis	7	0,02
351	3-metilcrotonil glicinuria	7	0,02
352	Enfermedad de almacenamiento de glucogeno por deficit de fosforilasa quinasa muscular	7	0,02
353	Sindrome de Weaver Williams	7	0,02
354	Hidrocefalia talla alta hiperlaxitud	7	0,02
355	Anomalias cardiacas - heterotaxia	7	0,02
356	Sindrome de hiper-IgE autosomico dominante	7	0,02
357	Hirschsprung - hipoplasia de uñas - dismorfia	7	0,02
358	Paraplejia espastica familiar	7	0,02
359	Displasia ectodermica - con inmunodeficit anhidrotico	7	0,02
360	Distrofia muscular de cinturas autosomica recesiva tipo 2A	7	0,02
361	Sindrome de Parkes Weber	7	0,02
362	Vasculitis leucocitoclastica hipocomplementemica	7	0,02
363	Enfermedad de Crouzon	6	0,02
364	Osteogenesis imperfecta - retinopatia - convulsiones - deficit intelectual	6	0,02
365	Problemas de crecimiento - braquidactilia - dismorfismo	6	0,02
366	Sindrome W	6	0,02
367	Neuropatia visceral - anomalias cerebrales - dismorfismo facial - retraso en el desarrollo	6	0,02
368	Crioglobulinemia mixta	6	0,02
369	Síndrome de Microduplicacion Xq28 distal	6	0,02
370	Neuropatia autonomica y sensitiva hereditaria 2	6	0,02
371	Sindrome de autismo y macrocefalia	6	0,02
372	Obstrucción de Arterias Pulmonares por Estenosis Congénita de Arterias Pulmonares	6	0,02
373	Nevus melanocitico congenito grande	6	0,02
374	Atrofia muscular espinal proximal infantil autosomica dominante	6	0,02
375	Distrofia muscular congenita de Ullrich	6	0,02
376	Miopatia ligada al cromosoma X con atrofia del musculo postural	6	0,02
377	Craneosinostosis calcificaciones intracraneales	6	0,02
378	Miopatia tipo Bethlem	6	0,02
379	Sindrome MELAS	6	0,02
380	Monosomia 18p	6	0,02
381	Enfermedar tubular renal - cardiomiopatia	6	0,02
382	Deficit congenito de proteina C	6	0,02
383	Braquidactilia de Hirschsprung	6	0,02
384	Sindrome de microdelecion 2q24	6	0,02
385	Neuropatia sensorial y motora de inicio facial	6	0,02
386	Neurofibromatosis tipo 2	6	0,02
387	Macrotrombocitopenia con formacion anomala de proplaquetas autosomica dominante	6	0,02
388	Sindrome de Miller Dieker	6	0,02
389	Hirschsprung polidactilia sordera	6	0,02
390	Cardiopatia congenita - miembros cortos	6	0,02
391	Enfermedad de Niemann-Pick	6	0,02
392	Esclerosis endosteal - Hipoplasia cerebelar	6	0,02
393	Paralisis periodica hipocalemica	6	0,02
394	Disqueratosis congenita	6	0,02
395	Sindrome de Coffin-Lowry	6	0,02
396	Anencefalia/exencefalia aislada	6	0,02
397	Trisomia 8q	6	0,02
398	Sindrome de Sezary	6	0,02
399	Deficit de N-acetil-alfa-D-galactosaminidasa	6	0,02
400	Anemia hemolitica no esferocitica por deficit de hexoquinasa	6	0,02

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INFORME DE EVENTO

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Colombia, periodo epidemiológico XIII, 2019

31.213

Casos notificados desde 2016 hasta periodo epidemiológico XIII de 2019

ANEXO 1. Proporción de notificación de enfermedades huérfanas - raras, Colombia, 2016 hasta periodo epidemiológico XIII de 2019

No.	Enfermedad Huérfana - Rara	Casos	%
401	Síndrome de NLRP1 Autoinflamación con artritis y disqueratosis	5	0,02
402	Sindrome de Rett atipico	5	0,02
403	Agamaglobulinemia (sin bases moleculares conocidas)	5	0,02
404	Anoftalmia - microftalmia atresia esofagica	5	0,02
405	Sindrome KBG	5	0,02
406	Lisencefalia tipo 2	5	0,02
407	Sindrome de Floating-Harbor	5	0,02
408	Polirradiculoneuropatia desmielinizante inflamatoria aguda	5	0,02
409	Sindrome de Secrecion inapropiada de hormona antidiuretica	5	0,02
410	Sindrome de Parsonage-Turner	5	0,02
411	Desordenes del tejido conectivo no especificados	5	0,02
412	Hipocondroplasia	5	0,02
413	Histiocitosis sinusal con linfadenopatia masiva	5	0,02
414	Neutropenia congenita grave	5	0,02
415	PLAID (mutacion en PlCG22 Hipogamaglobulinemia urticaria por frio)	5	0,02
416	Obesidad - colitis - hipotiroidismo - hipertrofia cardiaca - retraso del desarrollo	5	0,02
417	Ataxia cerebelosa autosomica recesiva - intrusion sacadica	5	0,02
418	Displasia espondiloepimetafisaria	5	0,02
419	Neurodegeneracion con acumulo cerebral de hierro	5	0,02
420	Dermatitis seborreica-like con elementos psoriasiformes	5	0,02
421	Proteinosis alveolar pulmonar idiopatica	5	0,02
422	Tirosinemia tipo 1	5	0,02
423	Sindrome de McCune-Albright	5	0,02
424	Neuropatia hereditaria con hipersensibilidad a la presion	5	0,02
425	Displasia ectodermica hipohidrotica forma dominante	5	0,02
426	Retraso mental ligado al cromosoma X - hipotonia - dismorfismo facial - comportamiento agresivo	5	0,02
427	Anemia diseritropoyetica congenita	5	0,02
428	Trastorno del metabolismo de los carbohidratos no especificado	5	0,02
429	Sindrome de microdelecion 8q22.1	5	0,02
430	Sindrome de Potocki-Shaffer	5	0,02
431	Sindrome de Wiedemann-Rautenstrauch	5	0,02
432	Sindrome de microdelecion 12q14	5	0,02
433	Diarrea intratable - atresia coanal - anomalias en los ojos	5	0,02
434	Encefalitis focal de Rasmussen	5	0,02
435	Deficiencia de dihidrolipoil deshidrogenasa	5	0,02
436	Fibrosis Retroperitoneal Idiopatica	5	0,02
437	Coloboma ocular	5	0,02
438	Sindrome de Pitt Hopkins	5	0,02
439	Enfermedad de Erdheim-Chester	5	0,02
440	Trastornos del desarrollo sexual con cariotipo 46XY por deficit de 17-beta-hidroxiesteroide deshidrogenasa	5	0,02
441	Sindrome linfoproliferativo autoinmune	5	0,02
442	Anemia de cuerpos de Heinz	5	0,02
443	Killian Pallister Nicola	5	0,02
444	Acidemia cadena media	5	0,02
445	Sindrome de aneurisma aortico de tipo Loeys-Dietz	5	0,02
446	Deficiencia de IgA con subclases de IgG	5	0,02
447	Sindrome de Klippel-Feil aislado	5	0,02
448	Otros trastornos del metabolismo de los acidos grasos	5	0,02
449	Alfa talasemia - deficit intelectual ligado al cromosoma X	5	0,02
450	Enfermedad de Niemann-Pick tipo B	4	0,01
451	Sindrome de Peutz-Jeghers	4	0,01
452	Comunicacion interauricular con defecto de conduccion	4	0,01
453	Pancreatitis aguda recurrente	4	0,01
454	Sindrome de Smith-Magenis	4	0,01
455	Sindrome de Hurler	4	0,01
456	Lipodistrofia tipo Berardinelli	4	0,01
457	Delecion 8p	4	0,01
458	Hipertensión Arterial Pulmonar Heredable	4	0,01
459	Fiebre mediterranea familiar	4	0,01
460	Deficit congenito de proteina S	4	0,01
461	Fiebre reumatica	4	0,01
462	Polisindactilia - malformacion cardiaca	4	0,01
463	Enfermedad del riñon poliquistico autosomica dominante de tipo 1 y con esclerosis tuberosa	4	0,01
464	Lesion cerebral isquemica e hipoxica neonatal	4	0,01
465	Enfermedad de Menkes	4	0,01
466	Ataxia espinocerebelosa tipo 1	4	0,01
467	Hipoparatiroidismo familiar aislado debido a agenesia de la glandula paratiroidea	4	0,01
468	Deficit de biotinidasa	4	0,01
469	Hipogonadismo hipogonadotropico congenito	4	0,01
470	Lipodistrofia parcial adquirida	4	0,01
471	Sindrome de Pfeiffer	4	0,01
472	Plagiocefalia retraso mental ligado al cromosoma X	4	0,01
473	Disgenesia del cuerpo calloso compleja ligada al cromosoma X	4	0,01
474	Miopatia hereditaria de cuerpos de inclusion - contracturas de las articulaciones - oftalmoplegia	4	0,01
475	Trastornos del metabolismo de las lipoproteinas	4	0,01
476	Disostosis acrofacial no especificada	4	0,01
477	Sindrome neuroleptico maligno	4	0,01
478	Sindrome oral-facial-digital no especificado	4	0,01
479	Sindrome de Ochoa	4	0,01
480	Distrofia muscular autosomica recesiva ligada a una epidermolisis ampollosa	4	0,01
481	Mutación de la protocadherina 19 Encefalopatía epiléptica infantil temprana 9	4	0,01
482	Sindrome de microdelecion 2p21	4	0,01
483	Deficiencia de Factor I	4	0,01
484	Calcificacion del sistema nervioso central - sordera - acidosis tubular - anemia	4	0,01
485	Enfermedad de orina con olor a jarabe de arce	4	0,01
486	Sindrome de Lesch-Nyhan	4	0,01
487	Osteocondrodisplasia hipertricosis	4	0,01
488	Dismorfia facial macrocefalia miopia Dandy Walker	4	0,01
489	Miopatia hereditaria con fallo respiratorio precoz	4	0,01
490	Sindrome de Holt-Oram	4	0,01
491	Delecion 5q35	4	0,01
492	Esquisencefalia	4	0,01
493	Sindrome de Char	4	0,01
494	Enfermedad de Dent	4	0,01
495	Acidemia glutarica I	4	0,01
496	Craneosinostosis tipo Boston	4	0,01
497	Osteopatia estriada esclerosis craneana	4	0,01
498	Anemia sideroblastica ligada al cromosoma X	4	0,01
499	Enanismo tanatoforico	4	0,01
500	Convulsiones neonatales-infantiles familiares benignas	4	0,01

No.	Enfermedad Huérfana - Rara	Casos	%
501	Distrofia muscular de cinturas autosomica recesiva tipo 2D	4	0,01
502	Retinitis pigmentaria sordera hipogenitalismo	4	0,01
503	Aciduria 3-metilglutaconica tipo 1	4	0,01
504	Sordera con aplasia del laberinto microtia y microdoncia	4	0,01
505	Acidemia propionica	4	0,01
506	Enanismo metatropico	4	0,01
507	Enfermedad de Gaucher tipo 3	4	0,01
508	Retraso mental severo - epilepsia - anomalias anales -hipoplasia de las falanges distales	4	0,01
509	Sindrome de Dubowitz	4	0,01
510	Enanismo osteocondrodisplasico - sordera - retinitis pigmentosa	4	0,01
511	Deficit congenito del factor X	4	0,01
512	Microcefalia fisura palatina autosomico dominante sindrome de	4	0,01
513	Sindrome de Ehlers-Danlos tipo cifoescoliosis – TIPO VI	4	0,01
514	Atrofia progresiva bifocal de la coroides y la retina	4	0,01
515	Duplicacion 6p	4	0,01
516	Hipopituitarismo microftalmia	4	0,01
517	Otros trastornos del metabolismo de las lipoproteinas no especificados	4	0,01
518	Piebaldismo	4	0,01
519	Progeria	4	0,01
520	Xeroderma pigmentoso	4	0,01
521	Acidemia isovalerica	4	0,01
522	Otros trastornos del metabolismo de las purinas no especificados	4	0,01
523	Enfermedad de Tay-Sachs	3	0,01
524	Inmunodeficiencia comienzo adulto	3	0,01
525	Sindrome de Camurati Engelmann	3	0,01
526	Deficiencia aislada de subclases de IgG	3	0,01
527	Sindrome PFAPA	3	0,01
528	Desordenes del sistema inmune no especificados	3	0,01
529	Sindrome de Vater-like con hipertension pulmonar anomalias de las orejas y retraso del crecimiento	3	0,01
530	Microdelecion 9q22.3	3	0,01
531	Microftalmia con anomalias de las extremidades	3	0,01
532	Ataxia cerebelosa arreflexia pie cavo atrofia optica y sordera neurosensorial	3	0,01
533	Hiperinmunoglobulinemia D con fiebre recurrente	3	0,01
534	Sindrome de Ondine	3	0,01
535	Acidemia organica no especificada	3	0,01
536	Ictiosis neonatal - colangitis esclerosante	3	0,01
537	Miositis focal	3	0,01
538	Alcaptonuria	3	0,01
539	Craneosinostosis braquidactilia	3	0,01
540	Retinosis Pigmentaria	3	0,01
541	Distrofia muscular congenita con deficit de integrina	3	0,01
542	Inmunodeficiencia por expresion deficiente del HLA de clase 2	3	0,01
543	Sindrome CLAPO	3	0,01
544	Sindrome de Usher tipo 2	3	0,01
545	Distrofia muscular de cinturas autosomica recesiva tipo 2M	3	0,01
546	Esquizofrenia retraso mental sordera retinitis	3	0,01
547	Deficit de guanidinoacetato metiltransferasa	3	0,01
548	Xerodermia pies cavos esmalte anomalia de	3	0,01
549	Sindrome de inmunodeficiencia primaria por deficit de p14	3	0,01
550	Enfermedad de la arteria coronaria - hiperlipidemia - hipertension - diabetes - osteoporosis	3	0,01
551	Sindrome de Aicardi-Goutieres	3	0,01
552	Asociación VATER con macrocefalia y ventriculomegalia	3	0,01
553	Sindrome de Seckel	3	0,01
554	Displasia espondiloepifisaria congenita	3	0,01
555	Sindrome de Usher no especificado	3	0,01
556	Degeneracion cortico-basal	3	0,01
557	Osteomielitis multifocal cronica recurrente juvenil	3	0,01
558	Retraso mental dismorfia hipogonadismo diabetes mellitus	3	0,01
559	Otras atelosteogenesis no especificadas	3	0,01
560	Atrofia muscular espinal - malformacion de Dandy- Walker - cataratas	3	0,01
561	Agenesia gonadal	3	0,01
562	Enfermedad de Thomsen y Becker	3	0,01
563	NOMID or CINCA	3	0,01
564	Cromosoma 18 en anillo	3	0,01
565	Sindrome de Acalasia microcefalia	3	0,01
566	Ictiosis ligada al cromosoma X	3	0,01
567	Mastocitosis sistemica indolente	3	0,01
568	Sindrome de insensibilidad a los androgenos	3	0,01
569	Hemimelia tibial	3	0,01
570	Sindrome de rubeola congenita	3	0,01
571	Síndrome Cardiofacio Cutaneo	3	0,01
572	Sindrome de la persona rigida	3	0,01
573	Abscesos asepticos sensibles a corticosteroides	3	0,01
574	Sindrome de Hiper igD	3	0,01
575	Sindrome de Kearns-Sayre	3	0,01
576	Trastorno de la fosforilacion oxidativa mitocondrial debido a anomalias del ADN nuclear	3	0,01
577	Acrocefalosindactilia (termino generico)	3	0,01
578	Glaucoma - apnea del sueño	3	0,01
579	Estatura baja - cuello ancho - trastorno cardiaco	3	0,01
580	Conjuntivitis leñosa	3	0,01
581	Osteodistrofia hereditaria de Albright	3	0,01
582	Pulgares en aduccion - artrogriposis tipo Dundar	3	0,01
583	Sindrome Maroteaux Lamy	3	0,01
584	Retraso global del desarrollo - osteopenia - defecto ectodermico	3	0,01
585	Feocromocitoma secretante	3	0,01
586	Retraso mental ligado al cromosoma X - hipogonadismo - ictiosis - obesidad - baja estatura	3	0,01
587	Displasia renal-hepatica-pancreatica - quistes de Dandy-Walker	3	0,01
588	Retraso mental ligado al cromosoma X - malformacion de Dandy Walker - Enfermedad de los ganglios basales - Convulsiones	3	0,01
589	Sindrome de Wolfram	3	0,01
590	Ataxia espinocerebelosa infantil	3	0,01
591	Anoftalmia - microftalmia aislada	3	0,01
592	Hemicrania paroxistica	3	0,01
593	Dandy Walker polidactilia postaxial	3	0,01
594	Deficiencia de Lipasa Acida	3	0,01
595	Variante neurologica del Sindrome de Waardenburg-Shah	3	0,01
596	Miopatia nemalinica	3	0,01
597	Osteogenesis imperfecta microcefalia cataratas	3	0,01
598	Epidermodisplasia verruciforme 1 (Mutacion en EVER 1)	3	0,01
599	Enfermedad de sintesis de acidos biliares	3	0,01
600	Ataxia espinocerebelosa tipo 3	3	0,01

INS

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INFORME DE
EVENTO

ENFERMEDADES HUÉRFANAS-RARAS

Colombia, periodo epidemiológico XIII, 2019

31.213

Casos notificados desde 2016 hasta periodo epidemiológico XIII de 2019

ANEXO 1. Proporción de notificación de enfermedades huérfanas - raras, Colombia, 2016 hasta periodo epidemiológico XIII de 2019

No.	Enfermedad Huérfana - Rara	Casos	%
601	Paquioniquia congenita	3	0,01
602	Sindrome de Cantrell Haller Ravitsch	3	0,01
603	Cabello escaso - baja estatura - pulgares hipoplasticos - hipodoncia - anomalias de la piel	3	0,01
604	Sindrome de Crigler-Najjar	3	0,01
605	Acidemia metilmalonica - vitamina B12 sensible tipo cbl A	3	0,01
606	Anquiloblefaron filiforme - imperforacion anal	3	0,01
607	Distrofia muscular congenita por deficit de laminas A/C	3	0,01
608	Deficit congenito de sintesis de acidos biliares tipo 4	3	0,01
609	Estatura baja - defectos en el cerebelo e hipofisis - silla turca pequeña	3	0,01
610	Sindrome de Ellis-Van Creveld	3	0,01
611	Macrocefalia - deficiencia inmunitaria - anemia	3	0,01
612	Epidermolisis ampollosa juntural	3	0,01
613	Utero doble-hemivagina-agenesia renal	3	0,01
614	Sindrome de la cimitarra	3	0,01
615	Sindrome de Lewis-Summer	3	0,01
616	Displasia inmuno osea de Schimke	3	0,01
617	Paraplejia-braquidactilia-epifisis en cono	2	0,01
618	Enfermedad de deposito de glucogeno por deficit de LAMP-2	2	0,01
619	Sindrome de Pearson	2	0,01
620	Deficit de 3-hidroxiacil-CoA deshidrogenasa de acidos grasos de cadena larga	2	0,01
621	Dermatosis pustulosa subcornea	2	0,01
622	Sindrome de Bernard-Soulier	2	0,01
623	AR-HIES (Sindrome de Hiper IgE) DOCK8	2	0,01
624	Estesioneuroblastoma	2	0,01
625	Deficiencia de CD40 ligando	2	0,01
626	Disquinesia paroxistica no cinesigenica (PNKD)	2	0,01
627	Miocardiopatia restrictiva aislada familiar	2	0,01
628	Albinismo cutaneo fenotipo Hermine	2	0,01
629	Sindrome cerebro-oculo-nasal	2	0,01
630	Trastorno del desarrollo sexual - retraso mental	2	0,01
631	Anemia microcitica con sobrecarga hepatica de hierro	2	0,01
632	Sindrome de Werner	2	0,01
633	Sindrome de Myhre Ruvalcaba Graham	2	0,01
634	Anemia hemolitica por deficit de glucosa fosfato isomerasa	2	0,01
635	Sindrome de Kleefstra	2	0,01
636	Microtia anomalias esqueleticas talla baja	2	0,01
637	Microtia bilateral - sordera - paladar hendido	2	0,01
638	Sindrome acro-reno-ocular	2	0,01
639	Malabsorcion de glucosa-galactosa	2	0,01
640	Deficit de adhesion leucocitaria tipo I	2	0,01
641	Demencia frontotemporal con inclusiones Tau	2	0,01
642	Proteinosis alveolo-pulmonar (mutacion en CSF2RA)	2	0,01
643	Hiperostosis vertebral anquilosante con tilosis	2	0,01
644	Mioclonia ataxia cerebelosa sordera	2	0,01
645	Displasia de timo - riñon - ano - pulmon	2	0,01
646	Sindrome de Lipodistrofia - retraso mental - sordera	2	0,01
647	Deficiencia selectiva de IgM	2	0,01
648	Diarrea congenita con malabsocion debido a insuficiencia de celulas enteroendocrinas	2	0,01
649	Camptodactilia - talla alta - escoliosis - perdida de audicion	2	0,01
650	Aplasia cutis congenita de miembros forma recesiva	2	0,01
651	Encefalomiopatia mitocondrial infantil asociada con FASTKD2	2	0,01
652	Retraso en el desarrollo - sordera tipo Hildebrand	2	0,01
653	Enfermedad de Coats	2	0,01
654	Epilepsia con crisis parciales migrantes del lactante	2	0,01
655	Hipotonia con acidemia lactica e hiperamonemia	2	0,01
656	Hemimelia fibular	2	0,01
657	Sindrome de Li-Fraumeni	2	0,01
658	Condrodisplasia punctata ligada al cromosoma X dominante	2	0,01
659	Hipertermia maligna artrogriposis torticolis	2	0,01
660	Queratoderma palmoplantar difuso - acrocianosis	2	0,01
661	Cataratas nefropatia encefalopatia	2	0,01
662	Hipoperistaltismo intestinal - microcolon - hidronefrosis	2	0,01
663	Embriopatia por virus de la varicela	2	0,01
664	Talla baja tipo Bruselas	2	0,01
665	Cistinuria	2	0,01
666	Xantomatosis cerebrotendinosa	2	0,01
667	Anomalias del arco aortico- dismorfismo - deficit intelectual	2	0,01
668	Sindrome de Waardenburg-Shah	2	0,01
669	Distrofia muscular de cinturas autosomica recesiva tipo 2E	2	0,01
670	Afasia progresiva no fluida	2	0,01
671	Agenesia parcial de pancreas	2	0,01
672	Sindrome de Rothmund-Thomson	2	0,01
673	Sindrome de Wieacker-Wolff	2	0,01
674	Taquicardia ventricular polimorfica catecolinergica	2	0,01
675	Sindrome de Smith-Lemli-Opitz	2	0,01
676	Sindrome de Kallmann	2	0,01
677	Distonia mioclonica 15	2	0,01
678	Desordenes peroxisomales no especificados	2	0,01
679	Cataratas microcornea	2	0,01
680	Sindrome de delecion 6q16	2	0,01
681	Síndrome de ataxia-pancitopenia	2	0,01
682	Obesidad debida a la deficiencia congenita de leptina	2	0,01
683	Distonia dopa-sensible	2	0,01
684	Sindrome de Lowry-Wood	2	0,01
685	Dermatitis granulomatosa intersticial con artritis	2	0,01
686	Cordoma	2	0,01
687	Sindrome de Cohen	2	0,01
688	Malfomacion cerebral - enfermedad cardiaca congenita	2	0,01
689	Sindrome de Fanconi asociado a cadenas ligeras Ig monoclonal	2	0,01
690	Enfermedad de Upington	2	0,01
691	Microftalmia sindromica debido a una mutacion en OTX2	2	0,01
692	Aciduria 4 hidroxi-butirica	2	0,01
693	Distrofia muscular de cinturas autosomica recesiva tipo 2I	2	0,01
694	Sindrome de Bannayan-Riley-Ruvacalva	2	0,01
695	Delecion terminal 6q	2	0,01
696	Deficit de LCAT	2	0,01
697	Atrofia optica autosomica dominante y cataratas	2	0,01
698	Cardiomiopatia - intolerancia al ejercicio por una deficiencia de glicogeno en musculo y corazon	2	0,01
699	Timoma con inmunodeficiencia	2	0,01
700	TNF receptor asociado a fiebres periodicas TRAPS	2	0,01

No.	Enfermedad Huérfana - Rara	Casos	%
701	Ptosis - estrabismo - pupilas ectopicas	2	0,01
702	Enfermedad de Sandhoff	2	0,01
703	Hiperqueratosis palmoplantar paraparesia espastica	2	0,01
704	Distrofia neuroaxonal infantil	2	0,01
705	Hermafroditismo verdadero XX	2	0,01
706	Hipertricosis lanuginosa congenita	2	0,01
707	Sindrome MERRF	2	0,01
708	Mutacion de ganancia en funcion CMC-STAT 1	2	0,01
709	Sindrome de Susac	2	0,01
710	Mastocitosis no especificada	2	0,01
711	Disgenesia gonadal anomalias multiples	2	0,01
712	Hipomielinizacion - hipogonadismo hipogonadotropico - hipodontia	2	0,01
713	Trastorno desintegrativo de la infancia	2	0,01
714	Migraña hemiplejica familiar o esporadica	2	0,01
715	Sindrome de Muckle-Wells	2	0,01
716	Deficiencia de MASP2	2	0,01
717	Sindrome de CDG tipo Ig	2	0,01
718	Hipoplasia tiroidea	2	0,01
719	Espino cerebelosa degeneracion distrofia corneal	2	0,01
720	Sindrome de Shprintzen-Goldberg	2	0,01
721	APECED (APS-1)	2	0,01
722	Sindrome de Cogan	2	0,01
723	Sindrome de Aase-Smith	2	0,01
724	AR-DKC (Mutacion en RTEL1)	2	0,01
725	Displasia ectodermica "pura" tipo cabello-uña	2	0,01
726	Osteodisplasia poliquistica lipomembranosa con leudoencefalopatia esclerosante	2	0,01
727	Sindrome de CDG	2	0,01
728	Sindrome de antisintetasas	2	0,01
729	Trigonocefalia talla baja retraso de crecimiento	2	0,01
730	Retraso mental ligado al cromosoma X - coreoatetosis - comportamiento anormal	2	0,01
731	Deficiencia de oxoacyl CoA deshidrogenasa	2	0,01
732	Distonia de torsion de aparicion temprana	2	0,01
733	Deficit de N5-metilhomocisteina transferasa	2	0,01
734	Sindrome LEOPARD	2	0,01
735	Amioplasia congenita	2	0,01
736	Atrofia muscular espinal proximal de tipo 4	2	0,01
737	Sindrome de Nevus epidermico	2	0,01
738	Tirosinemia transitoria	2	0,01
739	Distrofia muscular de cinturas autosomica dominante tipo 1A	2	0,01
740	Mielodisplasia con hipogamaglobulinemia	2	0,01
741	SCN4 todas las otras	2	0,01
742	Sindrome de Sillence	2	0,01
743	Ceguera - escoliosis- aracnodactilia	2	0,01
744	Leucodistrofia metacromatica	2	0,01
745	Miopatia mitocondrial con anemia sideroblastica	2	0,01
746	Mano hendida urinarias anomalias espina bifida anomalia de diafragma	2	0,01
747	Sindrome de Atkin Flaitz Patil Smith	2	0,01
748	Sindrome de Van Der Woude	2	0,01
749	Sindrome de Baraitser Brett Piesowicz	2	0,01
750	Distrofia de conos y bastones	2	0,01
751	Sindrome de Brown-Vialetto-van Laere	2	0,01
752	Linfedema - anomalia arteriovenosa cerebral	2	0,01
753	Retraso en el crecimiento por deficit en el factor de crecimiento insulinico de tipo 1	2	0,01
754	Sindrome de Allan-Herndon-Dudley	2	0,01
755	Megalencefalia - polimicrogiria - polidactilia postaxial - hidrocefalia	2	0,01
756	Amaurosis - hipertricosis	2	0,01
757	Sindrome de Carey-Fineman-Ziter	2	0,01
758	Sindrome de Treacher-Collins	2	0,01
759	Deficiencia de PI3 kinasa	2	0,01
760	Sindrome de Walker-Warburg	2	0,01
761	Deficiencia de proteina relacionada con el Factor H	2	0,01
762	Paralisis bulbar progresiva de la niñez	2	0,01
763	Celiaca enfermedad epilepsia calcificaciones occipitales	2	0,01
764	Quadriparesia retraso mental retinitis pigmentaria	2	0,01
765	Hiperfenilalalinemia	2	0,01
766	Deficit de transportador de creatina ligado al cromosoma X	2	0,01
767	Retraso mental ligado al cromosoma X - epilepsia - contracturas progresivas de las articulaciones - rostro tipico	2	0,01
768	Disgenesia gonadal 46 XY - neuropatia motora y sensorial	2	0,01
769	Sindrome de Duane	2	0,01
770	Queratosis folicular enanismo atrofia cerebral	2	0,01
771	Nefropatia sordera hiperparatiroidismo	2	0,01
772	Tricomegalia cataratas esferocitosis	2	0,01
773	Neurodegeneracion debida a deficit en 3-hidroxisobutiril-CoA-hidrolasa	2	0,01
774	Enfermedad de Best	2	0,01
775	Hiperoxaluria primaria de tipo 1	2	0,01
776	Hamartomatosis quistica de pulmon y riñon	2	0,01
777	Encefalopatia etilmalonica	2	0,01
778	Ictiosis congenita tipo feto Arlequin	2	0,01
779	Sindrome de Hallermann Streiff Francois	2	0,01
780	Acatalasemia	2	0,01
781	Microcefalia braquidactilia cifoescoliosis	2	0,01
782	Sindrome de Waardenburg (termino generico)	2	0,01
783	Sindrome de Jacobsen	2	0,01
784	Paniculitis histiocitica citofagica	2	0,01
785	Epilepsia microcefalia displasia esqueletica	2	0,01
786	Aniridia ataxia cerebelosa y retraso mental	2	0,01
787	Sindrome de Kasabach-Merritt	2	0,01
788	Sindrome de Zellweger	2	0,01
789	Sindrome de la piel rizada	2	0,01
790	Craneosinostosis alopecia ventriculo cerebral anormal	2	0,01
791	Obesidad debida a deficiencia de prohormona convertasa-I	2	0,01
792	Sindrome acrorenal recesivo	2	0,01
793	Mastocitosis sistemica agresiva	2	0,01
794	Anoftalmia - megalocornea - cardiopatia - anomalias esqueleticas	2	0,01
795	Coloboma microftalmia cardiopatia sordera	2	0,01
796	Sinostosis humeroradiocubital	2	0,01
797	Hipoparatiroidismo familiar aislado	2	0,01
798	Sordera - anomalias genitales - sinostosis de metacarpianos y metatarsianos	2	0,01
799	Osteocondromatosis carpotarsiana	2	0,01
800	Dacriocistitis osteopoiquilosis	2	0,01

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INFORME DE EVENTO

ENFERMEDADES HUÉRFANAS-RARAS

Colombia, periodo epidemiológico XIII, 2019

31.213

Casos notificados desde 2016 hasta periodo epidemiológico XIII de 2019

ANEXO 1. Proporción de notificación de enfermedades huérfanas - raras, Colombia, 2016 hasta periodo epidemiológico XIII de 2019

No.	Enfermedad Huérfana - Rara	Casos	%
801	Duplicacion 12p	2	0,01
802	Plaquetario familiar con predisposicion a leucemia mielogenica aguda sindrome	2	0,01
803	Anomalia de Poland	2	0,01
804	Trastorno neurometabolico por deficiencia de serina	2	0,01
805	Sindrome de Opitz ligado al cromosoma X	2	0,01
806	Acrodermatitis enteropatica	2	0,01
807	Sindrome de Pallister-Hall	2	0,01
808	Deficiencia de C3	2	0,01
809	Osteopetrosis autosomica recesiva leve forma intermedia	2	0,01
810	Mioclonia atrofia muscular distal	2	0,01
811	Desmielinizacion cerebral debido a un deficit de metionina adenosiltransferasa	2	0,01
812	Enfermedad de Krabbe	2	0,01
813	Sindrome de Cabezas	1	0,00
814	Disgenesia cerebral congenita debida a deficiencia de glutamina sintetasa	1	0,00
815	Sindrome de Ictiosis y nacimiento prematuro	1	0,00
816	Anomalia acro-pecto-renal	1	0,00
817	Hipertricosis cervical anterior aislada	1	0,00
818	Enfermedad de Wolman	1	0,00
819	Enfermedad de McCardle	1	0,00
820	Histiocitosis progresiva mucinosa hereditaria	1	0,00
821	Sindrome de deplecion del ADN mitocondrial forma encefalomiopatica con aciduria metilmalonica	1	0,00
822	Enfermedad neurodegenerativa progresiva - hiperlaxitud articular - cataratas	1	0,00
823	Queratitis estromal	1	0,00
824	Lipodistrofia familiar parcial por mutaciones en AKT2	1	0,00
825	Mutacion y delecion de la cadena pesada de ig	1	0,00
826	Mucolipidosis tipo 4	1	0,00
827	Deficiencia de STAT2	1	0,00
828	Paraplejia espastica ligada al cromosoma X tipo 2	1	0,00
829	Otras ataxias episodicas	1	0,00
830	Retraso mental ligado al cromosoma X - acromegalia - hiperactividad	1	0,00
831	Retraso mental hipotriquia braquidactilia	1	0,00
832	Metahemoglobinemia hereditaria recesiva de tipo 2	1	0,00
833	Sindrome de Fraser	1	0,00
834	Anadisplasia metafisaria	1	0,00
835	Hipomielinizacion con atrofia de los ganglios basales y del cerebelo	1	0,00
836	Agnatia holoprosencefalia situs inversus	1	0,00
837	MSMD (IL12RB)	1	0,00
838	Sindrome de Maffucci	1	0,00
839	Nail Patella like enfermedad renal	1	0,00
840	Granulomatosis autoinflamatoria infantil	1	0,00
841	Criptomicrotia braquidactilia anomalias de dermatoglifos	1	0,00
842	Lesiones ''Donut'' de la calvaria - fragilidad osea	1	0,00
843	Displasia epifisiaria-falangica en foma de angel	1	0,00
844	Fistula arteriovenosa cerebral	1	0,00
845	Deficiencia de ?c	1	0,00
846	Displasia espondilometafisaria con inmunodeficiencia combinada	1	0,00
847	Sindrome CINCA	1	0,00
848	Auriculo-osteo-displasia	1	0,00
849	Penfigoide paraneoplasico	1	0,00
850	Encefalopatia aguda necrosante familiar	1	0,00
851	Pseudohipoaldosteronismo tipo 1	1	0,00
852	Ataxia episodica tipo 3	1	0,00
853	Neuroaxonal distrofia acidosis tubular	1	0,00
854	Dilatacion aortica - hipermovilidad de las articulaciones - tortuosidad arterial	1	0,00
855	Enfermedad autoinflamatoria debido a deficiencia de antagonista del receptor de interleuquina 1	1	0,00
856	Hipogonadismo hipogonadotropico - retinitis pigmentaria	1	0,00
857	Sindrome de Nance-Horan	1	0,00
858	Trastorno del habla y del lenguaje tipo 1	1	0,00
859	Sindrome de Cobb	1	0,00
860	Displasia acromesomelica tipo Brahimi Bacha	1	0,00
861	Disostosis acrofacial tipo Nager	1	0,00
862	Sindrome de hipercoagulabilidad por deficit de glicosilfosfatidilinositol	1	0,00
863	Desordenes de los lipidos no especificados	1	0,00
864	Gigantismo cerebral quistes maxilares	1	0,00
865	Sindrome CDG tipo Ic	1	0,00
866	AD-DKC (Mutacion en TINF2)	1	0,00
867	Pulgares ausentes talla baja inmunodeficiencia	1	0,00
868	Neutropenia congenita severa bases desconocidas	1	0,00
869	Atelosteogenesis I	1	0,00
870	Lipodistrofia familiar parcial tipo Dunnigan	1	0,00
871	Displasia craneo-metafisaria	1	0,00
872	Tortuosidad de las arterias retinianas	1	0,00
873	Enfermedad de Tangier	1	0,00
874	Enfermedad de Stargardt	1	0,00
875	Hipoparatiroidismo - sordera - enfermedad renal	1	0,00
876	Acidemia metilmalonica - homocistinuria tipo cbl C	1	0,00
877	Angiomatosis cutanea y digestiva	1	0,00
878	Sindrome IBIDS	1	0,00
879	Acromelanosis	1	0,00
880	Deficiencia de GLUT1	1	0,00
881	Pseudoacondroplasia	1	0,00
882	Hiperlipoproteinemia tipo 3	1	0,00
883	Coloboma del iris con ptosis - deficit intelectual	1	0,00
884	Hipersomnia idiopatica	1	0,00
885	Disfuncion inmune - poliendocrinopatia - enteropatia ligada al cromosoma X	1	0,00
886	Deficit de adenosina monofosfato deaminasa	1	0,00
887	Sindrome letal onfalocele fisura palatina	1	0,00
888	Distrofia muscular de cinturas autosomica recesiva tipo 2L	1	0,00
889	Encefalopatia debida a deficit de GLUT1	1	0,00
890	Anemia hemolitica letal anomalias genitales	1	0,00
891	Urolitiasis 28 dihidroxi-adenina	1	0,00
892	Mucolipidosis tipo 2	1	0,00
893	Crecimiento excesivo - deficiencia de aprendizaje	1	0,00
894	Deficiencia de MBL	1	0,00
895	Queratosis palmaris et plantaris - clinodactilia	1	0,00
896	Fibrodisplasia osificante progresiva	1	0,00
897	XL-DKC	1	0,00
898	Sindrome oculo-digito-esofagico-duodenal (ODED)	1	0,00
899	Sindrome de Aarskog-Scott	1	0,00
900	Sindrome Ablefaron macrostomia	1	0,00

No.	Enfermedad Huérfana - Rara	Casos	%
901	Colestasis - retinopatia pigmentaria - fisura palatina	1	0,00
902	Tricodisplasia - amelogenesis imperfecta	1	0,00
903	Disgenesia gonadal tipo XX	1	0,00
904	Sindrome de Christian de Myer Franken	1	0,00
905	Hendidura laringotraqueoesofagica	1	0,00
906	AR-DKC (Mutacion en NOLA2)	1	0,00
907	Hidrocefalia - displasia costoventral - anomalia de Sprengel	1	0,00
908	Sindrome de la triple H (HHH)	1	0,00
909	Sindrome de Barth	1	0,00
910	Deficiencia de ?5	1	0,00
911	Enfermedad de deposito lisosomal no especificada	1	0,00
912	Cirrosis hereditaria de los niños indios de America del Norte	1	0,00
913	Leprechaunismo	1	0,00
914	Sindrome de Ehlers-Danlos tipo artrocalasia – TIPO VII	1	0,00
915	Sindrome de Pterigium antecubital	1	0,00
916	Síndrome de Bohring-Opitz	1	0,00
917	Resistencia periferica a las hormonas tiroideas	1	0,00
918	Atransferrinemia	1	0,00
919	Sindrome de Usher	1	0,00
920	Deficit de 3-hidroxi 3-metilglutaril-CoA (HMG) sintetasa	1	0,00
921	Conodisplasia craneofacial	1	0,00
922	Hipotricosis hereditaria de Marie Unna	1	0,00
923	Sindrome de Cowden	1	0,00
924	Sindrome Blau (NOD2 or CARD15)	1	0,00
925	Síndrome Pseudo TORCH 2	1	0,00
926	Hipertricosis cubital talla baja	1	0,00
927	Cromosoma 1 en anillo	1	0,00
928	Paraplejia espastica autosomica dominante tipo 8	1	0,00
929	Obesidad por deficit de pro-opiomelanocortin	1	0,00
930	Espasticidad - deficit intelectual - epilepsia ligado al cromosoma X	1	0,00
931	Insensibilidad congenita al dolor	1	0,00
932	Displasia ectodermica hipohidrosis grupo hipotiroidismo	1	0,00
933	Sindrome de Schwartz-Jampel	1	0,00
934	Blefaroptosis miopia ectopia lentis	1	0,00
935	Dermatoleucodistrofia	1	0,00
936	Miopatia distal con afectacion respiratoria precoz	1	0,00
937	Sindrome PHACE	1	0,00
938	Sindrome de Roberts	1	0,00
939	Sindrome de Costello	1	0,00
940	Retraso mental ligado al cromosoma X epilepsia psoriasis	1	0,00
941	Erliquiosis	1	0,00
942	Diatesis hemorragica por un defecto del receptor de colageno	1	0,00
943	Miopatia tibial de Udd	1	0,00
944	Interrupcion del arco aotico	1	0,00
945	Sindrome de Schinzel-Giedion	1	0,00
946	Sindrome de Goodman	1	0,00
947	Sindrome de Laron	1	0,00
948	Artrogriposis - disfuncion renal - colestasis	1	0,00
949	Sindrome de Saethre-Chotzen	1	0,00
950	Displasia osea terminal - defectos pigmentarios	1	0,00
951	Poroqueratosis palmoplantar de Mantoux	1	0,00
952	Enfermedad hepatica veno-oclusiva -inmunodeficiencia	1	0,00
953	Síndrome MIRAGE	1	0,00
954	Ictiosis alopecia ectropion retraso mental	1	0,00
955	Ataxia letal con sordera y atrofia optica	1	0,00
956	Enfermedad de la motoneurona inferior autosomica recesiva de la infancia	1	0,00
957	Osteoporosis hipopigmentacion oculo cutanea	1	0,00
958	Cutis gyrata - acantosis nigricans - craneosinostosis	1	0,00
959	Displasia mandibuloacra	1	0,00
960	Arrinia atresia de coanas microftalmia	1	0,00
961	Heterotaxia	1	0,00
962	Sindrome de Hermansky-Pudlak	1	0,00
963	Sindrome oculo osteo cutaneo	1	0,00
964	Deficiencia de Receptor BAFF	1	0,00
965	Albinismo ocular ligado al cromosoma X recesivo	1	0,00
966	Nefrosis - sordera - anomalias del tracto urinario y digitales	1	0,00
967	Linfangiectasias quisticas pulmonares	1	0,00
968	Hipoplasia pontocerebelosa tipo 6	1	0,00
969	Ulceracion umbilical atresia intestinal	1	0,00
970	Deficiencias distales de las extremidades - sindrome de micrognatia	1	0,00
971	Aracnodactilia retraso mental dismorfia	1	0,00
972	Hipoplasia cartilago cabello	1	0,00
973	Neutropenia ligada al cromosoma X / Mielodisplasia	1	0,00
974	Toraco pelvica disostosis	1	0,00
975	Macrocefalia - malformacion capilar	1	0,00
976	Sindrome acromegaloide hipertricosis	1	0,00
977	Desorden del metabolismo de los metales no especificados	1	0,00
978	Deficit de glucogeno sintasa hepatica	1	0,00
979	Sindrome CDG tipo Ia	1	0,00
980	Camptodactilia - hiperplasia del tejido fibroso - displasia esqueletica	1	0,00
981	Sindrome de EEM	1	0,00
982	Otros trastornos del ciclo de la urea no especificados	1	0,00
983	Sindrome de Hartsfield Bixler Demyer	1	0,00
984	Sindrome de Ehlers-Danlos tipo dermatosparaxis – TIPO VII C	1	0,00
985	Paraplejia espastica autosomica recesiva tipo 30	1	0,00
986	Acromatopsia	1	0,00
987	Sindrome de Simpson-Golabi-Behmel	1	0,00
988	Ictiosis ampollosa de Siemens	1	0,00
989	Enfermedad de Gaucher tipo 2	1	0,00
990	Acidemia glutarica II	1	0,00
991	Hemiplejia alternante familiar nocturna benigna infantil	1	0,00
992	Sarcosinemia	1	0,00
993	Sindrome de Neurodegerativo ligado al cromosoma X de tipo Hamel	1	0,00
994	Distrofia muscular oculofaringea	1	0,00
995	Sindrome de Ackerman	1	0,00
996	Anomalia de Duane - miopatia - escoliosis	1	0,00
997	Malformaciones del desarrollo - sordera - distonia	1	0,00
998	Sindrome de Chediak-Higashi	1	0,00
999	Amaurosis congenita de Leber	1	0,00
1000	Queratoderma palmoplantar - amiotrofia	1	0,00

INS

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INFORME DE
EVENTO

ENFERMEDADES HUÉRFANAS - RARAS

Colombia, periodo epidemiológico XIII, 2019

31.213

Casos notificados desde 2016 hasta periodo epidemiológico XIII de 2019

ANEXO 1. Proporción de notificación de enfermedades huérfanas - raras, Colombia, 2016 hasta periodo epidemiológico XIII de 2019

No.	Enfermedad Huérfana - Rara	Casos	%
1001	Angiomatosis neurocutanea hereditaria	1	0,00
1002	Sindrome de Laron con inmunodeficiencia	1	0,00
1003	Paraplejia espastica autosomica recesiva tipo 14	1	0,00
1004	Cutis laxa	1	0,00
1005	Anoftalmia - insuficiencia hipotalamo-pituitaria	1	0,00
1006	MSMD (Deficiencia STAT1)	1	0,00
1007	Deficiencia de IgAlpha	1	0,00
1008	Miopatia con autofagia excesiva	1	0,00
1009	Retinosquisis ligada al cromosoma X	1	0,00
1010	Deficiencia de IL-10R?	1	0,00
1011	Sindrome de CLOVE's	1	0,00
1012	Leucoencefalopatia asociada al tronco del encefalo y a la medula espinal - elevacion del lactato	1	0,00
1013	Aceruloplasminemia	1	0,00
1014	Deficiencia de cadena ?	1	0,00
1015	Paralisis periodica hipercalemica	1	0,00
1016	Paraplejia espastica autosomica dominante tipo 17	1	0,00
1017	Glucogenosis de Bickel-Fanconi	1	0,00
1018	Aciduria orotica hereditaria	1	0,00
1019	Hemocromatosis neonatal	1	0,00
1020	Sindrome CAMOS	1	0,00
1021	Sindrome de Stern Lubinsky Durrie	1	0,00
1022	Displasia espondiloepifisaria tardia	1	0,00
1023	AD-DKC (Mutacion en TERT)	1	0,00
1024	Deficiencia de MAGT1	1	0,00
1025	Ausencia de dermatogifos sindactilia miliar	1	0,00
1026	Arteriris temporal juvenil	1	0,00
1027	Enfermedad de Paget juvenil	1	0,00
1028	Fisura palatina sinequias laterales sindrome de	1	0,00
1029	Sindrome de Sakati Nyhan	1	0,00
1030	Sindrome BOR	1	0,00
1031	Displasia espondilo encondral	1	0,00
1032	Agenesia de cuerpo calloso ligado al cromosoma X con mutacion en el gen Alfa 4	1	0,00
1033	Sinostosis radio-ulnar - trombocitopenia amegakaryocitica	1	0,00
1034	Deficiencia de C4a	1	0,00
1035	Miopatia distal con debilidad de cuerdas vocales	1	0,00
1036	Sindrome de Wells	1	0,00
1037	Fisura media del labio inferior	1	0,00
1038	Sindrome oto-palato-digital	1	0,00
1039	Retraso mental ligado al cromosoma X de tipo Schimke	1	0,00
1040	Deficiencia de JAK3	1	0,00
1041	Miopatia distal tipo Nonaka	1	0,00
1042	Enfermedad de Lhermitte-Duclos	1	0,00
1043	Ectopia tiroidea	1	0,00
1044	Ataxia espinocerebelosa tipo 29	1	0,00
1045	Enfermedad de Netherton	1	0,00
1046	Miopatia congenita letal tipo Compton-North	1	0,00
1047	Hipomielinizacion - catarata congenita	1	0,00
1048	Sindrome de Scheie	1	0,00
1049	Deficit de fosfoenolpiruvato carboxiquinasa	1	0,00
1050	Encefalopatia grave de aparicion neonatal autosomica dominante	1	0,00
1051	Sindrome de Peters-Plus	1	0,00
1052	Queratosis palmoplantar - periodontopatia - onicogriposis	1	0,00
1053	Hemangiomatosis Capilar Pulmonar	1	0,00
1054	Trisomia terminal 10q	1	0,00
1055	Sindrome de Worster-Drought	1	0,00
1056	Enfisema lobar congenito	1	0,00
1057	Displasia craneo fronto nasal.	1	0,00
1058	Atrofia dentato-rubro-palido-luisiana	1	0,00
1059	Onicotricodisplasia y neutropenia	1	0,00
1060	Sindrome de encefalopatia mioneurogastrointestinal	1	0,00
1061	Retraso mental severo ligado al cromosoma X tipo Gustavson	1	0,00
1062	Sindrome facio-cardio-melico	1	0,00
1063	Diabetes mellitus neonatal	1	0,00
1064	Hipoqueratosis circunscrita palmo-plantar	1	0,00
1065	Sindrome de Sanfilippo tipo A	1	0,00
1066	Sindrome de Suarez-Stickler	1	0,00
1067	Enfermedad de Niemann-Pick tipo A	1	0,00
1068	Sindrome de Dincsoy Salih Patel	1	0,00
1069	Disinostosis craneofacial	1	0,00
1070	Craneosinostosis - enfermedad cardiaca congenita - deficit intelectual	1	0,00
1071	Sindrome de sordera branquiogenica	1	0,00
1072	Neutropenia ciclica	1	0,00
1073	Sindrome de cataratas congenitas dismorfia facial y neuropatia (CCFDN)	1	0,00
1074	Oto dental displasia	1	0,00
1075	Disfasia congenita familiar	1	0,00
1076	Aniridia agenesia renal retraso psicomotor	1	0,00
1077	Sindrome de Cockayne	1	0,00
1078	Despigmentacion aguda bilateral del iris	1	0,00
1079	Cardiomiopatia amiloidotica familiar relacionado con Transtirretina	1	0,00
1080	Neutropenia congenita grave autosomica y dominante	1	0,00
1081	Anquilosis glosopalatina	1	0,00
1082	Craniorrinia	1	0,00
1083	Deficiencia de IFNAR2	1	0,00
1084	Displasia dermo facial focal	1	0,00
1085	Sindrome de Shwachman-Diamond	1	0,00
1086	Sindrome de microlisencefalia - micromelia	1	0,00
1087	Trastornos del metabolismo de las purinas	1	0,00
1088	Leucoencefalopatia - ataxia - hipodontia - hipomielinizacion	1	0,00
1089	Enfermedad de Griscelli	1	0,00
1090	Retino hepato endocrinologico sindrome	1	0,00
1091	Fascitis eosinofilica	1	0,00
1092	Sindrome de Majeed (mutacion de LPIN2)	1	0,00
1093	Taquiarritmia atrial con intervalo PR corto	1	0,00
1094	Sindrome de Schnitzler	1	0,00
1095	Paraplejia espastica autosomica recesiva tipo 15	1	0,00
1096	Trastorno del desarrollo sexual 46 XY insuficiencia adrenal	1	0,00
1097	Sindrome de Carpenter	1	0,00
1098	Neutropenia congenita grave ligada al cromosoma X	1	0,00
1099	Sindrome de Brugada	1	0,00
1100	Paralisis periodica normocalemica	1	0,00
1101	Camptodactilia no especificada	1	0,00
1102	Retraso mental - cataratas - cifosis	1	0,00
1103	Displasia oto-espondilo-megaepifisaria	1	0,00
1104	Condrodisplasia metafisaria - retinitis pigmentosa	1	0,00
1105	Sindrome de cefalopolisindactilia de Greig	1	0,00
1106	Mucosulfatidosis	1	0,00
1107	Retraso mental ligado al cromosoma X sindromico 7	1	0,00
1108	Enfermedad de jarabe de arce	1	0,00
1109	Tiro cerebro renal sindrome	1	0,00
1110	Sindrome de aniridia - retraso mental	1	0,00
1111	Trastornos del desarrollo sexual 46 XX - anomalias esqueleticas	1	0,00
1112	Acrania	1	0,00
1113	Poliomiositis	1	0,00
1114	Anomalia de Axenfeld-Rieger - hidrocefalia - esqueleto anormal	1	0,00
1115	Neuropatia con discapacidad auditiva	1	0,00
1116	Fisura labiopalatina malrotacion cardiopatia	1	0,00
1117	Sinfalangismo distal	1	0,00
1118	Sindrome de Stickler	1	0,00
1119	Enfermedad de Gaucher - oftalmoplejia - calcificacion cardiovascular	1	0,00
1120	Sindrome de tortuosidad arterial	1	0,00
1121	Traqueobroncomegalia	1	0,00
1122	Neutropenia congenita benigna	1	0,00
1123	Aciduria metilmalonica con homocistinuria	1	0,00
1124	Predisposicion mendeliana a infecciones por micobacterias atipicas	1	0,00
1125	Calcinosis bilateral estriato-palido-dentada	1	0,00
1126	Displasia ectodermica - sindrome de fragilidad de la piel	1	0,00
1127	Displasia espondilometafisaria tipo Kozlowski	1	0,00
1128	Colitis colagenosa	1	0,00
1129	Anemia sideroblastica ligada al cromosoma X con ataxia	1	0,00
1130	Cardiomiopatia - anomalias renales	1	0,00
1131	Sindrome tricorrinofalangico tipo 1 y 3	1	0,00
1132	Enfermedad de von Hippel-Lindau	1	0,00
1133	Hemimelia tibial fisura labiopalatina	1	0,00
1134	Oculo trico displasia	1	0,00
1135	Sinfalangismo anomalias multiples manos y pies	1	0,00
1136	Retraso mental ligado al cromosoma X de tipo Stevenson	1	0,00
1137	Osteolisis del talon rotula y escafoides sindrome de	1	0,00
1138	Sindrome de Marden-Walker	1	0,00
1139	Sindrome de Muenke	1	0,00
1140	CARD11 mutacion con ganancia de funcion	1	0,00
1141	Sindrome de Nevo	1	0,00
1142	(en blanco)	1	0,00
1143	Enfermedad por deposito de lipidos neutros	1	0,00
1144	Sindactilia - telecanto - malformaciones renales y anogenitales	1	0,00
1145	Displasia epifisaria multiple	1	0,00
1146	Hiperekplexia - epilepsia	1	0,00
1147	Eritrodermia congenita letal	1	0,00
1148	Distrofia muscular oculo gastrointestinal	1	0,00
1149	Sindrome de Hiper IgM	1	0,00
1150	Retinopatia hereditaria vascular	1	0,00
1151	Sindrome de Alpers	1	0,00
1152	Atresia de coanas - sordera - cardiopatia	1	0,00
1153	Hipertricosis cervical neuropatia	1	0,00
1154	Sindrome de Fuhrmann	1	0,00
1155	Disostosis acro fronto facio nasal	1	0,00
1156	Anomalias auriculares - fisura labial con o sin fisura palatina - anomalias oculares	1	0,00
1157	Deficiencia de CD40	1	0,00
1158	Enanismo diastrofico	1	0,00
1159	Sindrome de anemia megaloblastica sensible a tiamina	1	0,00
1160	Sindrome CHANDS	1	0,00
1161	Sindrome de Proteus	1	0,00
1162	Ataxia - apraxia - retraso mental ligado al cromosoma X	1	0,00
1163	Sindrome de Rambaud Gallian Touchard	1	0,00
1164	Sindrome pneumo-renal de Goodpasture	1	0,00
1165	Osteopetrosis dominante de tipo 1	1	0,00
1166	Displasia odontomaxilar segmentaria	1	0,00
1167	Inmunodeficiencia debida a deficit de CD25	1	0,00

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Principles of Accounting

Volume 2

Managerial Accounting

Principles of Accounting, Volume 2: Managerial Accounting

SENIOR CONTRIBUTING AUTHORS
Mitchell Franklin, Le Moyne College (Financial Accounting)
Patty Graybeal, University of Michigan-Dearborn (Managerial Accounting)
Dixon Cooper, Ouachita Baptist University

OpenStax
Rice University
6100 Main Street MS-375
Houston, Texas 77005

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start of the period. For example, if you wanted to deposit a lump sum of money into an account and make monthly rent payments starting today, the first payment would be made the same day that you made the deposit into the funding account. Because of this timing difference in the withdrawals from the annuity due, the process of calculating annuity due is somewhat different from the methods that you've covered for ordinary annuities.

YOUR TURN

Determining Present Value

Determine the present value for each of the following situations. Use the present value tables provided in Appendix B when needed, and round answers to the nearest cent where required.

a. You are saving for college and you want to return a sum of $100,000 in 12 years. The bank returns an interest rate of 5% after these 12 years.
b. You need to borrow money for college and can afford a yearly payment to the lending institution of $1,000 per year for the next 8 years. The interest rate charged by the lending institution is 3% per year.

Solution

a. Use PV of $1 table. Present value factor where n = 12 and i = 5 is 0.557. 0.557 × $100,000 = $55,700. b. Use PV of an ordinary annuity table. Present value factor where n = 8 and i = 3 is 7.020. 7.020 × $1,000 = $7,020.

LINK TO LEARNING

For a lucky few, winning the lottery can be a dream come true and the option to take a one-time payout or receive payments over several years does not seem to matter at the time. This lottery payout calculator (https://openstax.org/l/50LotteryCalc) shows how time value of money may affect your take-home winnings.

11.4 Use Discounted Cash Flow Models to Make Capital Investment Decisions

Your company, Rudolph Incorporated, has begun analyzing two potential future project alternatives that have passed the basic screening using the non–time value methods of determining the payback period and the accounting rate of return. Both proposed projects seem reasonable, but your company typically selects only one option to pursue. Which one should you choose? How will you decide? A discounted cash flow model can assist with this process. In this section, we will discuss two commonly used time value of money–based options: the net present value method (NPV) and the internal rate of return (IRR). Both of these methods are based on the discounted cash flow process.

Fundamentals of the Discounted Cash Flow Model

The **discount cash flow model** assigns a value to a business opportunity using time-value measurement tools. The model considers future cash flows of the project, discounts them back to present time, and compares the outcome to an expected rate of return. If the outcome exceeds the expected rate of return and initial investment cost, the company would consider the investment. If the outcome does not exceed the expected rate of return or the initial investment, the company may not consider investment. When considering the discounted cash flow process, the time value of money plays a major role.

Time Value-Based Methods

As previously discussed, time value of money methods assume that the value of money today is worth more now than in the future. The payback period and accounting rate of return methods do not consider this concept when performing calculations and analyzing results. That is why they are typically only used as basic screening tools. To decide the best option between alternatives, a company performs preference measurement using tools, such as net present value and internal rate of return that do consider the time value of money concept. **Net present value (NPV)** discounts future cash flows to their present value at the expected rate of return and compares that to the initial investment. NPV does not determine the actual rate of return earned by a project. The **internal rate of return (IRR)** shows the profitability or growth potential of an investment at the point where NPV equals zero, so it determines the actual rate of return a project earns. As the name implies, net present value is stated in dollars, whereas the internal rate of return is stated as an interest rate. Both NPV and IRR require the company to determine a rate of return to be used as the target return rate, such as the minimum required rate of return or the weighted average cost of capital, which will be discussed in Balanced Scorecard and Other Performance Measures.

A positive NPV implies that the present value of the cash inflows from the project are greater than the present value of the cash outflows, which represent the expenses and costs associated with the project. In an NPV calculation, a positive NPV is typically considered a potentially good investment or project. However, other extenuating circumstances should be considered. For example, the company might not wish to borrow the necessary funding to make the investment because the company might be anticipating a downturn in the national economy.

An IRR analysis compares the calculated IRR with either a predetermined rate of return or the cost of borrowing the money to invest in the project in order to determine whether a potential investment or project is favorable. For example, assume that the investment or equipment purchase is expected to generate an IRR of 15% and the company's expected rate of return is 12%. In this case, similar to the NPV calculation, we assume that the proposed investment would be undertaken. However, remember that other factors must be considered, as they are with NPV.

When considering cash inflows—whether using NPV or IRR—the accountant should examine both profits generated or expenses reduced. Investments that are made may generate additional revenue or could reduce production costs. Both cases assume that the new product or other type of investment generates a positive cash inflow that will be compared to the cost outflows to determine whether there is an overall positive or negative net present value.

Additionally, a company would determine whether the projects being considered are mutually exclusive or not. If the projects or investment options are mutually exclusive, the company can evaluate and identify more than one alternative as a viable project or investment, but they can only invest in one option. For example, if a

company needs one new delivery truck, it might solicit proposals from five different truck dealers and conduct NPV and IRR evaluations. Even if all proposals pass the financial requirements of the NPV and IRR methods, only one proposal will be accepted.

Another consideration occurs when a company has the ability to evaluate and accept multiple proposals. For example, an automobile manufacturer is considering expanding its number of dealerships in the United States over the next ten-year period and has allocated $30,000,000 to buy the land. They could purchase any number of properties. They conduct NPV and IRR analyses of fifteen properties and determine that four meet their required standards and market feasibility needs and then purchase those four properties. The opportunities were not mutually exclusive: the number of properties purchased was driven by research and expansion projections, not by their need for only one option.

CONTINUING APPLICATION AT WORK

Capital Budgeting Decisions

Gearhead Outfitters has expanded to many locations throughout its twenty-plus years in business. How did company management decide to expand? One of the financial tools a business can use is capital budgeting, which addresses many different issues involving the use of current cash flow for future return. As you've learned, capital outlay decisions can be evaluated through payback period, net present value, and methods involving rates of return.

With this in mind, think about the capital budgeting issues Gearhead's management might have faced. For example, in deciding to expand, should the company buy a building or lease one? What method should be used to evaluate this? Purchasing a building might require more initial outlay, but the company will retain an asset. How will such a decision affect the bottom line? With respect to equipment, Gearhead could maintain a fleet of vehicles. Should the vehicles be purchased or leased? What will need to be considered in the process?

In developing and maintaining its strategy for sustainability, a business must not only consider day-to-day operations, but also address long-term decisions. Common capital budgeting items like equipment purchases to increase efficiency or reduce costs, decisions about replacement versus repair, and expansion all involve significant cash outlay. How will these items be evaluated? How long will recouping the initial investment take? How much revenue will be generated (or costs saved) through capital outlay? Does the company require a minimum rate of return before it moves forward with investment? If so, how is that return determined? Considering Gearhead's decision to expand, what are some specific capital budgeting decisions important for the company to consider in their long-term strategy?

Basic Characteristics of the Net Present Value Model

Net present value helps companies choose between alternatives at a particular point in time by determining which produces the higher NPV. To determine the NPV, the initial investment is subtracted from the present value of cash inflows and outflows associated with a project at a required rate of return. If the outcome is positive, the company should consider investment. If the outcome is negative, the company would forgo investment.

We previously discussed the calculation for present value using the present value tables, where *n* is the

number of years and *i* is the expected interest rate. Once the present value factor is determined, it is multiplied by the expected net cash flows to produce the present value of future cash flows. The initial investment is subtracted from this present value calculation to determine the net present value.

Net present value = Sum of Present Value of net cash flows – Initial Investment

Recall that the Present Value of $1 table is used for a lump sum payout, whereas the Present Value of an Ordinary Annuity table is used for a series of equal payments occurring at the end of each period. Taking this distinction one step further, NPV requires use of different tables depending on whether the future cash flows are equal or unequal in each time period. If the cash flows each period are equal, the company uses the Present Value of an Ordinary Annuity table, where the present value factor is multiplied by the cash flow amount for one period to get the present value. If the cash flows each period are unequal, the company uses the Present Value of $1 table, where the total present value is the sum of each of the unequal cash flows multiplied by the appropriate present value factor for each time period. This concept is discussed in the following example.

Assume that your company, Rudolph Incorporated, is determining the NPV for a new X-ray machine. The X-ray machine has an initial investment of $200,000 and an expected cash flow of $40,000 each period for the next 10 years. The expected $40,000 cash flows from the new X-ray machine can be attributed to either additional revenue generated or cost savings realized by more efficient operations of the new machine. Since these annual cash flows of $40,000 are the same amount in each period over the ten-years this will be a stream of annuity amounts received. The required rate of return on such an investment is 8%. The present value factor (i = 8, n = 10) is 6.710 using the Present Value of an Ordinary Annuity table. Multiplying the present value factor (6.710) by the equal cash flow ($40,000) gives a present value of $268,400. NPV is found by taking the present value of $268,400 and subtracting the initial investment of $200,000 to arrive at $68,400. This is a positive NPV, so the company would consider investment.

Present Value of an Ordinary Annuity Table

Period (*n*)	Rate (*i*)				
	1%	2%	3%	5%	8%
1	0.990	0.980	0.971	0.952	0.926
2	1.970	1.942	1.913	1.859	1.783
3	2.941	2.884	2.829	2.723	2.577
4	3.902	3.808	3.717	3.546	3.312
5	4.853	4.713	4.580	4.329	3.993
6	5.795	5.601	5.417	5.076	4.623
7	6.728	6.472	6.230	5.786	5.206
8	7.652	7.325	7.020	6.463	5.747
9	8.566	8.162	7.786	7.108	6.247
10	9.471	8.983	8.530	7.722	**6.710**

If there are two investments that have a positive NPV, and the investments are mutually exclusive, meaning only one can be chosen, the more profitable of the two investments is typically the appropriate one for a company to choose. We can also use the profitability index to compare them. The profitability index measures the amount of profit returned for each dollar invested in a project. This is particularly useful when projects being evaluated are of a different size, as the profitability index scales the projects to make them comparable. The profitability index is found by taking the present value of the net cash flows and dividing by the initial investment cost.

$$\text{Profitability index} = \frac{\text{Present value of cash flows}}{\text{Initial investment cost}}$$

For example, Rudolph Incorporated is considering the X-ray machine that had present value cash flows of $268,400 (not considering salvage value) and an initial investment cost of $200,000. Another x-ray equipment option, option B, produces present value cash flows of $290,000 and an initial investment cost of $240,000. The profitability index is computed as follows.

$$\text{Option A: } \frac{\$268{,}400}{\$200{,}000} = 1.342$$

$$\text{Option B: } \frac{\$290{,}000}{\$240{,}000} = 1.208$$

Based on this outcome, the company would invest in Option A, the project with a higher profitability index of 1.342.

If there were unequal cash flows each period, the Present Value of $1 table would be used with a more complex calculation. Each year's present value factor is determined and multiplied by that year's cash flow. Then all cash flows are added together to get one overall present value figure. This overall present value figure is used when finding the difference between present value and the initial investment cost.

For example, let's say the X-ray machine information is the same, except now cash flows are as follows:

Year	Cash Flow Amount
1	$20,000
2	25,000
3	20,000
4	40,000
5	40,000
6	60,000
7	30,000
8	35,000
9	25,000
10	45,000

To find the overall present value, the following calculations take place using the present value of $1 table.

Year	Cash Flow Amount	Present Value Factor (i = 8, n = specific year)	Present Value
1	$ 20,000	(i = 8, n = 1) = 0.926	0.926 × $20,000 = $18,520
2	25,000	(i = 8, n = 2) = 0.857	0.857 × 25,000 = 21,425
3	20,000	(i = 8, n = 3) = 0.794	0.794 × 20,000 = 15,880
4	40,000	(i = 8, n = 4) = 0.735	0.735 × 40,000 = 29,400
5	40,000	(i = 8, n = 5) = 0.681	0.681 × 40,000 = 27,240
6	60,000	(i = 8, n = 6) = 0.630	0.630 × 60,000 = 37,800
7	30,000	(i = 8, n = 7) = 0.583	0.583 × 30,000 = 17,490
8	35,000	(i = 8, n = 8) = 0.540	0.540 × 35,000 = 18,900
9	25,000	(i = 8, n = 9) = 0.500	0.500 × 25,000 = 12,500
10	45,000	(i = 8, n = 10) = 0.463	0.463 × 45,000 = 20,835
Total	**$340,000**		**$219,990**

The Present Value of $1 table is used because, each year, a new "lump sum" cash flow is received, so the cash

flow in each period is different. The cash flows are treated as one-time lump sum payouts during that year. The present value for each period looks at each year's present value factor at an interest rate of 8%. All the PVs are added together for a total present value of $219,990. The initial investment of $200,000 is subtracted from the $219,990 to arrive at a positive NPV of $19,990. In this case, the company would consider investment since the outcome is positive. (More complex considerations, such as depreciation, the effects of income taxes, and inflation, which could affect the overall NPV, are covered in advanced accounting courses.)

YOUR TURN

Analyzing a Postage Meter Investment

Yellow Industries is considering investment in a new postage meter system. The postage meter system would have an initial investment cost of $135,000. Annual net cash flows are $40,000 for the next 5 years, and the expected interest rate return is 10%. Calculate net present value and decide whether or not Yellow Industries should invest in the new postage meter system.

Solution

Use the Present Value of an Ordinary Annuity table. Present value factor at $n = 5$ and $i = 10\%$ is 3.791. Present value = 3.791 × $40,000 = $151,640. NPV = $151,640 − $135,000 = $16,640. In this case, Yellow Industries should invest since the NPV is positive.

Calculation and Discussion of the Results of the Net Present Value Model

To demonstrate NPV, assume that a company, Rayford Machining, is considering buying a drill press that will have an initial investment cost of $50,000 and annual cash flows of $10,000 for the next 7 years. Assume that Rayford expects a 5% rate of return on such an investment. We need to determine the NPV when cash flows are equal. The present value factor ($i = 5$, $n = 7$) is 5.786 using the Present Value of an Ordinary Annuity table. We multiply 5.786 by the equal cash flow of $10,000 to get a present value of $57,860. NPV is found by taking the present value of $57,860 and subtracting the initial investment of $50,000 to arrive at $7,860. This is a positive NPV, so the company would consider the investment.

Present Value of an Ordinary Annuity Table

Period (*n*)	Rate (*i*)			
	1%	2%	3%	5%
1	0.990	0.980	0.971	0.952
2	1.970	1.942	1.913	1.859
3	2.941	2.884	2.829	2.723
4	3.902	3.808	3.717	3.546
5	4.853	4.713	4.580	4.329
6	5.795	5.601	5.417	5.076
7	6.728	6.472	6.230	**5.786**

Let's say Rayford Machining has another option, Option B, for a drill press purchase with an initial investment cost of $56,000 that produces present value cash flows of $60,500. The profitability index is computed as follows.

$$\text{Option A: } \frac{\$57{,}860}{\$50{,}000} = 1.157$$

$$\text{Option B: } \frac{\$60{,}500}{\$56{,}000} = 1.080$$

Based on this outcome, the company would invest in Option A, the project with a higher profitability potential of 1.157.

Now let's assume cash flows are unequal. Unequal cash flow information for Rayford Machining is summarized here.

Year	Net Cash Flow
1	$10,000
2	5,000
3	7,000
4	3,000
5	10,000
6	10,000
7	10,000

To find the overall present value, the following calculations take place using the Present Value of $1 table.

Year	Cash Flow Amount	Present Value Factor (i = 5, n = specific year)	Present Value
1	$10,000	(i = 5, n = 1) = 0.952	0.952 × $10,000 = $9,520
2	5,000	(i = 5, n = 2) = 0.907	0.907 × 5,000 = 4,535
3	7,000	(i = 5, n = 3) = 0.864	0.864 × 7,000 = 6,048
4	3,000	(i = 5, n = 4) = 0.823	0.823 × 3,000 = 2,469
5	10,000	(i = 5, n = 5) = 0.784	0.784 × 10,000 = 7,840
6	10,000	(i = 5, n = 6) = 0.746	0.746 × 10,000 = 7,460
7	10,000	(i = 5, n = 7) = 0.711	0.711 × 10,000 = 7,110
Total	**$55,000**		**$44,982**

The present value for each period looks at each year's present value factor at an interest rate of 5%. All individual year present values are added together for a total present value of $44,982. The initial investment of $50,000 is subtracted from the $44,982 to arrive at a negative NPV of $5,018. In this case, Rayford Machining would not invest, since the outcome is negative. The negative NPV value does not mean the investment would be unprofitable; rather, it means the investment does not return the desired 5% the company is looking for in the investments that it makes.

Basic Characteristics of the Internal Rate of Return Model

The internal rate of return model allows for the comparison of profitability or growth potential among alternatives. All external factors, such as inflation, are removed from calculation, and the project with the highest return rate percentage is considered for investment.

IRR is the discounted rate (interest rate) point at which NPV equals zero. In other words, the IRR is the point at which the present value cash inflows equal the initial investment cost. To consider investment, IRR needs to meet or exceed the required rate of return for the investment type. If IRR does not meet the required rate of return, the company will forgo investment.

To find IRR using the present value tables, we need to know the cash flow number of return periods (n) and

the intersecting present value factor. To calculate present value factor, we use the following formula.

$$\text{Present Value Factor} = \frac{\text{Initial Investment Cost}}{\text{Annual Net Cash Flows}}$$

We find the present value factor in the present value table in the row with the corresponding number of periods (*n*). We find the matching interest rate (*i*) at this present value factor. The corresponding interest rate at the number of periods (*n*) is the IRR. When cash flows are equal, use the Present Value of an Ordinary Annuity table to find IRR.

For example, a car manufacturer needs to replace welding equipment. The initial investment cost is $312,000 and each annual net cash flow is $49,944 for the next 9 years. We need to find the internal rate of return for this welding equipment. The expected rate of return for such a purchase is 6%. In this case, $n = 9$ and the present value factor is computed as follows.

$$\text{Present Value Factor} = \frac{\$312{,}000}{\$49{,}944} = 6.247 \text{ (rounded)}$$

Looking at the Present Value of an Ordinary Annuity table, where $n = 9$ and the present value factor is 6.247, we discover that the corresponding return rate is 8%. This exceeds the expected return rate, so the company would typically invest in the project.

Present Value of an Ordinary Annuity Table

Period (*n*)	Rate (*i*)					
	1%	2%	3%	5%	8%	10%
1	0.990	0.980	0.971	0.952	0.926	0.909
2	1.970	1.942	1.913	1.859	1.783	1.736
3	2.941	2.884	2.829	2.723	2.577	2.487
4	3.902	3.808	3.717	3.546	3.312	3.170
5	4.853	4.713	4.580	4.329	3.993	3.791
6	5.795	5.601	5.417	5.076	4.623	4.355
7	6.728	6.472	6.230	5.786	5.206	4.868
8	7.652	7.325	7.020	6.463	5.747	5.335
9	8.566	8.162	7.786	7.108	**6.247**	5.759

If there is more than one viable option, the company will select the alternative with the highest IRR that exceeds the expected rate of return.

Our tables are limited in scope, and therefore, a present value factor may fall in between two interest rates. When this is the case, you may choose to identify an IRR range instead of a single interest rate figure. A spreadsheet program or financial calculator can produce a more accurate result and can also be used when cash flows are unequal.

Calculation and Discussion of the Results of the Internal Rate of Return Model

Assume that Rayford Machining wants to know the internal rate of return for the new drill press. The drill press has an initial investment cost of $50,000 and an annual cash flow of $10,000 for each of the next seven years. The company expects a 7% rate of return on this type of investment. We calculate the present value factor as:

$$\text{Present Value Factor} = \frac{\$50{,}000}{\$10{,}000} = 5.000$$

Scanning the Present Value of an Ordinary Annuity table reveals that the interest rate where the present value factor is 5 and the number of periods is 7 is between 8 and 10%. Since the required rate of return was 7%, Rayford would consider investment in this metal press machine.

Present Value of an Ordinary Annuity Table

Period (*n*) \ Rate (*i*)	1%	2%	3%	5%	8%	10%
1	0.990	0.980	0.971	0.952	0.926	0.909
2	1.970	1.942	1.913	1.859	1.783	1.736
3	2.941	2.884	2.829	2.723	2.577	2.487
4	3.902	3.808	3.717	3.546	3.312	3.170
5	4.853	4.713	4.580	4.329	3.993	3.791
6	5.795	5.601	5.417	5.076	4.623	4.355
7	6.728	6.472	6.230	5.786	**5.206**	**4.868**
8	7.652	7.325	7.020	6.463	5.747	5.335
9	8.566	8.162	7.786	7.108	6.247	5.759

Consider another example using Rayford, where they have two drill press purchase options. Option A has an IRR between 8% and 10%. The other option, Option B, has an initial investment cost of $60,500 and equal annual net cash flows of $13,256 for the next seven years. We calculate the present value factor as:

$$\text{Present Value Factor} = \frac{\$60{,}500}{\$13{,}256} = 4.564 \text{ (rounded)}$$

Scanning the Present Value of an Ordinary Annuity table reveals that, when the present value factor is 4.564 and the number of periods is 7, the interest rate is 12%. This not only exceeds the 7% required rate, it also exceeds Option A's return of 8% to 10%. Therefore, if resources were limited, Rayford would select Option B over Option A.

Present Value of an Ordinary Annuity Table

Period (*n*) \ Rate (*i*)	1%	2%	3%	5%	8%	10%	12%
1	0.990	0.980	0.971	0.952	0.926	0.909	0.893
2	1.970	1.942	1.913	1.859	1.783	1.736	1.690
3	2.941	2.884	2.829	2.723	2.577	2.487	2.402
4	3.902	3.808	3.717	3.546	3.312	3.170	3.037
5	4.853	4.713	4.580	4.329	3.993	3.791	3.605
6	5.795	5.601	5.417	5.076	4.623	4.355	4.111
7	6.728	6.472	6.230	5.786	5.206	4.868	**4.564**

Final Summary of the Discounted Cash Flow Models

The internal rate of return (IRR) and the net present value (NPV) methods are types of discounted cash flow analysis that require taking estimated future payments from a project and discounting them into present values. The difference between the two methods is that the NPV calculation determines the project's estimated return in dollars and the IRR provides the percentage rate of return from a project needed to break even.

When the NPV is determined to be $0, the present value of the cash inflows and the present value of the cash outflows are equal. For example, assume that the present value of the cash inflows is $10,000 and the present value of the cash outflows is also $10,000. In this example, the NPV would be $0. At a net present value of zero,

the IRR would be exactly equal to the interest rate that was used to perform the NPV calculation. For example, in the previous example, where both the cash inflows and the cash outflows have present values of $10,000 and the NPV is $0, assume that they were discounted at an 8% interest rate. If you were to then calculate the internal rate of return, the IRR would be 8%, the same interest rate that gave us an NPV of $0.

Overall, it is important to understand that a company must consider the time value of money when making capital investment decisions. Knowing the present value of a future cash flow enables a company to better select between alternatives. The net present value compares the initial investment cost to the present value of future cash flows and requires a positive outcome before investment. The internal rate of return also considers the present value of future cash flows but considers profitability stated in terms of percentage of return on the investment or project. These models allows two or more options to be compared to eliminate bias with raw financial figures.

THINK IT THROUGH

Choosing Investments

Companies are presented with viable alternatives that sometimes produce nearly identical results and profitability goals. If they have the ability to invest in both alternatives, they may do so. But what about when resources are constrained? How do they choose which investment is best for their company?

Consider this: you have two projects that met the payback period and accounting rate of return screenings identically. Project 1 produced an NPV of $45,000 and had an IRR between 5% and 8%. Project 2 produced a NPV of $35,000 and had an IRR of 10%. This leaves you with a difficult choice, since each alternative has a measurement that exceeds the other and the other variables are the same. Which project would you invest in and why?

11.5 Compare and Contrast Non-Time Value-Based Methods and Time Value-Based Methods in Capital Investment Decisions

When an investment opportunity is presented to a company, there are many financial and non-financial factors to consider. Using capital budgeting methods to narrow down the choices by removing unviable alternatives is an important process for any successful business. The four methods for capital budgeting analysis—payback period, accounting rate of return, net present value, and internal rate of return—all have their strengths and weaknesses, which are discussed as follows.

Summary of the Strengths and Weaknesses of the Non-Time Value-Based Capital Budgeting Methods

Non-time value-based capital budgeting methods are best used in an initial screening process when there are many alternatives to choose from. Two such methods are payback method and accounting rate of return. Their strengths and weaknesses are discussed in Table 11.4 and Table 11.5.

The payback method determines the length of time needed to recoup an investment.