Horizon Pharma plc
Form 10-K
February 27, 2019

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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 (State or other jurisdiction of incorporation or organization)	Not Applicable (I.R.S. Employer Identification No.)
Connaught House, 1st Floor	Not Applicable

1 Burlington Road, Dublin 4, D04 C5Y6, Ireland
(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 expressi 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:

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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.

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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.

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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;

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- 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.

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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.

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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.

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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.

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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)
	(16,596)	54,276	657,074	1,442,481	338,285

Net cash (used in) provided by financing activities (6)	

(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	Amount	% of Total

			Net Sales				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, 2018	2017	Change $	Change %
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.

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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	Amount	% of Gross

		Sales		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

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	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.
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- $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.

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(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	17	16

outstanding at December 31, 2018 and December 31, 2017, respectively		
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
	—	—	—	—	—	—	7,210	7,210

Cumulative effect adjustment from adoption of ASU 2016-09								
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	3,541,933	1	—	—	16,972	—	—	16,973

units and stock option exercises								
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.

HORIZON PHARMA PLC

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

December 31, 2018, 2017 and 2016

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			For the Nine Months Ended		
September 30, 2018			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			For the Six Months Ended		
	June 30, 2018			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	Director	

Liam Daniel		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