Horizon Pharma plc
Form 10-K
February 27, 2017

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2016

or

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

Commission File Number 001-35238

HORIZON PHARMA PUBLIC LIMITED COMPANY

(Exact name of Registrant as specified in its charter)

Ireland (State or other jurisdiction of incorporation or organization)	Not Applicable (I.R.S. Employer Identification No.)
Connaught House, 1st Floor 1 Burlington Road, Dublin 4, D04 C5Y6, Ireland (Address of principal executive offices)	Not Applicable (zip code)

011 353 1 772 2100

(Registrant's telephone number, including area code)

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

Title of Each Class	Name of Each Exchange on Which Registered
Ordinary shares, nominal value $0.0001 per share	The NASDAQ Global Select Market

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

None

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

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

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

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

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

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company.

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

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

The aggregate market value of the registrant's voting ordinary shares held by non-affiliates of the registrant, based upon the $16.47 per share closing sale price of the registrant's ordinary shares on June 30, 2016 (the last business day of the registrant's most recently completed second quarter), was approximately $2.2 billion. Solely for purposes of this calculation, the registrant's directors and executive officers and holders of 10% or more of the registrant's outstanding ordinary shares have been assumed to be affiliates and an aggregate of 24,135,899 ordinary shares held by such persons on June 30, 2016 are not included in this calculation.

As of February 22, 2017, the registrant had outstanding 162,334,893 ordinary shares.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement for the registrant's 2017 Annual Meeting of Shareholders are incorporated by reference into Part III of this Annual Report on Form 10-K.

HORIZON PHARMA PLC

FORM 10-K — ANNUAL REPORT

For the Fiscal Year Ended December 31, 2016

TABLE OF CONTENTS

PART I

Special Note Regarding Forward-Looking Statements

This Annual Report on Form 10-K contains "forward-looking statements" — that is, statements related to future, not past, events — as defined in Section 21E of the Securities Exchange Act of 1934, as amended, that reflect our current expectations regarding our future growth, results of operations, financial condition, cash flows, performance, business prospects, and opportunities, as well as assumptions made by, and information currently available to, our management. Forward-looking statements include any statement that does not directly relate to a current or historical fact. We have tried to identify forward-looking statements by using words such as "believe," "may," "could," "will," "estimate "continue," "anticipate," "intend," "seek," "plan," "expect," "should," or "would." Among the factors that could cause actual re differ materially from those indicated in the forward-looking statements are risks and uncertainties inherent in our business including, without limitation: our ability to successfully execute our sales and marketing strategy, including continuing to successfully recruit and retain sales and marketing personnel and to successfully build the market for our medicines; whether we will be able to realize the expected benefits of strategic transactions, such as our acquisitions of Hyperion Therapeutics Inc., Crealta Holdings LLC and Raptor Pharmaceutical Corp., including whether and when such transactions will be accretive to our net income; the rate and degree of market acceptance of, and our ability and our distribution and marketing partners' ability to obtain coverage and adequate reimbursement and pricing for, our medicines from government and third-party payers and risks relating to the success of our patient access programs; our ability to maintain regulatory approvals for our medicines; our ability to conduct clinical development and obtain regulatory approvals for our medicine candidates, including potential delays in initiating and completing studies and filing for and obtaining regulatory approvals and whether data from clinical studies will support regulatory approval; our need for and ability to obtain additional financing; the accuracy of our estimates regarding future financial results; our ability to successfully execute our strategy to develop or acquire additional medicines or companies, including disruption from any future acquisition or whether any acquired development programs will be successful; our ability to manage our anticipated future growth; the ability of our medicines to compete with generic medicines, especially those representing the active pharmaceutical ingredients in our medicines as well as new medicines that may be developed by our competitors; our ability and our distribution and marketing partners' ability to comply with regulatory requirements regarding the sales, marketing and manufacturing of our medicines and medicine candidates; the performance of our third-party distribution partners, licensees and manufacturers over which we have limited control; our ability to obtain and maintain intellectual property protection for our medicines; our ability to defend our intellectual property rights with respect to our medicines; our ability to operate our business without infringing the intellectual property rights of others; the loss of key commercial or management personnel; regulatory developments in the United States and other countries, including potential changes in healthcare laws and regulations; and other risks detailed below in Part I — Item 1A. "Risk Factors."

Although we believe that the expectations reflected in our forward-looking statements are reasonable, we cannot guarantee future results, events, levels of activity, performance or achievement. We undertake no obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, unless required by law.

Item 1. Business

Unless otherwise indicated or the context otherwise requires, references to the "Company", "we", "us" and "our" refer to Horizon Pharma plc and its consolidated subsidiaries, including its predecessor Horizon Pharma, Inc., or HPI. All references to "Vidara" are references to Horizon Pharma plc (formerly known as Vidara Therapeutics International Public Limited Company) and its consolidated subsidiaries prior to the effective time of the merger of the businesses of HPI and Vidara on September 19, 2014, or the Vidara Merger. The disclosures in this report relating to the pre-Vidara Merger business of Horizon Pharma plc, unless noted as being the business of Vidara prior to the Vidara Merger, pertain to the business of HPI prior to the Vidara Merger.

1

Overview

We are a biopharmaceutical company focused on improving patients' lives by identifying, developing, acquiring and commercializing differentiated and accessible medicines that address unmet medical needs. We market eleven medicines through our orphan, rheumatology and primary care business units. Our marketed medicines are ACTIMMUNE® (interferon gamma-1b), BUPHENYL® (sodium phenylbutyrate) Tablets and Powder, DUEXIS® (ibuprofen/famotidine), KRYSTEXXA® (pegloticase), MIGERGOT® (ergotamine tartrate & caffeine suppositories), PENNSAID® (diclofenac sodium topical solution) 2% w/w, or PENNSAID 2%, PROCYSBI® (cysteamine bitartrate) delayed-release capsules, QUINSAIR™ (aerosolized form of levofloxacin), RAVICTI® (glycerol phenylbutyrate) Oral Liquid, RAYOS® (prednisone) delayed-release tablets and VIMOVO® (naproxen/esomeprazole magnesium).

Our Strategy

Our strategy is to continue to build a well-balanced, diversified, high-growth biopharmaceutical company. We are executing our strategy through the successful commercialization of our existing medicines, a strong commitment to patient access and support and business development efforts focused on transformative acquisitions to accelerate our rare disease leadership as well as on-market and development-stage medicines to fill out our pipeline.

We are building a sustainable biopharmaceutical company by helping ensure that patients have access to their medicines and support services, and by investing in the further development of medicines for patients with rare or underserved diseases. Our growing business is diversified across three business units: orphan, rheumatology and primary care, and is driven by a successful commercial model that focuses on differentiated, long-life medicines, innovative patient access programs and a disciplined business development strategy. Our key areas of focus are:

Revenue diversification – We have successfully diversified our portfolio of medicines from two in 2013 to eleven in December 2016. Our intent is to continue to generate organic growth, broaden our medicine portfolio to ensure net revenues are not dominated by any one medicine and increase the proportion of net revenues derived from our orphan medicines.

Clinical development – We work diligently to unlock the full therapeutic potential of our medicines by working closely with regulatory agencies, premier academic centers with established study consortiums, healthcare professionals and patient groups to facilitate our clinical development programs and generate data for possible new indications that may help more patients in need. We also continue to look at opportunities to augment our rare disease pipeline through development-stage acquisitions.

Business development – We have a disciplined and robust acquisition strategy, and our focus is on rapid value creation and improving the performance of each of the medicines we acquire. We have completed seven acquisitions over the past five years, including two transformative transactions in 2016 that brought us three new rare disease medicines. While we remain focused on acquiring clinically-differentiated medicines and executing transactions that are accretive and net present value positive, we have expanded our acquisition criteria to potentially include medicines in late-stage development.

Our Company

We are a public limited company formed under the laws of Ireland. Our predecessor, HPI, was originally incorporated in Delaware in March 2010 and Vidara was originally incorporated in Ireland in December 2011. We operate through a number of international and U.S. subsidiaries with principal business purposes to perform research and development or manufacturing operations, serve as distributors of our medicines, hold intellectual property assets or provide us with services and financial support.

Our principal executive offices are located at Connaught House, 1st Floor, 1 Burlington Road, Dublin 4, D04 C5Y6, Ireland and our telephone number is 011 353 1 772 2100. Our website address is www.horizonpharma.com. Information found on, or accessible through, our website is not a part of, and is not incorporated into, this Annual Report on Form 10-K.

Mergers and Acquisitions

The Vidara Merger occurred on September 19, 2014 and was accounted for as a reverse acquisition under the acquisition method of accounting for business combinations, with HPI treated as the acquiring company for accounting purposes. As part of the Vidara Merger, a wholly owned subsidiary of Vidara merged with and into HPI, with HPI surviving the Vidara Merger as a wholly owned subsidiary of Vidara. Prior to the Vidara Merger, Vidara changed its name to Horizon Pharma plc. Upon the consummation of the Vidara Merger, the historical financial statements of HPI became our historical financial statements. Accordingly, the historical financial statements of HPI are included in the 2014 comparative periods.

On October 17, 2014, we acquired the U.S. rights to PENNSAID 2% from Nuvo Research Inc., or Nuvo, for $45.0 million in cash.

On May 7, 2015, we completed our acquisition of Hyperion Therapeutics Inc., or Hyperion, in which we acquired all of the issued and outstanding shares of Hyperion's common stock for $46.00 per share in cash or approximately $1.1 billion on a fully-diluted basis. Hyperion marketed RAVICTI and BUPHENYL. Following the completion of the acquisition, Hyperion became our wholly owned subsidiary and was renamed Horizon Therapeutics, Inc. (which subsequently converted to a limited liability company, Horizon Therapeutics, LLC).

On January 13, 2016, we completed our acquisition of Crealta Holdings LLC, or Crealta, for approximately $539.7 million, including cash acquired of $24.9 million. Crealta marketed KRYSTEXXA and MIGERGOT. Following the completion of the acquisition, Crealta became our wholly owned subsidiary and was renamed Horizon Pharma Rheumatology LLC.

On October 25, 2016, we completed our acquisition of Raptor Pharmaceutical Corp., or Raptor, in which we acquired all of the issued and outstanding shares of Raptor's common stock for $9.00 per share in cash. The total consideration was $860.8 million, including cash acquired of $24.9 million and $56.0 million to repay Raptor's outstanding debt. Raptor marketed PROCYSBI and QUINSAIR. Following completion of the acquisition, Raptor became our wholly owned subsidiary and converted to a limited liability company, changing its name to Horizon Pharmaceutical LLC.

The consolidated financial statements presented herein include the results of operations of the acquired Vidara, Hyperion, Crealta and Raptor businesses from the applicable dates of acquisition.

Our Medicines

We believe our medicines address unmet therapeutic needs in orphan diseases, arthritis, pain and inflammation and inflammatory diseases and provide significant advantages over existing therapies.

Our current marketed medicine portfolio consists of the following:

Medicine	Disease	Marketing Rights
ORPHAN BUSINESS UNIT MEDICINES:		
ACTIMMUNE	Chronic granulomatous disease and severe, malignant osteopetrosis	United States and selected foreign countries
BUPHENYL	Urea cycle disorders	Worldwide (1)
PROCYSBI	Nephropathic cystinosis	Worldwide
QUINSAIR	Treatment of chronic pulmonary infections due to pseudomonas aeruginosa in cystic fibrosis patients	Worldwide (2)
RAVICTI	Urea cycle disorders	Worldwide (3)
RHEUMATOLOGY BUSINESS UNIT MEDICINES:		
KRYSTEXXA	Chronic refractory gout	Worldwide
RAYOS/LODOTRA	Rheumatoid arthritis, polymyalgia rheumatic, systemic lupus erythematosus and multiple other indications	Worldwide (4)
PRIMARY CARE BUSINESS UNIT MEDICINES:		
DUEXIS	Signs and symptoms of osteoarthritis and rheumatoid arthritis	Worldwide (5)
MIGERGOT	Vascular headache	United States
PENNSAID 2%	Pain of osteoarthritis of the knee(s)	United States
VIMOVO	Signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis	United States

(1) BUPHENYL is known as AMMONAPS in certain European countries. The distribution rights for BUPHENYL in Europe, certain Asian, Latin American, Middle Eastern, North African and other countries have been granted to Swedish Orphan Biovitrum AB, or SOBI. Orphan Pacific, Inc. holds an exclusive distribution agreement for the distribution of AMMONAPS in Japan.

(2) We have not received regulatory approval to distribute QUINSAIR in the United States.

(3) RAVICTI distribution rights in the Middle East and North Africa have been granted to SOBI. In June 2016, we partnered with Clinigen Group plc's Idis managed access division to initiate a managed access program in selected European countries, which agreement terminates on April 10, 2017 and after which we will partner with SOBI to

continue our managed access program in selected European countries. We expect to commercially launch RAVICTI in Europe in 2017 through an exclusive distribution agreement with SOBI.

(4) Mundipharma International Corporation Limited, or Mundipharma, is our exclusive distributor for LODOTRA in Europe, Asia and Latin America. The majority of LODOTRA sales are in Germany and Italy where reimbursement has been approved.

(5) DUEXIS rights in Latin America have been licensed to Grünenthal S.A., or Grünenthal.

ORPHAN BUSINESS UNIT

Market

Chronic Granulomatous Disease

Chronic granulomatous disease, or CGD, is a genetic disorder of the immune system. It is described as a primary immunodeficiency disorder, which means it is not caused by another disease or disorder. In people who have CGD, a type of white blood cell, called a phagocyte, is defective. These defective phagocytes cannot generate superoxide, leading to an inability to kill harmful microorganisms such as bacteria and fungi. As a result, the immune system is weakened. People with CGD are more likely to have certain problems such as recurrent severe bacterial and fungal infections and chronic inflammatory conditions. These patients are prone to developing masses called granulomas, which can occur repeatedly in organs throughout the body and cause a variety of problems. CGD is considered to be a condition that patients can live with and manage. Studies suggest overall survival has improved over the last decade with more patients living well into adulthood. Approximately 1 out of every 100,000 to 200,000 babies in the United States is born with CGD.

Severe, Malignant Osteopetrosis

Severe, malignant osteopetrosis, or SMO, is a form of osteopetrosis and is sometimes referred to as marble bone disease or malignant infantile osteopetrosis because it occurs in very young children. While exact numbers are not known, it has been estimated that 1 out of 250,000 children is born with SMO. During normal bone development, existing bone material is constantly being replaced by new bone. Cells called osteoblasts cause new bone formation while other cells called osteoclasts remove old bone through a process called resorption. In people with osteopetrosis, this balance is not maintained because their osteoclasts do not function properly. As a result, resorption of old bone material decreases while the formation of new bone continues. This leads to an abnormal increase in bone mass, which can make the bones more brittle. Because abnormal bone development affects many different systems in the body, osteopetrosis may cause problems such as blood disorders, decreased ability to fight infection, bone fractures, problems with vision and hearing, and abnormal appearance of the face and head.

Urea Cycle Disorders

Urea cycle disorders, or UCDs, are inherited metabolic diseases caused by a deficiency of one of the enzymes or transporters that constitute the urea cycle. The urea cycle involves a series of biochemical steps in which ammonia, a potent neurotoxin, is converted to urea, which is excreted in the urine. UCD patients may experience episodes where they get symptoms from the ammonia in their blood being excessively high – called hyperammonemic crises – which may result in irreversible brain damage, coma or death. UCD symptoms may first occur at any age depending on the severity of the disorder, with more severe defects presenting earlier in life. We estimate that there are approximately 2,000 patients with UCDs living in the United States.

Nephropathic Cystinosis

We estimate that there are approximately 500 patients diagnosed with cystinosis living in the United States and an estimated 2,000 patients worldwide. Nephropathic cystinosis comprises ninety-five percent of known cases of cystinosis. In these patients, elevated cystine leads to cellular dysfunction and death; without treatment, the disease is usually fatal by the end of the first decade of life. Cystinosis is progressive, eventually causing irreversible tissue damage and multi-organ failure, including kidney failure, blindness, muscle wasting and premature death. Nephropathic cystinosis is usually diagnosed in infancy after children display symptoms to physicians, including markedly increased urination, thirst, dehydration, gastrointestinal distress, failure to thrive, rickets, photophobia and kidney symptoms specific to Fanconi syndrome. Management of cystinosis requires lifelong therapy.

Pseudomonas Aeruginosa Infection in Cystic Fibrosis

Cystic fibrosis is a rare, life-threatening genetic disease affecting approximately 70,000 people worldwide. Cystic fibrosis is caused by a mutation in the cystic fibrosis transmembrane conductance regulator, or CFTR, gene. Defective or missing CFTR protein causes poor flow of salt and water into or out of the cell in several organs, including the lungs. This leads to the buildup of abnormally thick secretions that can cause chronic lung infections and progressive lung damage in many patients that eventually leads to death.

Patients with cystic fibrosis are highly susceptible to colonization with bacterial infections of the lung, largely because their pulmonary mucous secretions are thicker, stickier, and more difficult to expectorate than those of healthy individuals. This creates an environment in the lung that favors bacterial proliferation. As of 2014, a median of approximately thirty-five percent of all patients with cystic fibrosis in the European Union, or EU, were colonized with Pseudomonas aeruginosa, a gram-negative bacterial infection. Infection rates climb as patients age.

Our Solutions

ACTIMMUNE

ACTIMMUNE is a biologically manufactured protein called interferon gamma-1b that is similar to a protein the human body makes naturally. In the body, interferon gamma is produced by cells of the immune system and helps to prevent infection in patients with CGD and enhances osteoclast function in patients with SMO. ACTIMMUNE is approved by the U.S. Food and Drug Administration, or FDA, to reduce the frequency and severity of serious infections associated with CGD and for delaying time to disease progression in patients with SMO. The precise way that ACTIMMUNE works to help prevent infection in patients with CGD and slow the worsening of SMO is not fully understood, but ACTIMMUNE is believed to work by modifying the cellular function of various cells, including those in the immune system and those that help form bones.

Efficacy in CGD

The International Chronic Granulomatous Disease Cooperative Study Group conducted a controlled clinical trial in 128 patients (ages ranging from one to forty-four years old) at thirteen medical centers across four countries. The purpose of this clinical trial was to evaluate the safety and efficacy of ACTIMMUNE in reducing the frequency and severity of serious infections in patients with CGD. Patients enrolled in the trial were randomly selected to receive either ACTIMMUNE or placebo in addition to antibiotics. The number and timing of serious infections were tracked in all patients for up to 1 year. Investigators concluded that ACTIMMUNE is an effective and safe therapy for patients with CGD, because the therapy statistically reduced the frequency of serious infections.

Efficacy in SMO

In a controlled clinical trial, sixteen patients were randomized to receive either ACTIMMUNE with calcitriol or calcitriol alone. The age of patients ranged from one month to eight years; with a mean age of one and one-half years. The median time to progression in the ACTIMMUNE plus calcitriol arm was 165 days versus a median of sixty-five days in the calcitriol only arm. In a separate analysis that combined data from a second trial, nineteen of twenty-four patients on ACTIMMUNE therapy (with or without calcitriol) for at least six months had reduced trabecular bone volume compared to baseline.

Commercial Status

ACTIMMUNE is the only drug currently approved by the FDA for the treatment for CGD and SMO. Our licenses allow us to market and sell ACTIMMUNE in the United States, Canada and Japan. We currently commercialize ACTIMMUNE in the United States and also supply ACTIMMUNE to patients in Canada, if so requested by way of a prescription from their treating physicians, through Health Canada’s, or HC, Special Access Program, which provides access to non-marketed drugs in Canada for practitioners treating patients with serious or life-threatening conditions when conventional therapies have failed, are unsuitable or are unavailable. We have not registered or sold ACTIMMUNE in Japan.

On May 18, 2016, we entered into a definitive agreement with Boehringer Ingelheim International GmbH, or Boehringer Ingelheim International, to acquire certain rights to interferon gamma-1b, which Boehringer Ingelheim International currently commercializes under the trade names IMUKIN, IMUKINE, IMMUKIN and IMMUKINE in

an estimated thirty countries, primarily in Europe and the Middle East. The transaction is expected to close in 2017 and we are continuing to work with Boehringer Ingelheim International to enable the transfer of applicable marketing authorizations.

BUPHENYL

BUPHENYL tablets for oral administration and BUPHENYL powder for oral, nasogastric, or gastrostomy tube administration are indicated as adjunctive therapy in the chronic management of patients with UCDs involving deficiencies of carbamoyl phosphate synthetase, ornithine transcarbamylase or argininosuccinic acid synthetase.

BUPHENYL is indicated in all patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy. It is important that the diagnosis be made early and treatment initiated immediately to improve chances of survival. BUPHENYL must be combined with dietary protein restriction and, in some cases, essential amino acid supplementation.

Commercial Status

BUPHENYL was approved by the FDA in the United States in 1996 and by the European Medicines Agency, or EMA, in Europe in 1999. We commercially market and distribute BUPHENYL in the United States. BUPHENYL is known as AMMONAPS in certain European countries, and the marketing and distribution rights are granted to SOBI through the end of 2021. We provide BUPHENYL in certain other countries through various Special Access Programs and licensed distributors.

PROCYSBI

PROCYSBI is an approved therapy for the management of nephropathic cystinosis. PROCYSBI capsules contain cysteamine bitartrate in the form of innovative microspheronized beads that are individually coated to create delayed and extended-release properties, allowing patients to maintain consistent therapeutic systemic drug levels over a twelve-hour dosing period. The enteric-coated beads are pH sensitive and bypass the stomach for dissolution and absorption in the more alkaline environment of the proximal small intestine. Randomized controlled clinical trials and extended treatment with PROCYSBI therapy demonstrated consistent cystine depletion as monitored by levels of the biomarker (and surrogate marker), white blood cell cystine.

In addition to the population of patients who have already been identified, we believe that a number of patients with atypical phenotypic presentation and end-stage renal disease have their condition as a result of undiagnosed late-onset nephropathic cystinosis, and would benefit from treatment with PROCYSBI.

Commercial Status

PROCYSBI received marketing approval from the FDA in April 2013 for the management of nephropathic cystinosis in adults and children six years and older. In August 2015, the FDA approved PROCYSBI for expanded use to treat children two to six years of age with nephropathic cystinosis. In Europe, PROCYSBI received marketing authorization in September 2013 from the European Commission, or EC, for marketing in the EU countries as an orphan medicine for the management of proven nephropathic cystinosis. The EU marketing authorization allows us to commercialize PROCYSBI in the 28 Member States of the EU plus Norway, Liechtenstein and Iceland. PROCYSBI received seven years of market exclusivity, through 2020, for patients six years of age and older as an orphan drug in the United States, and ten years of market exclusivity, through 2023, as an orphan drug in Europe. PROCYSBI received orphan drug designation in the United States for the treatment of patients aged two to six years of age, through 2022.

QUINSAIR

QUINSAIR is a formulation of the antibiotic drug levofloxacin, suitable for inhalation via a nebulizer. This route of delivery allows higher concentrations of drug in the lung sputum than can be achieved via systemic (for example, oral) administration. QUINSAIR, as approved, is administered twice daily in twenty-eight-day cycles, using a hand-held nebulizer with a disposable handset known as the Zirela® device, manufactured by our partner PARI Pharma GmbH, or PARI, and configured specifically for use with QUINSAIR.

Commercial Status

QUINSAIR is the first fluoroquinolone inhaled antibiotic to be approved in Canada and the EU for the treatment of chronic pulmonary infections due to Pseudomonas aeruginosa in cystic fibrosis patients. QUINSAIR was approved in the EU and Canada on the basis of three randomized, controlled studies, one Phase 2 and two Phase 3. In the EU, QUINSAIR is eligible for “new data” regulatory exclusivity of ten years after approval, beginning with its March 2015 marketing authorization, a period which is concurrent with, and independent from, the period of any applicable patent. QUINSAIR is not approved in the United States. Raptor launched QUINSAIR in Germany and Denmark in the first half of 2016 and we launched QUINSAIR in Canada in December 2016. We do not plan to pursue approval in the United States for QUINSAIR as a treatment of pseudomonas aeruginosa in adults with cystic fibrosis.

RAVICTI

RAVICTI is indicated for use as a nitrogen-binding agent for chronic management of adult and pediatric patients two years of age and older (two months of age and older in Europe) with UCDs that cannot be managed by dietary protein restriction and/or amino acid supplementation alone. RAVICTI must be used with dietary protein restriction and, in some cases, dietary supplements (for example, essential amino acids, arginine, citrulline or protein-free calorie supplements).

Efficacy in the Treatment of UCDs in Adult Patients

A randomized, double-blind, active-controlled, crossover, non-inferiority study compared RAVICTI to sodium phenylbutyrate by evaluating venous ammonia levels in patients with UCDs that had been on sodium phenylbutyrate prior to enrollment for control of their UCD. Patients adhered to a low-protein diet and received amino acid supplements throughout the study. After two weeks of dosing, by which time patients had reached a steady state on each treatment, all patients had twenty-four hours of ammonia measurements.

Another study was conducted to assess monthly ammonia control and hyperammonemic crisis over a twelve-month period. A total of fifty-one adults were in the study and all but six had been converted from sodium phenylbutyrate to RAVICTI. Venous ammonia levels were monitored monthly. Of fifty-one adult patients participating in the twelve-month, open-label treatment with RAVICTI, seven patients (fourteen percent) reported a total of ten hyperammonemic crises.

The efficacy of RAVICTI in pediatric patients two to seventeen years of age was evaluated in two fixed-sequence, open-label, sodium phenylbutyrate to RAVICTI switchover studies, seven and ten days in duration. These studies compared blood ammonia levels of patients on RAVICTI to venous ammonia levels of patients on sodium phenylbutyrate in twenty-six pediatric UCD patients. Twenty-four hour blood ammonia levels of UCD patients six to seventeen years of age (Study 3) and patients two to five years of age (Study 4) were similar between treatments but trended higher with sodium phenylbutyrate.

Long-term (twelve-month), uncontrolled, open-label studies were conducted to assess monthly ammonia control and hyperammonemic crisis over a twelve-month period. Of the twenty-six pediatric patients six to seventeen years of age participating in these two trials, five patients (nineteen percent) reported a total of five hyperammonemic crises.

Commercial Status

RAVICTI was approved for marketing in the United States in 2013. Current FDA approval is for patients from two years of age and older only.

In November 2015, the EC adopted a binding decision to approve RAVICTI for use as an adjunctive therapy for chronic management of adult and pediatric patients two months of age and older with six subtypes of UCDs. This decision followed the Positive Opinion previously adopted on September 24, 2015 by the Committee for Medicinal Products for Human Use, or CHMP, of the EMA. The approval authorizes us to market RAVICTI in all twenty-eight Member States of the EU and the centralized marketing authorization will form the basis for recognition by the Member States of the European Economic Area, or EEA, namely Norway, Iceland and Liechtenstein, for the medicine to be placed on the market. In June 2016, we partnered with Clinigen Group plc’s Idis managed access division to initiate a managed access program in selected European countries, which agreement will terminate on April 10, 2017 and after which we will partner with SOBI to continue our managed access program in selected European countries. We expect to commercially launch RAVICTI in Europe in 2017 through an exclusive distribution agreement with SOBI.

We have worldwide rights to market and distribute RAVICTI. In relation to marketing and distribution rights in the Middle East and North Africa region, we have entered into a distribution agreement with SOBI through 2018. In March 2016, HC issued a Notice of Compliance for RAVICTI for use as an adjunctive therapy for chronic management of adult and pediatric patients two years of age and older with UCDs, and we launched RAVICTI in Canada in November 2016.

We are in the process of seeking approval for label expansions for RAVICTI, with assessments in progress studying the use of RAVICTI in patients both from two months to two years (on June 29, 2016 we submitted a supplemental new drug application, or sNDA, with the FDA for this indication) and from birth to two months (targeted sNDA submission in the first quarter of 2018). In patients with UCDs for which RAVICTI is an FDA-approved medicine, there is a variable age of diagnosis (from newborn to adulthood), and the severity of the disease can be associated with the age of onset and enzymatic deficit. However, a prompt diagnosis and careful management of the disease can lead to good clinical outcomes.

Competition

ACTIMMUNE presently faces limited competition. ACTIMMUNE is the only drug currently approved by the FDA specifically for the treatment for CGD and SMO. While there are additional or alternative approaches used to treat patients with CGD and SMO, including the increasing trend towards the use of bone marrow transplants in patients with CGD, there are currently no medicines on the market that compete directly with ACTIMMUNE.

In the United States, RAVICTI and BUPHENYL compete with generic forms of sodium phenylbutyrate. In Europe and certain other countries, RAVICTI and BUPHENYL compete with Pheburane, which is a sugar-coated version of sodium phenylbutyrate. Pheburane claims a taste advantage over BUPHENYL. However the volume of Pheburane that must be ingested multiple times per day is much greater than BUPHENYL, and significantly greater than RAVICTI, and is a barrier to patient compliance.

Other than PROCYSBI, we are aware of two pharmaceutical products currently approved to treat cystinosis. Cystagon® (immediate-release cysteamine bitartrate capsules), is a systemic cystine-depleting therapy for cystinosis in the United States manufactured by Mylan N.V., and by Orphan Europe SARL in markets outside of the United States. Cystagon was approved by the FDA in 1994 and by the EC in 1997. Cystaran® (cysteamine ophthalmic solution) was approved by FDA in 2012 for treatment of corneal crystal accumulation in patients with cystinosis and is marketed by Sigma Tau Pharmaceuticals, Inc.

While we believe that PROCYSBI will continue to be well received in the market, Cystagon remains on the market and we expect it will compete with PROCYSBI for the foreseeable future. We are not aware of any pharmaceutical company with an active program to develop an alternative therapy for cystinosis. Academic researchers in the United States and Europe are pursuing gene therapy and stem cell therapy, as well as pro-drug and PEGylated drug approaches as alternatives to cysteamine bitartrate. We believe that the development timeline to an approved product for these approaches is many years with substantial uncertainty.

In relation to QUINSAIR, chronic pulmonary infections due to Pseudomonas aeruginosa are currently treated primarily with inhaled antibiotics, including tobramycin, an aminoglycoside-class antibiotic sold by Novartis Pharmaceuticals Corporation as TOBI® or in dry-powder-inhalation format as TOBI Podhaler® and sold by others in generic form, aztreonam, a monobacter-class antibiotic which is marketed in an inhaled formulation by Gilead Sciences, Inc. under the tradename Cayston®, and colistimethate sodium, a polymixin-class antibiotic which is approved and marketed in inhaled formulations in Europe. Tobramycin, aztreonam and colistimethane are primarily effective against gram-negative bacteria such as Pseudomonas aeruginosa. However, the prevalence of multi-drug-resistant Pseudomonas aeruginosa is growing. Thus, we believe there is an unmet need that might be addressed with a new class of inhaled antibiotic such as the fluoruquinolone class that levofloxacin represents.

RHEUMATOLOGY BUSINESS UNIT

Market

Chronic Refractory Gout

Chronic refractory gout, or CRG, is a type of arthritis that occurs when uric acid build-up in the blood remains high and inflammation persists even after treatment with conventional therapies. Gout is one of the most common forms of inflammatory arthritis, estimated to affect 8.3 million in the United States, with CRG impacting 40,000 to 50,000 people in the United States. CRG frequently causes crippling disabilities and significant joint damage.

Rheumatoid Arthritis

Rheumatoid arthritis, or RA, is a chronic disease that causes pain, stiffness and swelling, primarily in the joints. According to a 2006 DataMonitor report, 2.9 million people in the United States suffer from RA, of which 1.8 million are diagnosed and treated with various drugs. RA has no known cause, but unlike osteoarthritis, or OA, RA is not associated with factors such as aging. RA occurs when the body's immune system malfunctions, attacking healthy tissue and causing inflammation, which leads to pain and swelling in the joints and may eventually cause permanent joint damage and painful disability. The primary symptoms of RA include progressive immobility and pain, especially in the morning, with long-term sufferers experiencing continual joint destruction for the remainder of their lives. There is no known cure for RA. Once the disease is diagnosed, treatment is prescribed for life to alleviate symptoms and/or to slow or stop disease progression. RA treatments include medications, physical therapy, exercise, education and sometimes surgery. Early, aggressive treatment of RA can delay joint destruction. Treatment of RA usually includes multiple drug therapies taken concurrently. Disease-modifying anti-rheumatic drugs, or DMARDs, are the current standard of care for the treatment of RA, in addition to rest, exercise and anti-inflammatory drugs such as nonsteroidal anti-inflammatory drugs, or NSAIDs.

Polymyalgia Rheumatica

Polymyalgia rheumatica, or PMR, is an inflammatory disorder that causes significant muscle pain and stiffness. The pain and stiffness often occur in the shoulders, neck, upper arms and hip with pronounced morning stiffness lasting at least one hour. Most people who develop PMR are older than sixty-five years of age. It rarely affects people younger than fifty. There are approximately 1.1 million patients with PMR in the United States and it afflicts one in every 133 people over the age of fifty. Prednisone is the standard of care for treating PMR and treatment is generally initiated at a relatively high dose (for example, 10-20 mg per day) and reduced as clinical improvement is seen. Treatment usually lasts eighteen to twenty-four months. Similar to RA, PMR is associated with circadian patterns of Interleukin 6, or IL-6, elevation in early morning hours.

Systemic Lupus Erythematosus

Systemic lupus erythematosus, or SLE, is a chronic autoimmune disease that causes inflammation and pain in the joints and muscles as well as overall fatigue. SLE affects from 161,000 to 322,000 adults in the United States. More than 90 percent of cases of SLE occur in women, frequently starting at childbearing age. In addition to affecting the muscles and joints, it can affect other organs in the body such as the kidneys, tissue lining the lungs (pleura), heart (pericardium), and brain. Most patients feel fatigue and have rashes, arthritis (painful and swollen joints) and fever. SLE flares vary from mild to serious.

In November 2015, we announced our collaboration with the Alliance for Lupus Research, or ALR, to study the effect of RAYOS on the fatigue experienced by SLE patients. SLE is a chronic autoimmune disease that causes inflammation and pain in the joints and muscles, as well as overall fatigue. RAYOS is currently indicated for patients with SLE. The first study planned as part of the collaboration is an investigator-initiated, randomized, double-blind, active comparator, cross-over study in which patients will be randomized to receive either prednisone for three months or RAYOS at 10 p.m. for three months, and then switched to the alternative medication for an additional three months. Approximately sixty-two patients across twenty-five sites will be enrolled in the United States. Fatigue will be measured by the Functional Assessment of Chronic Illness Therapy-Fatigue and the Fatigue Severity Scale, as well as the Vitality scale of the Medical Outcome Study thirty-six-item short form health survey.

Market Opportunity and Limitations of Existing Treatments

Morning Stiffness, Pain and Immobility

A Medical Marketing Economics May 2008 study of 150 RA patients in the United States, which we sponsored, showed that despite the use of a combination of currently available treatments for RA, more than ninety percent of the patients reported suffering from morning stiffness, pain and immobility, which is linked to peak IL-6 levels in the early morning hours. We believe an optimal treatment would reduce IL-6 levels in the early morning hours.

Side Effects of Current High-Dose Corticosteroid Treatments

According to the 2006 DataMonitor report, approximately 50 percent of RA patients in the United States, Japan, France, Italy, Spain, Germany and the United Kingdom are prescribed combination therapy which often includes corticosteroids, with prednisone being one of the most common. Corticosteroids, including prednisone, are used to suppress various autoimmune, inflammatory and allergic disorders by inhibiting the production of various pro-inflammatory cytokines. Joint inflammation in RA is driven by excessive production of inflammatory mediators and cytokines, such as IL-6 and TNF-alpha. While corticosteroids are potent and effective agents to treat patients with RA, they are often used at high doses to treat RA flares or significant inflammation. High-dose oral corticosteroid treatment is not a viable long-term treatment option due to adverse side effects such as osteoporosis, cardiovascular disease and weight gain. However, clinical studies have shown that the long-term use of low-dose prednisone (<10 mg per day) does not dramatically increase total adverse events. In addition, low doses, typically less than 10 mg daily, of corticosteroids such as prednisone have been shown to treat the symptoms of RA while slowing the overall progression of the disease.

Our Solutions

KRYSTEXXA

KRYSTEXXA is an orphan biologic medicine which is the first and only FDA-approved medicine for the treatment of CRG. KRYSTEXXA is a PEGylated uric acid specific enzyme (uricase) indicated for the treatment of CRG in adult patients that are refractory to conventional therapy. Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated. KRYSTEXXA has a unique mechanism of action which rapidly reverses disease progression. A PEGylated uric acid specific enzyme catalyzes the conversion of serum uric acid to allantoin, which is then excreted in urine. This PEGylated uric acid specific enzyme is given via an intravenous infusion to patients every two weeks.

Commercial Status

KRYSTEXXA was launched in the United States in January 2011.

RAYOS/LODOTRA

The medicine sold and marketed as RAYOS in the United States is known as LODOTRA outside the United States. While the FDA has approved RAYOS for the treatment of RA, ankylosing spondylitis, or AS, PMR, primary systemic amyloidosis, asthma, chronic obstructive pulmonary disease, SLE and a number of other conditions, we have focused our promotion of RAYOS/LODOTRA on rheumatology indications, including RA and PMR.

The proprietary formulation technology of RAYOS/LODOTRA enables a delayed-release of prednisone approximately four hours after administration. The RAYOS/LODOTRA proprietary delivery system synchronizes the prednisone delivery time with the patient's elevated cytokine levels, thereby taking effect at a physiologically optimal point to inhibit cytokine production, and thus significantly reduces the signs and symptoms of RA and PMR.

RAYOS/LODOTRA was developed using Vectura Group plc's (as successor in interest to SkyePharma AG, or SkyePharma), or Vectura, proprietary GeoClock™ and GeoMatrix™ technologies, for which we hold an exclusive worldwide license for the delivery of glucocorticoid, a class of corticosteroid. RAYOS/LODOTRA is composed of an active core containing prednisone, which is encapsulated by an inactive porous shell. The inactive shell acts as a barrier between the medicine's active core and a patient's gastrointestinal, or GI, fluids. RAYOS/LODOTRA is intended to be administered at bedtime. At approximately four hours following bedtime administration of RAYOS/LODOTRA, water in the digestive tract diffuses through the shell, causing the active core to expand, which

leads to a weakening and breakage of the shell and allows the release of prednisone from the active core. Our pharmacokinetic studies have shown that the blood concentration of prednisone from RAYOS/LODOTRA is similar to immediate release prednisone except for the intended time delay of medicine release after administration.

Commercial Status

We began marketing RAYOS to U.S. rheumatologists in December 2012. LODOTRA received its first approval in Europe in March 2009. Mundipharma is our exclusive distributor for LODOTRA in Europe, Asia and Latin America. The majority of LODOTRA sales are in Germany and Italy where reimbursement has been approved.

Competition

As the only FDA approved medication for the treatment of CRG, KRYSTEXXA faces limited direct competition. We believe that the complexity of manufacturing KRYSTEXXA provides a barrier to potential generic competition. However, a number of competitors have medicines in Phase 1 or Phase 2 trials. On December 22, 2015, AstraZeneca AB, or AstraZeneca, secured approval from the FDA for Zurampic® (lesinurad) 200mg tablets in combination with a xanthine oxidase inhibitor, or XOI, for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with an XOI alone. In April 2016, the U.S. rights to Zurampic were licensed to Ironwood Pharmaceuticals Inc. Although Zurampic is not a direct competitor because it has not been approved for CRG, this therapy could be used prior to use of KRYSTEXXA, and if effective, could reduce the target patient population for KRYSTEXXA.

RAYOS/LODOTRA competes with a number of medicines in the market to treat RA, including corticosteroids, such as prednisone, traditional DMARDs, such as methotrexate, and biologic agents, such as Humira and Enbrel. The majority of RA patients are treated with DMARDs, which are typically used as initial therapy in patients with RA. Biologic agents are typically added to DMARDs as combination therapy. It is common for an RA patient to take a combination of a DMARD, an oral corticosteroid, an NSAID, and/or a biologic agent. We are not currently aware of any other delayed-release prednisone medicine in development.

PRIMARY CARE BUSINESS UNIT

Market

Pain is a serious and costly public health concern. In 2010, the U.S. National Center for Health Statistics reported that approximately 30 percent of U.S. adults 18 years of age and over reported recent symptoms of pain, aching or swelling around a joint within the past 30 days.

Some of the most common and debilitating chronic inflammation and pain-related diseases are OA, RA and acute and chronic pain. According to National Health Interview Survey data analyzed by the U.S. Centers for Disease Control and Prevention, from 2010-2012, 52.5 million U.S. adults eighteen years of age and over had reported being diagnosed with some form of arthritis. With the aging of the U.S. population, the prevalence of arthritis is expected to rise by approximately forty percent by 2030, impacting sixty-seven million people in the United States.

Osteoarthritis

OA is a type of arthritis that is caused by the breakdown and eventual loss of the cartilage of one or more joints. Cartilage is a protein substance that serves as a cushion between the bones of the joints. Among the over 100 different types of arthritis conditions, OA is the most common and occurs more frequently with age. OA commonly affects the hands, feet, spine and large weight-bearing joints, such as the hips and knees. Symptoms of OA manifest in patients as joint pain, tenderness, stiffness, limited joint movement, joint cracking or creaking (crepitation), locking of joints and local inflammation. OA can also lead to joint deformity in later stages of the disease. Many drugs are used to treat the inflammation and pain associated with OA, including aspirin and other NSAIDs, such as ibuprofen, naproxen and diclofenac that have a rapid analgesic and anti-inflammatory response.

Rheumatoid Arthritis

The market for RA has been discussed above in the Rheumatology Business Unit section (refer to Page 10).

Ankylosing Spondylitis

AS is a type of arthritis that affects the spine. AS symptoms include pain and stiffness from the neck down to the lower back. The spine’s bones (vertebrae) may grow or fuse together, resulting in a rigid spine. These changes may be mild or severe, and may lead to a stooped-over posture. Early diagnosis and treatment helps control pain and stiffness and may reduce or prevent significant deformity.

Market Opportunity and Limitations of Existing Treatments

GI-Associated Adverse Events

NSAIDs are very effective at providing pain relief, including pain associated with OA and RA; however, there are significant upper GI-associated adverse events that can result from the use of NSAIDs. According to a 2004 article published in Alimentary Pharmacology & Therapeutics, significant GI side effects, including serious ulcers, afflict up to approximately twenty-five percent of all chronic arthritis patients treated with NSAIDs for three months, and OA and RA patients are two to five times more likely than the general population to be hospitalized for NSAID-related GI complications. It is estimated that NSAID-induced GI toxicity causes over 16,500 related deaths in OA and RA patients alone and over 107,000 hospitalizations for serious GI complications each year. In more than seventy percent of patients with these serious GI complications, there are no prior symptoms.

Despite the fact that GI ulcers are one of the most prevalent adverse events resulting from the use of NSAIDs in the United States, according to a 2006 article published in BMC Muskoskeletal Disorders, eleven observational studies indicated that physicians do not commonly co-prescribe GI protective agents to high-risk patients. Physicians prescribe concomitant therapy to only twenty-four percent of NSAID users, and studies show sub-optimal patient compliance with concomitant prophylaxis therapy. According to a 2003 article published in Alimentary Pharmacology & Therapeutics, in a study of 784 patients, thirty-seven percent of patients were non-compliant, a rate increasing to sixty-one percent in patients treated with three or more drugs. This noncompliance results in a substantial unmet clinical need, which we believe can be appropriately addressed with DUEXIS or VIMOVO, creating smarter solutions for both patients and physicians.

Topical NSAIDs

Within the NSAID market there exists a significant niche for topical NSAIDs, which are prescribed more than five million times per year. Topical NSAID treatment may be appropriate for some patients, such as patients who may benefit from the lower systemic exposure in a topical NSAID, patients with OA in just one joint such as the knee, patients who have trouble taking oral medications, or patients who are older. However, applying the correct dosage of the topical NSAID amount can often be a barrier to patient compliance, and there exists a market for a more convenient and more accurate application technique.

Our Solutions

DUEXIS

DUEXIS tablets are a proprietary, single-tablet combination containing a fixed-dose combination of ibuprofen, the most widely prescribed NSAID, and famotidine, a well-established GI agent used to treat dyspepsia, gastroesophageal reflux disease and active ulcers, in one pill. Based on clinical study results, DUEXIS has been proven to reduce the risk of ibuprofen-induced upper GI ulcers in patients taking ibuprofen for OA or RA.

Ibuprofen: One of the World’s Most Widely Prescribed NSAIDs

Ibuprofen continues to be one of the most widely prescribed NSAIDs worldwide. According to Intercontinental Marketing Services, or IMS, in the United States alone, there were over 42 million prescriptions written for ibuprofen in 2015. Ibuprofen’s flexible three times daily dosing allows it to be used for both chronic conditions such as arthritis and chronic back pain, and acute conditions such as sprains and strains.

Famotidine: A Safe and Effective GI Agent

Famotidine is the most potent marketed drug in the class of histamine-2 receptor antagonists, or H2RA. H2RAs are a class of drugs used to block the action of histamine on the cells in the stomach that secrete gastric acid. Famotidine was chosen as the ideal GI protectant to be combined with ibuprofen as it is a well-studied compound with an estimated 18.8 million patients treated worldwide that provides distinct advantages including:

- rapid onset of action; and
- well-tolerated with a low incidence of adverse drug reactions and a demonstrated safety margin of up to eight times the approved prescription dose for an extended period of greater than twelve months.

Although famotidine as a standalone product is not indicated for risk reduction of GI ulcers, two well-controlled clinical trials of famotidine formulated in DUEXIS found a significant decrease in the risk of developing upper GI ulcers, which in the clinical trials was defined as a gastric and/or duodenal ulcer in patients who are taking ibuprofen for those indications. Additionally, over-the-counter dosages of famotidine have been shown to be ineffective.

Benefits of a Fixed-Dose Combination Therapy

Numerous studies have demonstrated that fixed-dose combination therapy provides significant advantages over taking multiple pills. Specifically, fixed-dose combinations can reduce the number of pills, ensure that the correct dosage of each component is taken at the correct time and improve compliance, often associated with better treatment outcomes. DUEXIS has been formulated to provide an optimal dosing regimen of ibuprofen and famotidine together in the convenience of a single pill. Data shows that physicians co-prescribe GI protective agents less than twenty-five percent of the time when prescribing an NSAID. On occasions where a patient is co-prescribed a GI protective agent, data shows that after three prescriptions, sixty-one percent of patients no longer take a GI protective agent.

Commercial Status

DUEXIS is indicated for the relief of signs and symptoms of RA and OA and to decrease the risk of developing upper-GI ulcers (which in the clinical trials was defined as a gastric and/or duodenal ulcer) in patients who are taking ibuprofen for these indications. We began marketing DUEXIS to U.S. physicians in December 2011.

In June 2012, we licensed DUEXIS rights in Latin America to Grünenthal, a private company focused on the promotion of pain medicines.

PENNSAID 2%

PENNSAID 2% is a topical NSAID that is applied directly to the knee and is indicated for the treatment of pain of OA of the knee(s). PENNSAID 2% contains diclofenac sodium, a commonly prescribed NSAID to treat OA pain. PENNSAID 2% also includes dimethyl sulfoxide, or DMSO, a penetrating agent that helps ensure that diclofenac sodium is absorbed through the skin to the site of inflammation and pain. Topical NSAIDs such as PENNSAID 2% are an alternative to oral NSAID treatment because they reduce systemic exposure to a fraction of that provided by an oral NSAID. PENNSAID 2% is the only topical NSAID offered with the convenience of a metered-dose pump, which ensures that the patient will get the correct amount of PENNSAID 2% solution each time. PENNSAID 2% is easy to apply for patients because PENNSAID 2% is applied in two pumps, twice daily, delivering relief right to the site of OA knee pain.

Commercial Status

On January 16, 2014, the FDA approved PENNSAID 2% for the treatment of the pain of OA of the knee(s). We acquired the U.S. rights to PENNSAID 2% in October 2014, and began marketing PENNSAID 2% with our primary care sales force in early January 2015.

VIMOVO

VIMOVO is a proprietary, fixed-dose, delayed-release tablet. VIMOVO combines enteric-coated naproxen, an NSAID, surrounded by a layer of immediate-release esomeprazole magnesium surrounding the core. Naproxen has proven anti-inflammatory and analgesic properties and esomeprazole magnesium reduces the stomach acid secretions that can cause upper GI ulcers. Both naproxen and esomeprazole magnesium have well-documented and excellent long-term safety profiles and both medicines have been used by millions of patients worldwide. Based on clinical trial results, VIMOVO has been shown to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID associated gastric ulcers.

Naproxen: One of the World’s Most Widely Prescribed NSAIDs

Naproxen is another of the most widely prescribed NSAIDs worldwide. According to IMS, in the United States alone, there were more than seventeen million prescriptions written for naproxen in 2015. In addition, naproxen’s twice daily dosing allows it to be used for chronic conditions such as arthritis and AS.

Esomeprazole Magnesium: A Safe and Effective GI Agent

Esomeprazole magnesium, a gastroprotective agent, is a proton pump inhibitor, or PPI, that works by inhibiting the secretion of gastric acid thus decreasing the amount of acid in the stomach. PPIs are considered to be very potent inhibitors of acid secretion. Esomeprazole magnesium is indicated for reducing the risk of NSAID-induced gastric ulcers.

Benefits of a Fixed-Dose Combination Therapy

VIMOVO is specifically formulated to allow esomeprazole magnesium to achieve its gastroprotective impact before naproxen is released into the system. VIMOVO's design is intended to produce a sequential delivery of gastroprotective esomeprazole before exposure to naproxen. Data shows that physicians co-prescribe GI protective agents less than 25 percent of the time when prescribing an NSAID. On occasions where a patient is co-prescribed a GI protective agent, data shows that after three prescriptions, 61 percent of patients no longer take a GI protective agent.

Commercial Status

Following our acquisition of the U.S. rights to VIMOVO in November 2013, we began marketing VIMOVO in early January 2014. VIMOVO is indicated for the relief of signs and symptoms of OA, RA and AS and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers. VIMOVO is not interchangeable with the individual components of naproxen and esomeprazole magnesium.

MIGERGOT

MIGERGOT is indicated as therapy to abort or prevent vascular headaches, such as migraines, migraine variants or so-called "histaminic cephalalgia". MIGERGOT is not promoted by our sales representatives.

Competition

Our competitors in our primary care markets include large pharmaceutical and biotechnology companies, specialty pharmaceutical companies and generic drug companies, although we are not currently aware of any other ibuprofen/famotidine combination medicine or naproxen/esomeprazole magnesium combination medicine in development.

DUEXIS and VIMOVO compete with other NSAIDs, including Celebrex® which was marketed by Pfizer Inc., and is also a generic medicine known as celecoxib and supplied by other pharmaceutical companies. Celecoxib is an NSAID that selectively inhibits the COX-2 enzyme and is an effective anti-arthritic agent that reduces the risk of ulceration compared to traditional NSAIDs such as ibuprofen. DUEXIS and VIMOVO also compete with TIVORBEX™ (indomethacin) capsules, marketed by Iroko Pharmaceuticals, LLC.

In general, DUEXIS and VIMOVO also face competition from the separate use of NSAIDs for pain relief and GI medications to address the risk of NSAID-induced ulcers. Use of these therapies separately in generic form may be less expensive than DUEXIS and VIMOVO. We expect to compete with the separate use of NSAIDs and ulcer medications primarily through DUEXIS' and VIMOVO's advantages in dosing convenience and patient compliance, and by educating physicians about such advantages. DUEXIS is the only NSAID medicine containing a histamine-2 receptor antagonist with an indication to reduce the risk of NSAID-induced upper GI ulcers and VIMOVO is the only NSAID medicine containing a PPI with an indication to reduce the risk of NSAID-induced ulcers. Data shows that physicians co-prescribe GI protective agents less than twenty-five percent of the time when prescribing an NSAID. On occasions where a patient is co-prescribed a GI protective agent, data shows that after three prescriptions, sixty-one percent of patients no longer take a GI protective agent.

PENNSAID 2% faces competition from generic versions of diclofenac sodium topical solutions which are priced significantly lower than the price we charge for PENNSAID 2%. PENNSAID 2% competes primarily with Diclofenac, a market leader in the topical NSAID category. We expect to compete with these other medicines primarily through PENNSAID 2%'s dosing convenience and patient compliance. Unlike the other two medicines that are dosed four times per day and require the patient to measure out the correct dose, only PENNSAID 2% is easy to apply with the convenience of twice-daily dosing and a metered-dose pump, which ensures that the patient will get the correct amount of PENNSAID 2% solution each time.

Distribution

Finished tablets of DUEXIS, VIMOVO, RAYOS, MIGERGOT, BUPHENYL and PROCYSBI, vials of ACTIMMUNE and KRYSTEXXA, bottles of RAVICTI, PENNSAID 2% and QUINSAIR and powder of BUPHENYL are shipped to central third-party logistics FDA-compliant warehouses for storage and distribution into the supply chain. Our third-party logistics providers specialize in integrated operations that include warehousing and transportation services that can be scaled and customized to our needs based on market conditions and the demands and delivery service requirements for our medicines and materials. Their services eliminate the need to build dedicated internal infrastructures that would be difficult to scale without significant capital investment. Our third-party logistics providers warehouse all medicines in controlled FDA-registered facilities. Incoming orders are prepared and shipped through an order entry system to ensure just in time delivery of the medicines.

Sales and Marketing

As of December 31, 2016, our sales force was composed of approximately 480 sales representatives consisting of approximately 20 orphan disease sales representatives, 100 rheumatology sales specialists and 360 primary care sales representatives.

Our orphan disease representatives focus on marketing our orphan medicines to a limited number of healthcare practitioners who specialize in fields such as pediatric immunology, allergy, infectious diseases and metabolic disorders to help them understand the potential benefits of our medicines. We have entered into, and may continue to enter into, agreements with third parties for commercialization of our medicines outside the United States.

Part of our commercial strategy for RAYOS and our primary care medicines is to offer physicians the opportunity to have their patients fill prescriptions through pharmacies participating in our HorizonCares patient access program. For commercial patients who are prescribed our primary care medicines or RAYOS, the HorizonCares program offers co-pay assistance when a third-party commercial payer covers a prescription but requires an eligible patient to pay a co-pay or deductible, and offers full subsidization when a third-party commercial payer rejects coverage for an eligible patient. During 2016, we entered into business arrangements with pharmacy benefit managers, or PBMs, and other payers to secure formulary status and reimbursement of our medicines, such as our arrangements with Express Scripts, Inc., CVS Caremark and Prime Therapeutics LLC. While we believe that this strategy will result in broader inclusion of certain of our primary care medicines on healthcare plan formularies, and therefore increase payer reimbursement and lower our cost of providing patient access programs, these arrangements generally require us to pay administrative and rebate payments to the PBMs and/or other payers and regardless of our agreements with the PBMs, the extent of formulary status and reimbursement will ultimately depend to a large extent upon individual healthcare plan formulary decisions.

We have a comprehensive compliance program in place to address adherence with various laws and regulations relating to our sales, marketing, and manufacturing of our medicines, as well as certain third-party relationships, including pharmacies. Specifically with respect to pharmacies, the compliance program utilizes a variety of methods and tools to monitor and audit pharmacies, including those that participate in our patient access programs, to confirm their activities, adjudication and practices are consistent with our compliance policies and guidance.

Manufacturing, Commercial and Supply Agreements

We have agreements with third parties for active pharmaceutical ingredients, or APIs, and manufacturing of our medicines, formulation and development services, fill, finish and packaging services, transportation, and distribution and logistics services for certain medicines. In most cases, we retain certain levels of safety stock or maintain alternate supply relationships that we can utilize without undue disruption of our manufacturing processes if a third party fails to perform its contractual obligations.

ACTIMMUNE

ACTIMMUNE is a recombinant protein that is produced by fermentation of a genetically engineered Escherichia coli bacterium containing the DNA which encodes for the human protein. Purification of the active drug substance is achieved by conventional column chromatography. The resulting active drug substance is then formulated as a highly purified sterile solution and filled in a single-use vial for subcutaneous injection, which is the ACTIMMUNE finished drug medicine. In support of its manufacturing process, we and Boehringer Ingelheim RCV GmbH & Co KG, or Boehringer Ingelheim, store multiple vials of the Escherichia coli bacterium master cell bank and working cell bank in order to ensure that it will have adequate backup should any cell bank be lost in a catastrophic event.

Boehringer Ingelheim Supply Agreement

In July 2013, Vidara and Boehringer Ingelheim entered into an exclusive supply agreement, which we assumed as a result of the Vidara Merger and amended effective as of June 1, 2015. Pursuant to the agreement, Boehringer Ingelheim manufactures the ACTIMMUNE active drug substance and commercial quantities of the ACTIMMUNE finished drug medicine. Boehringer Ingelheim is our sole source supplier for ACTIMMUNE active drug substance and finished drug medicine. Under the terms of this agreement, we are required to purchase minimum quantities of finished drug medicine of 75,000 vials per annum. Boehringer Ingelheim manufactures our commercial requirements of ACTIMMUNE on an annual basis, and based on our forecasts and the annual contractual minimum purchase quantity. The supply agreement has a term that runs until July 31, 2020 and which can be further renewed by agreement between parties. Under this supply agreement, either we or Boehringer Ingelheim may terminate the agreement for an uncured material breach by the other party or upon the other party's bankruptcy or insolvency.

In October 2016, we committed to purchase additional units of ACTIMMUNE from Boehringer Ingelheim in 2017. These additional units of ACTIMMUNE were intended to cover anticipated demand should the results of the Phase 3 trial, Safety, Tolerability and Efficacy of ACTIMMUNE Dose Escalation in Friedreich's Ataxia study, or STEADFAST, evaluating ACTIMMUNE for the treatment of Friedreich's ataxia, or FA, be successful and U.S. marketing approval for FA subsequently be received. In December 2016, we announced topline results from the study, and, based on the trial results, the decision to discontinue the STEADFAST program.

License Agreements

As a result of the Vidara Merger, we acquired a license agreement, as amended, with Genentech, Inc., or Genentech, who was the original developer of ACTIMMUNE. Under such agreement, we are or were obligated to pay royalties to Genentech on our net sales of ACTIMMUNE as follows:

- For the period from November 26, 2014 through May 5, 2018, a royalty in the twenty percent to thirty percent range for the first $3.7 million in net sales achieved in any calendar year, and in the one percent to nine percent range for all additional net sales in any year; and
- From May 6, 2018 and for so long as we continue to commercially sell ACTIMMUNE, an annual royalty in the low-single digits as a percentage of annual net sales.

Either Genentech or we may terminate the agreement if the other party becomes bankrupt or defaults, however, in the case of a default, the defaulting party has thirty days to cure the default before the license agreement may be terminated.

Under the terms of an assignment and option agreement with Connetics Corporation (which was the predecessor parent company to InterMune Pharmaceuticals Inc. and is now part of GlaxoSmithKline), or Connetics, we are obligated to pay royalties to Connetics on our net sales of ACTIMMUNE as follows:

- Low-single digits as a percentage of net sales of ACTIMMUNE in the United States.

RAVICTI

We have clinical and commercial supplies of glycerol phenylbutyrate API manufactured for us by two alternate suppliers, Helsinn Advanced Synthesis SA (Switzerland) and DSM Fine Chemicals Austria (now Patheon Austria GmbH & Co KG) on a purchase order basis. We have finished RAVICTI drug medicine manufactured by Lyne Laboratories, Inc. under a manufacturing agreement and we have an agreement in place for a fill/finish supplier, Halo Pharmaceuticals, Inc., for European supplies.

Ucyclyd Asset Purchase Agreement

As a result of the Hyperion acquisition, we acquired an asset purchase agreement with Ucyclyd Pharma, Inc., or Ucyclyd, pursuant to which we are obligated to pay to Ucyclyd tiered mid- to high- single digit royalties on our global net sales of RAVICTI. The asset purchase agreement cannot be terminated for convenience by either party. However, we have a license to certain Ucyclyd manufacturing technology, and Ucyclyd may have a license to certain of our technology, and the party granting a license is permitted to terminate the license if the other party fails to comply with any payment obligations relating to the license and does not cure such failure within a defined time period.

Brusilow License Agreement

As a result of the Hyperion acquisition, we acquired a license agreement with Saul W. Brusilow, M.D. and Brusilow Enterprises, Inc., or Brusilow, pursuant to which we license patented technology related to RAVICTI from Brusilow. Under such agreement, we are obligated to pay low-single digit royalties to Brusilow on net sales of RAVICTI that are covered by a valid claim of a licensed patent. The license agreement may be terminated for any uncured breach as well as bankruptcy. We may also terminate the agreement at any time by giving Brusilow prior written notice, in which case all rights granted to us would revert to Brusilow.

BUPHENYL

When Hyperion purchased BUPHENYL, Hyperion assumed all of Ucyclyd's rights and obligations under its manufacturing agreements for the medicine. We assumed these agreements when we acquired Hyperion. We purchase API for BUPHENYL from CU Chemie Uetikon GmbH and final manufacturing, testing and packaging of the medicine is provided by Pharmaceutics International Inc.

Amended and Restated Collaboration Agreement

Under the terms of an amended and restated collaboration agreement with Ucyclyd, we are obligated to pay to Ucyclyd tiered mid to high single-digit royalties on our net sales in the United States of BUPHENYL to UCD patients outside of the FDA approved labeled age range for RAVICTI.

PROCYSBI

PROCYSBI drug product is comprised of enteric coated beads of cysteamine bitartrate encapsulated in gelatin capsules. PROCYSBI drug product and API, cysteamine bitartrate, are manufactured on a contract basis by third parties.

Patheon Manufacturing Services Agreement

As a result of the Raptor acquisition, we assumed a manufacturing services agreement, as amended, with Patheon Pharmaceuticals Inc., or Patheon. Pursuant to the agreement, we must provide a rolling, non-binding forecast of PROCYSBI, with a portion of the forecast being a firm written order. The agreement has an initial term that runs until December 31, 2017 and which automatically renews for successive two year terms if not terminated at least eighteen months in advance. Notice of termination of the agreement was not given by any party by June 30, 2016, therefore the agreement will be in force until at least December 31, 2019.

Cambrex Profarmaco Milano Supply Agreement

As a result of the Raptor acquisition, we assumed an API supply agreement, as amended, with Cambrex Profarmaco Milano, or Cambrex. Pursuant to the agreement, we must provide rolling, non-binding forecasts, with a portion of the forecast being the minimum floor of the firm order that must be placed. The Cambrex supply agreement has an initial term that runs until November 30, 2020 and which automatically renews for successive two-year terms if not terminated at least one year in advance.

UCSD License Agreement

As a result of the Raptor acquisition, we assumed a license agreement, as amended, with The Regents of the University of California, San Diego, or UCSD. We must pay UCSD a royalty in the mid-single digits on net sales of PROCYSBI in countries where PROCYSBI is covered by a patent right, and a royalty in the low-single digits on net sales of PROCYSBI in countries where PROCYSBI is not covered by a patent right. We must pay UCSD a minimum

annual royalty in an amount less than $0.1 million. Royalties terminate upon the later of (a) the expiration date of the longest-lived patent rights on a country-by-country basis; and (b) ten years after first commercial sale of PROCYSBI. We may also be obligated to pay UCSD milestone payments for each orphan indication and for each non-orphan indication. We are also subject to diligence obligations relating to performing activities for specified indications, marketing licensed medicines in the United States, filling market demand for licensed medicines following commencement of marketing at any time during the agreement and obtaining all necessary governmental approvals for the manufacture, use and sale of licensed medicines.

QUINSAIR

QUINSAIR drug product, its API, levofloxacin hemihydrate, and the Zirela nebulizer device are all manufactured on a contract basis by third parties.

Teva Supply Agreement

The API is exclusively supplied by TEVA API Inc.. We must provide a twelve-month rolling forecast, and the first three months of this forecast is binding. The term of the TEVA supply agreement runs until April 11, 2021 with automatic one-year renewal periods unless notice is provided six months before termination.

Catalent Supply Agreement

QUINSAIR drug product is manufactured by Catalent Pharma Solutions, LLC. The term of the Catalent supply agreement runs until March 10, 2019. We must provide a twelve-month rolling forecast, and the first four months of this forecast is binding.

PARI Supply Agreement

Nebulizers are supplied by PARI in Starnberg, Germany. We are obligated to provide a twelve-month rolling forecast, and the first three months of this forecast is binding. The supply agreement runs until at least April 12, 2026.

RAYOS/LODOTRA

We rely on well-established third-party manufacturers for the manufacture of RAYOS/LODOTRA. We purchase the API for RAYOS/LODOTRA from Tianjin Tianyao Pharmaceuticals Co., Ltd. in China and from Sanofi Chimie SA in France. We have contracted with Jagotec AG, or Jagotec, for the production of RAYOS/LODOTRA tablets through its affiliate Vectura, and we entered into an agreement with Patheon for the packaging and assembling of RAYOS/LODOTRA.

Vectura and Jagotec Agreements

Development and License Agreement

In August 2004, we entered into a development and license agreement with Vectura, as successor in interest to SkyePharma, and Jagotec, a wholly owned subsidiary of Vectura, regarding certain proprietary technology and know-how owned by Vectura for the delayed-release of corticosteroids. Under the agreement, which was amended in August 2007, we received an exclusive, sub-licensable worldwide license to the oral formulation of any glucocorticoid, including prednisone, prednisolone, methylprednisolone and/or cortisone, with delayed-release technology covered by intellectual property rights and know-how owned by Vectura. We were also granted an option to acquire a royalty-free, exclusive and sub-licensable right to license and manufacture RAYOS/LODOTRA which we could exercise any time upon specified prior written notice, expiring no earlier than five years after the first launch of RAYOS/LODOTRA. We have exercised the option to acquire the manufacturing license, which became effective in April 2014.

In return for the grant of the license, Jagotec has the right to manufacture, package and supply RAYOS/LODOTRA to us in accordance with terms and conditions of a separate manufacturing and supply agreement we entered into with Jagotec. In addition, Jagotec is entitled to receive a single-digit percentage royalty on net sales of RAYOS/LODOTRA and on any sub-licensing income, which includes any payments not calculated based on the net sales of RAYOS/LODOTRA, such as license fees, and lump sum and milestone payments.

The agreement expires on a country-by-country basis, upon the expiration of the last patent rights for RAYOS/LODOTRA, which will occur between 2024 and 2028. In the event of expiration, the licenses under the agreement will be perpetual, fully paid-up and royalty-free. Either party may also terminate the agreement in the event of a liquidation or bankruptcy of the other party or upon an uncured breach by the other party.

Manufacturing and Supply Agreement

In August 2007, we entered into a manufacturing and supply agreement with Jagotec for RAYOS/LODOTRA. Under the agreement, which was amended in March 2011 and in January 2017, Jagotec or its affiliates manufacture and supply RAYOS/LODOTRA to us in bulk. The term of the agreement is to December 31, 2023, and the minimum purchase commitment is in force until that date. As of December 31, 2016, our total remaining minimum purchase commitment was approximately $6.9 million based on tablet pricing under the agreement as of that date, which amount is subject to volume and price adjustments due to, among other things, inflation, order quantities and launch and approval in certain EU countries. We also supply the prednisone API to Jagotec at our expense for use in the manufacture of RAYOS/LODOTRA.

We pay Jagotec, exclusive of any value added tax or similar governmental charges, a price for RAYOS/LODOTRA representing a negotiated mark-up over manufacturing costs. The price is adjusted annually to reflect changes in both manufacturing and materials costs as measured by the Ensemble price index. If Jagotec makes a major capital expenditure during the contract term to fulfill increased orders forecast by us, the price per unit will increase if the actual order falls short of the forecast.

KRYSTEXXA

KRYSTEXXA is a pegylated, recombinant protein that is produced by fermentation of a genetically engineered Escherichia coli bacterium containing the DNA which encodes for uricase. The cDNA coding for the uricase is based on mammalian sequences. Uricase is purified and is then PEGylated with a PEGylation agent to produce the bulk medicine, pegloticase. Pegylation and purification of the active drug substance is achieved by conventional column chromatography. The resulting highly purified sterile solution is filled in a single-use vial for intravenous infusion following dilution. In support of its manufacturing process, we store multiple vials of the Escherichia coli bacterium master cell bank and working cell bank at multiple locations in order to ensure that it will have adequate backup should any cell bank be lost in a catastrophic event.

NOF Supply Agreement

In August 2015, Crealta and NOF Corporation, or NOF, in Japan, entered into an exclusive supply agreement for the PEGylation agent used in the manufacture of KRYSTEXXA. Under the terms of this agreement, we are required to issue NOF forecasts of our requirements for the PEGylation agent, a portion of which are binding. The agreement expires in August 2020, however, either we or NOF may terminate the agreement for any reason upon 24 months' prior notice. Either we or NOF may also terminate the agreement upon a material breach, if not cured within a specified period of time, or in the event of the other party's insolvency. While there are no minimum purchase obligations under the agreement, we are required to use NOF as our exclusive supplier for the PEGylation agent, subject to certain exceptions if NOF is unable to supply the PEGylation agent.

Bio-Technology General (Israel) Supply Agreement

In March 2007, Savient Pharmaceuticals, Inc. (as predecessor in interest to Crealta), entered into a commercial supply agreement with Bio-Technology General (Israel) Ltd, or BTG Israel, for the production of the bulk KRYSTEXXA medicine, or bulk product. We assumed this agreement as part of the Crealta acquisition and amended the agreement in September 2016. Under this agreement, we have agreed to purchase certain minimum annual order quantities and are obligated to purchase at least 80 percent of our annual world-wide bulk product requirements from BTG Israel. The term of the agreement runs until December 31, 2030, and will automatically renew for successive three year periods unless earlier terminated by either party upon three years prior written notice. The agreement may be terminated earlier by either party in the event of a force majeure, liquidation, dissolution, bankruptcy or insolvency of the other party, uncured material breach by the other party or after January 1, 2024, upon three years prior written notice. Under the agreement if the manufacture of the bulk product is moved out of Israel, we may be required to obtain the approval of the Israeli Office of the Chief Scientist, or OCS, because certain KRYSTEXXA intellectual property was initially developed with a grant funded by the OCS and we may be required to pay the OCS additional amounts as a repayment for the OCS grant funding. We issue eighteen-month forecasts of the volume of KRYSTEXXA that we expect to order. The first six months of the forecast are considered binding firm orders.

Exelead PharmaSource Supply Agreement

In October 2008, Savient and Exelead, Inc. (formerly known as Sigma Tau PharmaSource, Inc. (as successor in interest to Enzon Pharmaceuticals, Inc.)), or Exelead, entered into a commercial supply agreement for the packaging and supply of the final drug medicine KRYSTEXXA, which we acquired as part of the Crealta acquisition. This agreement remains in effect until terminated, and either we or Exelead may terminate the agreement with three years notice, given thirty days prior to the agreement anniversary date. Either we or Exelead may also terminate the agreement upon a material default, if not cured within a specified period of time, or in the event of the other party’s insolvency or bankruptcy.

Duke University and Mountain View Pharmaceutical License Agreement

In August 1998, Savient entered into an exclusive, worldwide license agreement with Duke University, or Duke, and Mountain View Pharmaceuticals Inc., or MVP. Duke developed the recombinant uricase enzyme used in KRYSTEXXA and MVP developed the PEGylation technology used in the manufacture of KRYSTEXXA. Duke and MVP may terminate the agreement if we commit fraud or for our willful misconduct or illegal conduct; upon our material breach of the agreement, if not cured within a specified period of time; upon written notice if we have committed two or more material breaches under the agreement; or in the event of our bankruptcy or insolvency. Under the terms of the agreement, we are obligated to pay Duke a mid-single digit percentage royalty on our global net sales of KRYSTEXXA and a low-double digit percentage royalty on any global sublicense revenue. We are also obligated to pay MVP a mid-single digit percentage royalty on our net sales of KRYSTEXXA outside of the United States and a low-double digit percentage royalty on any sublicense revenue outside of the United States. Royalties terminate upon last to expire of licensed patents on a country-by-country basis, and royalties are reduced by a mid-double digit percentage in countries that never had patents.

DUEXIS

We purchase DUEXIS in final, packaged form exclusively from Sanofi-Aventis U.S. LLC, or Sanofi, for our commercial requirements in North America. The first API in DUEXIS is ibuprofen in a direct compression blend called DC85 and is supplied to Sanofi by BASF Corporation, or BASF, in Bishop, Texas. The second API in DUEXIS is famotidine, which is available from a number of international suppliers. Famotidine is currently sourced from two manufacturers, Dr. Reddy’s in India and also from Quimica Syntetica (Chemo) in Spain. We currently receive both APIs in powder form and each is blended with a number of U.S. Pharmacopeia inactive ingredients.

BASF Contract

In July 2010, we entered into a contract with BASF for the purchase of DC85, which was subsequently amended effective as of January 2016. Pursuant to the agreement, we are obligated to source a significant majority of our commercial demand for DC85 from BASF. The contract expires in December 2018. Thereafter, the agreement automatically renews for successive renewal terms of three years each until terminated by either party giving specified prior written notice to the other party. Either party may also terminate the agreement in the event of uncured breach by the other party.

Manufacturing and Supply Agreement with Sanofi

In May 2011, we entered into a manufacturing and supply agreement with Sanofi, which was amended in September 2013. Pursuant to the agreement, Sanofi is obligated to manufacture and supply DUEXIS to us in final, packaged form, and we are obligated to purchase DUEXIS exclusively from Sanofi for our commercial requirements in North America and certain countries and territories in Europe, including the EU member states and Scandinavia, and South America. Sanofi must acquire the components necessary to manufacture DUEXIS, including the APIs, and is obligated to acquire all DC85 under the terms of our agreements with suppliers, including the current BASF contract. In order to allow Sanofi to perform its obligations under the agreement, we granted Sanofi a non-exclusive license to our related intellectual property. The price for DUEXIS under the agreement varies depending on the volume of DUEXIS we purchase and is subject to annual adjustments to reflect changes in costs as measured by the Producer Price Index published by the U.S. Department of Labor, Bureau of Labor Statistics, and certain other changes and events set forth in the agreement. We have paid for the purchase and installation of equipment necessary to manufacture DUEXIS tablets, and Sanofi is obligated to pay the costs of routine maintenance of the equipment. Upon expiration or termination of the agreement we may also be obligated to reimburse Sanofi for the depreciated net book value of any other equipment purchased by Sanofi in order to fulfill its obligations under the agreement.

The agreement term extends until May 2019, and automatically extends for successive two-year terms unless terminated by either party upon two years prior written notice. Either party may terminate the agreement upon thirty days prior written notice to the other party in the event of breach by the other party that is not cured within thirty days of notice (which notice period may be longer in certain, limited situations) or in the event we lose regulatory approval to market DUEXIS in all countries worldwide, and either party may terminate the agreement without cause upon two years prior written notice to the other party at any time after the third anniversary of the first commercial sale of DUEXIS in any country worldwide.

VIMOVO

AstraZeneca License Agreement

In November 2013, we entered into a license agreement with AstraZeneca, or the AstraZeneca license agreement, pursuant to which AstraZeneca granted us an exclusive license under certain intellectual property (including patents, know-how, trademarks, copyrights and domain names) of AstraZeneca and its affiliates to develop, manufacture and commercialize VIMOVO in the United States. AstraZeneca also granted us a non-exclusive license under certain intellectual property of AstraZeneca and its affiliates to manufacture, import, export and perform research and development activities with respect to VIMOVO outside the United States but solely for purposes of commercializing VIMOVO in the United States. In addition, AstraZeneca granted us a non-exclusive right of reference and use under certain regulatory documentation controlled by AstraZeneca and its affiliates to develop, manufacture and commercialize VIMOVO in the United States and to manufacture, import, export and perform research and development activities with respect to VIMOVO outside the United States but solely for purposes of commercializing VIMOVO in the United States.

Under the AstraZeneca license agreement, we granted AstraZeneca a non-exclusive sublicense under such licensed intellectual property and a non-exclusive right of reference under certain regulatory documentation controlled by us to manufacture, import, export and perform research and development activities with respect to VIMOVO in the United States but solely for purposes of commercializing VIMOVO outside the United States.

Under the AstraZeneca license agreement, we and our affiliates are subject to certain limitations and restrictions on our ability to develop, commercialize and seek regulatory approval with respect to VIMOVO or other medicines that contain gastroprotective agents in a single fixed combination oral solid dosage form with NSAIDs (excluding DUEXIS). These limitations and restrictions include, among other things, restrictions on indications for which we may commercialize VIMOVO or any such other medicines, restrictions on our ability to develop or seek regulatory

approval with respect to such other medicines that contain esomeprazole, restrictions on our ability to develop or seek regulatory approval for VIMOVO for any indications other than the indications for which NSAIDs are indicated, and restrictions on our marketing activities with respect to VIMOVO and any such other medicines.

The AstraZeneca license agreement continues in full force and effect until terminated in accordance with its terms. Under the AstraZeneca license agreement, the parties may terminate upon mutual written agreement by the parties, or either party may terminate rights granted to us with respect to licensed trademarks and licensed domain names under the AstraZeneca license agreement upon uncured material breach by the other party of certain specified provisions of the AstraZeneca license agreement.

Amended and Restated Collaboration and License Agreement with Aralez; Letter Agreement with AstraZeneca and Aralez

We entered into a license agreement with Pozen Inc., who subsequently entered into a business combination with Tribute Pharmaceuticals Canada Inc. to become known as Aralez Pharmaceuticals Inc., or Aralez. Under this agreement, we were granted an exclusive, royalty-bearing license under certain of Aralez's intellectual property in the United States to manufacture, develop and commercialize VIMOVO and other medicines controlled by us that contain gastroprotective agents in a single fixed combination oral solid dosage form with NSAIDs, excluding DUEXIS, in the United States.

Under the Aralez license agreement, we are required to pay Aralez a flat ten percent royalty based on net sales of VIMOVO and such other medicines sold by us, our affiliates or sublicensees during the royalty term, subject to minimum annual royalty obligations of $7.5 million, which minimum royalty obligations will continue for each year during which one of Aralez's patents covers such medicines in the United States and there are no competing medicines in the United States. The royalty rate may be reduced to a mid-single digit royalty rate as a result of loss of market share to competing medicines. Our obligation to pay royalties to Aralez will expire upon the later of (a) expiration of the last-to-expire of certain patents covering such medicines in the United States, and (b) ten years after the first commercial sale of such medicines in the United States. In addition, we will be obligated to reimburse Aralez for costs, including attorneys' fees, incurred by Aralez in connection with VIMOVO patent litigation moving forward, subject to agreed caps.

We are responsible for, and are required to use diligent and reasonable efforts directed to commercializing VIMOVO or another qualified medicine in the United States. We also own and maintain all regulatory filings and marketing approvals in the United States for any such medicines, including all investigational new drugs, or INDs, and new drug applications, or NDAs, for VIMOVO. Aralez covenanted that it will not at any time prior to the expiration of the royalty term, and will ensure that its affiliates do not, directly or indirectly, develop or commercialize or license any third party to develop or commercialize certain competing medicines in the United States.

The Aralez license agreement, unless earlier terminated, will expire upon expiration of the royalty term for all such medicines in the United States. Either party has the right to terminate the agreement upon uncured material breach by the other party or upon the bankruptcy or similar proceeding of the other party. We also have the right to terminate the Aralez license agreement for cause upon certain defined medicine failures.

In November 2013, we, AstraZeneca and Aralez entered into a letter agreement in which Aralez consented to AstraZeneca's assignment of the Aralez license agreement to us and that addresses the rights and responsibilities of the parties in relation to the Aralez license agreement and the amended and restated collaboration and license agreement between Aralez and AstraZeneca for territories outside the United States, or the Aralez-AstraZeneca license agreement. Under the letter agreement, we and AstraZeneca agreed to pay Aralez milestone payments upon the achievement by us and AstraZeneca, collectively, of certain annual aggregate global net sales thresholds ranging from $550.0 million to $1.25 billion with respect to medicines licensed by Aralez to us under the Aralez license agreement and to AstraZeneca under the Aralez-AstraZeneca license agreement. The aggregate milestone payment amount that may be owed by AstraZeneca and us, collectively, under the letter agreement is $260.0 million, with the amount payable by each of us and AstraZeneca with respect to each milestone to be based upon the proportional sales achieved by each of us and AstraZeneca, respectively, in the applicable year.

The letter agreement will terminate with respect to Aralez and us upon the termination of the Aralez license agreement.

Patheon Agreement

In November 2013, we entered into a master manufacturing services agreement and product agreement, or, collectively, the Patheon manufacturing agreement, with Patheon who was AstraZeneca's contract manufacturer of VIMOVO, for the manufacture and supply of VIMOVO. Under the Patheon manufacturing agreement, we agreed to purchase a specified percentage of our VIMOVO requirements for the United States from Patheon or its affiliates. In addition, under the terms of the Patheon manufacturing agreement, we are able to enter into individual product agreements with Patheon for the manufacture of specific medicines in addition to VIMOVO if agreed by us and Patheon.

Pursuant to the Patheon manufacturing agreement, we are required to supply Patheon with any active materials for VIMOVO. We must pay an agreed price for final, packaged VIMOVO supplied by Patheon subject to adjustments, including certain unilateral adjustments by Patheon, such as annual adjustments for inflation and adjustments to account for certain increases in the cost of components of VIMOVO other than active materials.

The Patheon manufacturing agreement will be effective until December 31, 2019 and will automatically renew for successive terms of three years each if there is any product agreement in effect, unless either party gives written notice to the other party of its intention to terminate the agreement at least twenty-four months prior to the end of the then current term. Either party may terminate the Patheon manufacturing agreement or any product agreement early for uncured material breach by the other party or upon the other party's bankruptcy or insolvency. We may terminate any product agreement if any regulatory authority takes any action or raises any objection that prevents us from commercializing the medicines. Additionally, Patheon may terminate the Patheon manufacturing agreement or any product agreement early if we assign our rights or obligations under the Patheon manufacturing agreement or such product agreement to a competitor of Patheon or to a party that, in the reasonable opinion of Patheon, is not a credit worthy substitute for us, or in certain other circumstances where we assign the Patheon manufacturing agreement or product agreement without Patheon's consent.

Divis Agreement

In March 2014, we entered into a manufacturing and supply agreement with Divis Laboratories Limited, or Divis, in India for the supply of naproxen. Our contract term with Divis runs through December 2018, with provisions for a three-year extension at our sole option upon written notice at least six months prior to expiration of the then current term.

Minakem Agreement

In March 2014, we entered into a manufacturing and supply agreement with Minakem Holding SAS, or Minakem, in France for the supply of esomeprazole magnesium trihydrate. Our contract term with Minakem runs through December 2018, with provisions for a three-year extension at our sole option upon written notice at least six months prior to expiration of the then current term.

PENNSAID 2%

Nuvo Supply Agreement

In October 2014, in connection with the acquisition of the U.S. rights to PENNSAID 2% from Nuvo, we entered into an exclusive supply agreement with Nuvo, which was amended in February 2016, under which Nuvo will manufacture and supply PENNSAID 2% to us. We have committed to a binding purchase order to Nuvo for delivery of PENNSAID 2%. In addition, at least ninety days prior to the first day of each calendar month during the term of the supply agreement, we are required to submit a binding written purchase order to Nuvo for PENNSAID 2% in minimum batch quantities. The term of our supply agreement is through December 31, 2029, but the agreement may be terminated earlier by either party for any uncured material breach by the other party of its obligations under the supply agreement or upon the bankruptcy or similar proceeding of the other party.

A key excipient used in PENNSAID 2% as a penetration enhancer is DMSO. We and Nuvo rely on a sole proprietary form of DMSO for which we maintain a substantial safety stock. However, should this supply become inadequate, damaged, destroyed or unusable, we and Nuvo may not be able to qualify a second source.

MIGERGOT

MIGERGOT drug product is ergotamine tartrate and caffeine-containing suppositories. The APIs, ergotamine tartrate and caffeine, are sourced from Teva in Czech Republic and from BASF in Germany, respectively. G&W Laboratories Inc., or G&W, performs the sourcing and procurement of the APIs. MIGERGOT drug product is manufactured by G&W in South Plainfield, New Jersey under a supply agreement that expires on December 31, 2023.

Customers and Information About Geographic Areas

Information regarding our total revenues attributed to United States and non-United States sources in the years ended December 31, 2016, 2015 and 2014, as well as the location of our long-lived assets, is included in Note 13 to our consolidated financial statements included in Item 15 in this Annual Report on Form 10-K.

Research and Development

We devote significant resources to research and development activities associated with our current branded medicines. For the years ended December 31, 2016, 2015 and 2014, we incurred $60.7 million, $41.9 million and $17.5 million, respectively, in research and development expenses.

ACTIMMUNE

In July 2015, we announced our collaboration with Fox Chase Cancer Center to study ACTIMMUNE in combination with PD-1/PD-L1 inhibitors in various forms of cancer including advanced urothelial carcinoma (bladder cancer) and renal cell carcinoma (kidney cancer). Pre-clinical cell line research has indicated that interferon gamma enhances cellular PD-L1 expression on endothelial cells (inner lining of the blood vessel) and on some tumor cells. By enhancing cellular PD-L1 expression on tumor cells, interferon gamma may promote or enhance the effect of the PD-1 or PD-L1 inhibitors. In December 2015, we announced that an investigator-initiated Phase 1 clinical study had been initiated to evaluate ACTIMMUNE in combination with OPDIVO® (nivolumab), marketed by Bristol-Meyers Squibb, in advanced solid tumors. The Phase 1 open label study will evaluate the combination of ACTIMMUNE and nivolumab in patients with advanced solid tumors who have progressed on at least one prior systemic therapy, which may include prior immunotherapy. Patients will be treated with a one week induction phase of ACTIMMUNE (starting dose 50 mcg/m^2 subcutaneously every other day), followed by a combination phase with ACTIMMUNE and nivolumab (3 mg/kg intravenously) for three cycles, followed by a single-agent phase of nivolumab alone for up to one year. The study will primarily assess the safety and tolerability of the combination of ACTIMMUNE and nivolumab. Secondary objectives, including overall response rate, progression free survival and overall survival, will also be assessed, as will various correlative analyses. Initial subject enrollment will occur using a modified 3+3 design, and if endpoints for safety (using dose-limiting toxicity criteria) are met, expansion cohorts in renal cell carcinoma and urothelial carcinoma are planned for up to fifteen patients per cohort. On February 23, 2017, at the American Society for Clinical Oncology - Society for Immunotherapy of Cancer meeting, investigators from Fox Chase Cancer Center presented safety data from the first two cohorts of the Phase 1 dose escalation trial evaluating ACTIMMUNE as part of a combination therapy in solid tumors for certain cancers. The preliminary data showed that combination therapy of ACTIMMUNE with nivolumab, a PD-1 inhibitor, was safe and well-tolerated in the first two cohorts. The third cohort of patients receiving ACTIMMUNE is still under study.

We are supporting Indiana University to study ACTIMMUNE in the treatment of type 2 osteopetrosis, autosomal dominant osteopetrosis, or ADO2. ADO2 is a genetic condition characterized by generalized osteosclerosis predominating in some skeletal sites such as the spine and pelvis. The short term, open label treatment trial in ADO2 patients aims to determine if administration of ACTIMMUNE increases biochemical markers of bone turnover, and thus determine if the medicine can completely or partially reverse the defective osteoclastic bone resorption in ADO2 patients. The clinical study is expected to run over a period of three years, and commenced in July 2016.

On December 8, 2016, we announced that the STEADFAST study evaluating ACTIMMUNE for the treatment of FA, did not meet its primary endpoint of a statistically significant change from baseline in the modified Friedreich’s Ataxia Rating Scale at twenty-six weeks versus treatment with placebo. In addition, the secondary endpoints did not meet statistical significance. No new safety findings were identified on initial review of data other than those already noted in the ACTIMMUNE prescribing information for approved indications. We, in conjunction with the independent Data Safety Monitoring Board, the principal investigator and the Friedreich’s Ataxia Research Alliance Collaborative Clinical Research Network in FA, determined that, based on the trial results, the STEADFAST program would be discontinued, including the twenty-six week extension study and the long-term safety study.

RAVICTI

We are in the process of seeking approval for label expansions for RAVICTI, with assessments in progress studying the use of RAVICTI in patients both from two months to two years (sNDA submitted on June 29, 2016) and from

birth to two months (targeted sNDA submission in the first quarter of 2018). Current FDA approval is for patients from two years of age and older only. In patients with UCDs for which RAVICTI is an FDA-approved medicine, there is a variable age of diagnosis (from newborn to adulthood), and the severity of the disease can be associated with the age of onset and enzymatic deficit. However, a prompt diagnosis and careful management of the disease can lead to good clinical outcomes.

RAYOS

In November 2015, we announced our collaboration with the ALR to study the effect of RAYOS on the fatigue experienced by SLE patients. SLE is a chronic autoimmune disease that causes inflammation and pain in the joints and muscles, as well as overall fatigue. RAYOS is currently indicated for patients with SLE. The first study planned as part of the collaboration is an investigator-initiated, randomized, double-blind, active comparator, cross-over study in which patients will be randomized to receive either prednisone for three months or RAYOS at 10 p.m. for three months, and then switched to the alternative medication for an additional three months. Approximately sixty-two patients across twenty-five sites will be enrolled in the United States. Fatigue will be measured by the Functional Assessment of Chronic Illness Therapy-Fatigue and the Fatigue Severity Scale, as well as the Vitality scale of the Medical Outcome Study thirty-six-item short form health survey. The study is expected to start in the first quarter of 2017.

KRYSTEXXA

In January 2016, following our acquisition of Crealta, we assumed responsibility for a study designed to test the potential reduction of immunogenicity in KRYSTEXXA patients, known as the Tolerization Reduces Intolerance to Pegloticase and Prolongs the Urate Lowering Effect, or TRIPLE, study. The TRIPLE study is an investigator-initiated, post-market interventional, exploratory open-label, multicenter adaptive design study of approximately fifty-three patients to evaluate the effectiveness of a sixteen-week high zone tolerance regimen of KRYSTEXXA on response to therapy (serum uric acid <6 mg/dL) in adult hyperuricemic patients, < 120 kg and ≥ 120 kg in weight, with gout refractory to conventional therapy. We are also developing a potential registration study to expand the label should the TRIPLE study show positive results. Success in the TRIPLE study and the subsequent registration study would have the potential to significantly expand the patient population and usage of KRYSTEXXA.

As part of the TRIPLE study, initial, more frequent dosing is being examined to determine if this reduces antibody formation by inducing antigen specific non-responsiveness. This would prevent the formation of anti-pegloticase antibodies and prevent the loss of drug response. This involves evaluating the drug’s lowest trough level, which pharmacokinetically occurs between the first and second doses. Increasing this trough level should suppress the high titer antibody formation. Current labelling states that KRYSTEXXA should be given every two weeks. This study adds one extra dose that occurs one week after the initial dose.

Intellectual Property

Our objective is to aggressively patent the technology, inventions and improvements that we consider important to the development of our business. We have a portfolio of patents and applications based on clinical and pharmacokinetic/pharmacodynamic modeling discoveries, and our novel formulations. We intend to continue filing patent applications seeking intellectual property protection as we generate anticipated formulation refinements, new methods of manufacturing and clinical trial results.

We will only be able to protect our technologies and medicines from unauthorized use by third parties to the extent that valid and enforceable patents or trade secrets cover them. As such, our commercial success will depend in part on receiving and maintaining patent protection and trade secret protection of our technologies and medicines as well as successfully defending these patents against third-party challenges.

We have licenses to U.S. patents covering ACTIMMUNE. If not otherwise invalidated, those patents expire in 2022. We continue to prosecute and pursue patent protection to obtain additional patent coverage on ACTIMMUNE and its uses.

We have U.S. and foreign patents and patent applications covering PROCYSBI, as well as licenses from the University of California, San Diego to U.S. and foreign patents and patent applications covering PROCYSBI. If not

otherwise invalidated, those patents expire between 2027 and 2034. We continue to prosecute and pursue patent protection to obtain additional patent coverage on PROCYSBI and its uses.

PROCYSBI received marketing authorization in September 2013 from the EC for marketing in the EU as an orphan medicinal product for the management of proven nephropathic cystinosis.

PROCYSBI received seven years of market exclusivity, through 2020, for patients six years and older as an orphan drug in the United States, and ten years of market exclusivity, through 2023, as an orphan drug in Europe.

We also have U.S. and foreign patents and patent applications covering QUINSAIR, as well as licenses from PARI to U.S. and foreign patents and patent applications covering QUINSAIR. If not otherwise invalidated, those patents expire between 2020 and 2037. We continue to prosecute and pursue patent protection to obtain additional patent coverage on QUINSAIR and its uses.

QUINSAIR received ten years of market exclusivity in the EU, beginning with its March 2015 marketing authorization.

We also have an exclusive license to U.S. and foreign patents from Brusilow Enterprises LLC covering RAVICTI which expire in the United States in 2018 and if extended, in certain countries in Europe in 2021. We also have ownership of U.S. and foreign patents and patent applications covering RAVICTI. If not otherwise invalidated, those patents expire between 2030 and 2032. We continue to prosecute and pursue patent protection to obtain additional patent coverage on RAVICTI and its uses.

In the United States, RAVICTI has been granted seven years of orphan drug exclusivity, which will expire in 2020. In the EU, RAVICTI received ten years of marketing exclusivity protection, beginning with its December 2015 marketing authorization.

We also have licenses to U.S. and foreign patents and applications covering KRYSTEXXA. If not otherwise invalidated, those patents expire between 2019 and 2030. We continue to prosecute and pursue patent protection to obtain additional patent coverage on KRYSTEXXA and its uses.

In the United States, KRYSTEXXA has received twelve years of biologic exclusivity, expiring in 2022, and seven years of orphan drug exclusivity, expiring in September 2017.

We have an exclusive license to U.S. and foreign patents and patent applications from Vectura covering RAYOS/LODOTRA. If not otherwise invalidated, those in-licensed patents expire between 2024 and 2028. We continue to prosecute and pursue additional patent coverage on RAYOS/LODOTRA and its uses. However, under the Settlement Agreement with Actavis Laboratories FL, Inc. (formerly known as Watson Laboratories, Inc. – Florida), or Actavis, Actavis may enter the market on December 23, 2022, or earlier under certain circumstances.

In the EU, LODOTRA has received ten years of marketing exclusivity protection, beginning with its March 2009 marketing authorization in Germany.

We have multiple patents and patent applications related to DUEXIS. Unless otherwise invalidated, those patents expire in 2026. However, under the license agreement with Par Pharmaceutical, Inc. and Par Pharmaceutical Companies, Inc., or collectively Par, Par may enter the market on January 1, 2023, or earlier under certain circumstances.

We also have ownership of U.S. patents and patent applications covering PENNSAID 2% from Nuvo. We also co-own other U.S. patent applications with Mallinckrodt LLC. If not otherwise invalidated, those patents expire between 2027 and 2030. However, under the settlement agreements with Perrigo Company plc, or Perrigo, Taro Pharmaceuticals USA, Inc. and Taro Pharmaceutical Industries, Ltd., or collectively Taro, Amneal Pharmaceuticals LLC, or Amneal, and Teligent, Inc., or Teligent, Perrigo, Taro, Amneal, and/or Teligent may enter the market on January 10, 2029, or earlier under certain circumstances. We continue to prosecute and pursue patent protection in the United States to obtain additional patent coverage on PENNSAID 2% and its uses.

We also have licenses to U.S. patents and patent applications and trademarks covering VIMOVO from Aralez and AstraZeneca. We co-own other U.S. patents and patent applications with Aralez. If not otherwise invalidated, those in-licensed patents expire between 2018 and 2031. We continue to prosecute and pursue patent protection in the United States to obtain additional patent coverage on VIMOVO and its uses.

27

The patent positions of life sciences companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in such companies' patents has emerged to date in the United States. The patent situation outside the United States is even more uncertain. Changes in either the patent laws or in interpretations of patent laws in the United States or other countries may diminish the value of our intellectual property. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in our patents or in third-party patents. For example:

- we or our licensors might not have been the first to make the inventions covered by each of our pending patent applications and issued patents;
- we or our licensors might not have been the first to file patent applications for these inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies;
- it is possible that none of our pending patent applications or the pending patent applications of our licensors will result in issued patents;
- our issued patents and the issued patents of our licensors may not provide a basis for commercially viable drugs, or may not provide us with any competitive advantages, or may be challenged and invalidated by third parties;
- we may not be successful in any patent litigation to enforce our patent rights, including our pending patent litigation regarding, PENNSAID 2%, RAVICTI and/or VIMOVO;
- we may not develop additional proprietary technologies or medicine candidates that are patentable; or
- the patents of others may have an adverse effect on our business.

For a description of our legal proceedings, see Note 16 of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K.

Third-Party Coverage and Reimbursement

In both U.S. and foreign markets, our ability to commercialize our medicines successfully depends in significant part on the availability of coverage and adequate reimbursement to healthcare providers from third-party payers, including, in the United States, government payers such as the Medicare and Medicaid programs, managed care organizations and private health insurers. Third-party payers are increasingly challenging the prices charged for medicines and examining their cost effectiveness, in addition to their safety and efficacy. This is especially true in markets where over-the-counter and generic options exist. Even if coverage is made available by a third-party payer, the reimbursement rates paid for covered medicines might not be adequate. For example, third-party payers may use tiered coverage and may adversely affect demand for our medicines by not covering our medicines or by placing them in a more expensive formulary tier relative to competitive medicines (where patients have to pay relatively more out of pocket than for medicines in a lower tier). We cannot be certain that our medicines will be covered by third-party payers or that such coverage, where available, will be adequate, or that our medicines will successfully be placed on the list of drugs covered by particular health plan formularies. Many states have also created preferred drug lists and include drugs on those lists only when the manufacturers agree to pay a supplemental rebate. The industry competition to be included on such formularies and preferred drug lists often leads to downward pricing pressures on pharmaceutical companies. Also, third-party payers may refuse to include a particular branded drug on their formularies or otherwise restrict patient access to a branded drug when a less costly generic equivalent or other therapeutic alternative is available. In addition, because each third-party payer individually approves coverage and reimbursement levels, obtaining coverage and adequate reimbursement is a time-consuming and costly process. We may be required to provide scientific and clinical support for the use of any medicine to each third-party payer separately with no assurance that approval would be obtained, and we may need to conduct pharmacoeconomic studies to demonstrate the cost effectiveness of our medicines for formulary coverage and reimbursement. Even with studies, our medicines may be considered less safe, less effective or less cost-effective than competitive medicines, and third-party payers may not provide coverage and adequate reimbursement for our medicines or our medicine candidates. These pricing and reimbursement pressures may create negative perceptions to any medicine price increases, or limit the amount we may be able to increase our medicine prices, which may adversely affect our medicine sales and results of operations. Where coverage and reimbursement are not adequate, physicians may limit how much or under what circumstances they will prescribe or administer such medicines, and patients may decline to

purchase them. This, in turn, could affect our ability to successfully commercialize our medicines and impact our profitability, results of operations, financial condition, and future success.

The U.S. market has seen a trend in which retail pharmacies have become increasingly involved in determining which prescriptions will be filled with the requested medicine or a substitute medicine, based on a number of factors, including potentially perceived medicine costs and benefits, as well as payer medicine substitution policies. Many states have in place requirements for prescribers to indicate “dispense as written” on their prescriptions if they do not want pharmacies to make medicine substitutions; these requirements are varied and not consistent across states. We may need to increasingly spend time and resources to ensure the prescriptions written for our medicines are filled as written, where appropriate.

Coverage policies, third-party reimbursement rates and medicine pricing regulation have been subject to significant change, and may change further at any time, particularly given recent political focus on the pharmaceutical industry. Even if favorable coverage and adequate reimbursement status is attained for one or more medicines, less favorable coverage policies and reimbursement rates may be implemented in the future.

Government Regulation

The FDA and comparable regulatory agencies in state and local jurisdictions and in foreign countries impose extensive requirements upon the clinical development, pre-market approval, manufacture, labeling, marketing, promotion, pricing, import, export, storage and distribution of medicines. These agencies and other regulatory agencies regulate research and development activities and the testing, approval, manufacture, quality control, safety, effectiveness, labeling, storage, recordkeeping, advertising and promotion of drugs and biologics. Failure to comply with applicable FDA or foreign regulatory agency requirements may result in Warning Letters, fines, civil or criminal penalties, additional reporting obligations and/or agency oversight, suspension or delays in clinical development, recall or seizure of medicines, partial or total suspension of production or withdrawal of a medicine from the market.

In the United States, the FDA regulates drug products under the Federal Food, Drug, and Cosmetic Act and its implementing regulations and biologics additionally under the Public Health Service Act. The process required by the FDA before medicine candidates may be marketed in the United States generally involves the following:

- submission to the FDA of an IND, which must become effective before human clinical trials may begin and must be updated annually;
- completion of extensive preclinical laboratory tests and preclinical animal studies, all performed in accordance with the FDA’s Good Laboratory Practice, or GLP, regulations;
- performance of adequate and well-controlled human clinical trials to establish the safety and efficacy of the medicine candidate for each proposed indication;
- submission to the FDA of an NDA or biologics license application, or BLA, as appropriate, after completion of all pivotal clinical trials to demonstrate the safety, purity and potency of the medicine candidate for the indication for use;
- a determination by the FDA within 60 days of its receipt of an NDA or BLA to file the application for review;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facilities to assess compliance with the FDA’s current good manufacturing practices regulations for pharmaceuticals, or cGMPs; and
- FDA review and approval of an NDA or BLA prior to any commercial marketing or sale of the medicine in the United States.

The development and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our medicine candidates will be granted on a timely basis, if at all.

The results of preclinical tests (which include laboratory evaluation as well as GLP studies to evaluate toxicity in animals) for a particular medicine candidate, together with related manufacturing information and analytical data, are submitted as part of an IND to the FDA. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises concerns or questions about the conduct of the proposed clinical trial, including concerns that human research subjects will be exposed to unreasonable health risks. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. IND submissions may not result in FDA authorization to commence a clinical trial. A separate submission to an existing IND must also be made for each successive clinical trial conducted during medicine development. Further, an independent institutional review board, or IRB, for each medical center proposing to conduct the clinical trial must review and approve the plan for any clinical trial before it commences at that center and it must monitor the study until completed. The FDA, the IRB or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk. Clinical testing also must satisfy extensive good clinical practice regulations and regulations for informed consent and privacy of individually identifiable information. Similar requirements to the U.S. IND are required in the EEA and other jurisdictions in which we may conduct clinical trials.

Clinical Trials. For purposes of NDA or BLA submission and approval, clinical trials are typically conducted in the following sequential phases, which may overlap:

- Phase 1. Studies are initially conducted in a limited population to test the medicine candidate for safety, dose tolerance, absorption, distribution, metabolism, and excretion, typically in healthy humans, but in some cases in patients.
- Phase 2. Studies are generally conducted in a limited patient population to identify possible adverse effects and safety risks, explore the initial efficacy of the medicine for specific targeted indications and to determine dose range or pharmacodynamics. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more expensive Phase 3 clinical trials.
- Phase 3. These are commonly referred to as pivotal studies. When Phase 2 evaluations demonstrate that a dose range of the medicine is effective and has an acceptable safety profile, Phase 3 clinical trials are undertaken in large patient populations to further evaluate dosage, provide substantial evidence of clinical efficacy and further test for safety in an expanded and diverse patient population at multiple, geographically dispersed clinical trial centers.
- Phase 4. The FDA may approve an NDA or BLA for a medicine candidate, but require that the sponsor conduct additional clinical trials to further assess the medicine after approval under a post marketing commitment or post marketing requirement. In addition, a sponsor may decide to conduct additional clinical trials after the FDA has approved a medicine. Post-approval trials are typically referred to as Phase 4 clinical trials.

The results of drug development, preclinical studies and clinical trials are submitted to the FDA as part of an NDA or BLA, as appropriate. Applications also must contain extensive chemistry, manufacturing and control information. Applications must be accompanied by a significant user fee. Once the submission has been accepted for filing, the FDA's goal is to review applications within 12 months of submission or, if the application relates to an unmet medical need in a serious or life-threatening indication, eight months from submission. The review process is often significantly extended by FDA requests for additional information or clarification. The FDA will typically conduct a pre-approval inspection of the manufacturer to ensure that the medicine can be reliably produced in compliance with cGMPs and will typically inspect certain clinical trial sites for compliance with good clinical practice, or GCP. The FDA may refer the application to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it typically follows such recommendations. The FDA may deny approval of an application by issuing a Complete Response Letter if the applicable regulatory criteria are not satisfied. A Complete Response Letter may require additional clinical data and/or trial(s), and/or other significant, expensive and time- consuming requirements related to clinical trials, preclinical studies or manufacturing. Data from clinical trials are not always conclusive and the FDA may interpret data differently than we or our collaborators interpret data. Approval may occur with boxed warnings on medicine labeling or Risk Evaluation and Mitigation Strategies, or REMS, which limit the labeling, distribution or promotion of a medicine. Once issued, the FDA may withdraw medicine approval if ongoing regulatory requirements

are not met or if safety problems occur after the medicine reaches the market. In addition, the FDA may require testing, including Phase 4 clinical trials, and surveillance programs to monitor the safety effects of approved medicines which have been commercialized and the FDA has the power to prevent or limit further marketing of a medicine based on the results of these post-marketing programs or other information.

Orphan Medicines. Under the Orphan Drug Act, the FDA may designate a medicine as an "orphan drug" if it is intended to treat a rare disease or condition, meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a medicine available in the United States for treatment of the disease or condition will be recovered from sales of the medicine. A company must request orphan drug designation before submitting an NDA for the drug and rare disease or condition. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan drug designation does not shorten the Prescription Drug User Fee Act, or PDUFA, goal dates for the regulatory review and approval process, although it does convey certain advantages such as tax benefits and exemption from the PDUFA application fee.

If a medicine with orphan designation receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the medicine generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor's marketing application for the same drug for the same indication for seven years, except in certain limited circumstances. Orphan exclusivity does not block the approval of a different drug for the same rare disease or condition, nor does it block the approval of the same drug for different indications. If a drug designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity. Orphan exclusivity will not bar approval of another medicine under certain circumstances, including if a subsequent medicine with the same drug for the same indication is shown to be clinically superior to the approved medicine on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand.

In the EU, Regulation (EC) No 141/2000 and Regulation (EC) No. 847/2000 provide that a medicine can be designated as an orphan medicinal product by the EC if its sponsor can establish: that the medicine is intended for the diagnosis, prevention or treatment of (1) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the EU when the application is made, or (2) a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives the medicinal product is unlikely to be developed. For either of these conditions, the applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the EU or, if such method exists, the medicinal product will be of significant benefit to those affected by that condition. Once authorized, orphan medicinal products are entitled to ten years of market exclusivity in all EU Member States (extendable to twelve years for medicines that have complied with an agreed pediatric investigation plan pursuant to Regulation 1901/2006) and in addition a range of other benefits during the development and regulatory review process including scientific assistance for study protocols, authorization through the centralized marketing authorization procedure covering all member countries and a reduction or elimination of registration and marketing authorization fees. However, marketing authorization may be granted to a similar medicinal product with the same orphan indication during the ten year period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if this medicine is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if, at the end of the fifth year, it can be demonstrated on the basis of available evidence that the criteria for its designation as an orphan medicine are no longer satisfied, for example if the original orphan medicinal product has become sufficiently profitable not to justify maintenance of market exclusivity.

Other Regulatory Requirements. Medicines manufactured or distributed pursuant to FDA approvals are subject to continuing regulation by the FDA, including recordkeeping, annual medicine quality review, payment of medicine and manufacturing establishment fees and reporting requirements. Adverse event experience with the medicine must be reported to the FDA in a timely fashion and pharmacovigilance programs to proactively look for these adverse events are mandated by the FDA. Our medicines may be subject to REMS requirements that affect labeling, distribution or post market reporting. Drug manufacturers and their subcontractors are required to register their establishments with

the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMPs, which impose certain procedural and documentation requirements upon us and our third-party manufacturers. Following such inspections, the FDA may issue notices on Form 483 and Untitled Letters or Warning Letters that could cause us or our third-party manufacturers to modify certain activities. A Form 483 notice, if issued at the conclusion of an FDA inspection, can list conditions the FDA investigators believe may have violated cGMP or other FDA regulations or guidelines. In addition to Form 483 notices and Untitled Letters or Warning Letters, failure to comply with the statutory and regulatory requirements can subject a manufacturer to possible legal or regulatory action, such as suspension of manufacturing, seizure of medicine, injunctive action, additional reporting requirements and/or oversight by the agency, import alert or possible civil penalties. The FDA may also require us to recall a drug from distribution or withdraw approval for that medicine.

The FDA closely regulates the post-approval marketing and promotion of pharmaceuticals, including standards and regulations for direct-to-consumer advertising, dissemination of off-label information, industry-sponsored scientific and educational activities and promotional activities involving the Internet, including certain social media activities. Medicines may be marketed only for the approved indications and in accordance with the provisions of the approved label. Further, if there are any modifications to the medicine, including changes in indications, labeling, or manufacturing processes or facilities, we may be required to submit and obtain FDA approval of a new or supplemental application, which may require us to develop additional data or conduct additional preclinical studies and clinical trials. Failure to comply with these requirements can result in adverse publicity, Warning Letters or "untitled letters", corrective advertising and potential administrative, civil and criminal penalties, as well as damages, fines, withdrawal of regulatory approval, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs, additional reporting requirements and/or oversight by the agency, and imprisonment, any of which could adversely affect our ability to sell our medicines or operate our business and also adversely affect our financial results.

Physicians may, in their independent medical judgment, prescribe legally available pharmaceuticals for uses that are not described in the medicine's labeling and that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, impose stringent restrictions on manufacturers' communications regarding off-label use. Additionally, a significant number of pharmaceutical companies have been the target of inquiries and investigations by various U.S. federal and state regulatory, investigative, prosecutorial and administrative entities in connection with the promotion of medicines for off-label uses and other sales practices. These investigations have alleged violations of various U.S. federal and state laws and regulations, including claims asserting antitrust violations, violations of the Food, Drug and Cosmetic Act, false claims laws, the Prescription Drug Marketing Act, anti-kickback laws, and other alleged violations in connection with the promotion of medicines for unapproved uses, pricing and Medicare and/or Medicaid reimbursement. If our promotional activities, including any promotional activities that a contracted sales force may perform on our behalf, fail to comply with these regulations or guidelines, we may be subject to warnings from, or enforcement action by, these authorities. In addition, our failure to follow FDA rules and guidelines relating to promotion and advertising may cause the FDA to issue warning letters or untitled letters, suspend or withdraw an approved medicine from the market, require corrective advertising or a recall or institute fines or civil fines, additional reporting requirements and/or oversight or could result in disgorgement of money, operating restrictions, injunctions or criminal prosecution, any of which could harm our business. In addition, the distribution of prescription medicines is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription medicine samples and impose requirements to ensure accountability in distribution, including a drug pedigree which tracks the distribution of prescription drugs. Further, under the Drug Quality and Security Act, drug manufacturers are subject to a number of requirements, including, medicine identification, tracing and verification, among others, that are designed to detect and remove counterfeit, stolen, contaminated or otherwise potentially harmful drugs from the U.S. drug supply chain. These requirements will be phased in over several years and compliance will likely increase the costs of the manufacture and distribution of drug medicines.

Outside the United States, the ability of our partners and us to market a medicine is contingent upon obtaining marketing authorization from the appropriate regulatory authorities. The requirements governing marketing authorization, pricing and reimbursement vary widely from country to country and region to region.

The EU and the EEA consist of the 28 Member States of the EU, plus Norway, Iceland and Liechtenstein which are Member States of the EEA. These Member States have all acceded to the single market rules governing the supervision of medicinal products. Under the prevailing rules, medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. There are three procedures for an MA to be obtained:

- the Centralized MA, which is issued by the EC through the Centralized Procedure, based on the scientific opinion of the CHMP of the EMA, and which is valid throughout the entire territory of the EU/EEA. When decisions on granting of a Centralized MA are taken by the EU, the EEA Member States will take corresponding decisions on the basis the relevant acts to permit marketing of medicinal products. The Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products, and medicinal products containing a new active substance indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune and viral diseases. The Centralized Procedure is optional for products containing a new active substance not yet authorized in the EU/EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU.

- Decentralized Procedure MAs are available for products not falling within the mandatory scope of the Centralized Procedure. An identical dossier is submitted to the competent authorities of each of the Member States in which the MA is sought, one of which is selected by the applicant as the Reference Member State, or RMS, to lead the evaluation of the regulatory submission. The competent authority of the RMS prepares a draft assessment report, a draft summary of the product characteristics, or SmPC, and a draft of the labeling and package leaflet as distilled from the preliminary evaluation, which are sent to the other Member States (referred to as the Concerned Member States, or CMS) for their approval. If the CMS raise no objections, based on a potential serious risk to public health, to the assessment, SmPC, labeling, or packaging proposed by the RMS, the RMS records the agreement, closes the procedure and informs the applicant accordingly. Each Member State concerned by the procedure is required to adopt a national decision to grant a national MA in conformity with the approved assessment report, SmPC and the labeling and package leaflet as approved. Where a product has already been authorized for marketing in a Member State of the EEA, the granted national MA can be used for mutual recognition in other Member States through the Mutual Recognition Procedure, or MRP, resulting in progressive national approval of the product in the EU/EEA.
- National MAs, which are issued by a single competent authority of the Member States of the EEA and only covers their respective territory, are also available for products not falling within the mandatory scope of the Centralized Procedure. Once a product has been authorized for marketing in a Member State of the EEA through the National Procedure, this National MA can also be recognized in other Member States through the MRP.

Under the procedures described above, before granting the MA, the EMA or the competent authority(ies) of the Member State(s) of the EEA prepare an assessment of the risk-benefit balance of the product against the scientific criteria concerning its quality, safety and efficacy.

Under Regulation (EC) No 726/2004/EC and Directive 2001/83/EC (each as amended), the EU has adopted a harmonized approach to data and market protection or exclusivity (known as the 8 + 2 + 1 formula). The data exclusivity period begins to run on the date when the first MA is granted in the EU. It confers on the MA holder of the reference medicinal product eight years of data protection and ten years of market protection. A reference medicinal product is defined to mean a medicinal product authorized based on a full dossier consisting of pharmaceutical and preclinical testing results and clinical trial data, such as a medicinal product containing a new active substance. The ten-year market protection can be extended cumulatively to a maximum period of eleven years if during the first eight years of those ten years of protection period, the MA holder obtains an authorization for one or more new therapeutic indications that are deemed to bring a significant clinical benefit compared to existing therapies.

The protection period means that an applicant for a generic medicinal product is not permitted to rely on preclinical pharmacological, toxicological, and clinical data contained in the file of the reference medicinal product of the originator until the first eight years of data protection have expired. Thereafter, a generic product application may be submitted and generic companies may rely on the preclinical and clinical data relating to the reference medicinal product to support approval of the generic product. However, a generic cannot market until ten years have elapsed from the initial authorization of the reference medicinal product or eleven years if the protection period is extended, based on the formula of 8+2+1.

In addition to the above, where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication. Finally, where a change of classification of a medicinal product has been authorized on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorization for a change of classification of the same substance for one year after the initial change was authorized.

The 8 + 2 + 1 exclusivity scheme applies to products that have been authorized in the EU by either the EMA through the Centralized Procedure or the competent authorities of the Member States of the EEA nationally, including through the Decentralized and Mutual Recognition procedures.

For a medicinal product which is designated as orphan under Regulation 141/2000, it will benefit from a period of ten years of orphan market exclusivity which essentially constitutes a period of market monopoly. During this period of orphan market exclusivity, no EU regulatory authority is permitted to accept or approve an application for marketing authorization for a similar medicinal product or an extension application for the same therapeutic indication. This period can be extended cumulatively to a total of twelve years if the marketing authorization holder or applicant complies with the requirements for an agreed pediatric investigation plan pursuant to Regulation 1901/2006.

The holder of a Centralized MA or National MA is subject to various obligations under the applicable EU laws, such as pharmacovigilance obligations, requiring it to, among other things, report and maintain detailed records of adverse reactions, and to submit periodic safety update reports to the competent authorities. The holder must also ensure that the manufacturing and batch release of its product is in compliance with the applicable requirements. The MA holder is further obligated to ensure that the advertising and promotion of its products complies with applicable EU laws and industry code of practice as implemented in the domestic laws of the Member States of the EU/EEA. The advertising and promotional rules are enforced nationally by the EU/EEA Member States.

Healthcare Fraud and Abuse Laws. As a pharmaceutical company, certain federal and state healthcare laws and regulations pertaining to fraud and abuse and patients' rights are and will be applicable to our business. We may be subject to various federal and state laws targeting fraud and abuse in the healthcare industry. For example, in the United States, there are federal and state anti-kickback laws that prohibit the payment or receipt of kickbacks, bribes or other remuneration intended to induce the purchase or recommendation of healthcare products and services or reward past purchases or recommendations. Violations of these laws can lead to civil and criminal penalties, including fines, imprisonment, additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement, and exclusion from participation in federal healthcare programs. These laws are applicable to manufacturers of products regulated by the FDA, such as us, and pharmacies, hospitals, physicians and other potential purchasers of such products.

The federal Anti-Kickback Statute prohibits persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, to induce either the referral of an individual, or the furnishing, recommending, or arranging for a good or service, for which payment may be made under a federal healthcare program, such as the Medicare and Medicaid programs. The term "remuneration" is defined as any remuneration, direct or indirect, overt or covert, in cash or in kind, and has been broadly interpreted to include anything of value, including for example, gifts, discounts, the furnishing of supplies or equipment, credit arrangements, payments of cash, waivers of payment, ownership interests and providing anything at less than its fair market value. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute may have been violated, and enforcement will depend on the relevant facts and circumstances. The Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the ACA, among other things, amended the intent requirement of the federal Anti-Kickback Statute to state that a person or entity need not have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the ACA provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act (discussed below) or the civil monetary penalties statute, which imposes penalties against any person who is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent, or to have offered improper inducements to federal health care program beneficiaries to select a particular provider or supplier. The federal Anti-Kickback Statute is broad, and despite a series of narrow safe harbors, prohibits many arrangements and practices that are lawful in businesses outside of the healthcare industry. Many states have also adopted laws similar to the federal Anti-Kickback Statute, some of which apply to the referral of patients for healthcare items or services reimbursed by any source, not only the Medicare and Medicaid programs, and do not contain identical safe harbors. In addition, where such activities involve foreign government officials, they may also potentially be subject to the Foreign Corrupt Practices Act. Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities, including our activities with physician customers, pharmacies, and patients, as well as our activities pursuant to partnerships with other companies and pursuant to contracts with contract research organizations, could be subject to challenge under one or more of such laws.

The federal False Claims Act prohibits any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. A claim includes "any request or demand" for money or property presented to the U.S. government. In addition, the ACA specified that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act. The federal False Claims Act has been the basis for numerous enforcement actions and settlements by pharmaceutical and other healthcare companies in connection with various alleged financial relationships with customers. In addition, a number of pharmaceutical manufacturers have reached substantial financial settlements in connection with allegedly causing false claims to be submitted because of the companies' marketing of products for unapproved, and thus non-reimbursable, uses. Certain marketing practices, including off-label promotion, may also violate false claims laws, as might violations of the federal physician self-referral laws, such as the Stark laws, which prohibit a physician from making a referral to certain designated health services with which the physician or the physician's family member has a financial interest and prohibit submission of a claim for reimbursement pursuant to the prohibited referral. The "qui tam" provisions of the False Claims Act allow a private individual to bring civil actions on behalf of the federal government alleging that the defendant has submitted a false claim to the federal government, and to share in any monetary recovery. In addition, various states have enacted similar fraud and abuse statutes or regulations, including, without limitation, false claims laws analogous to the False Claims Act, and laws analogous to the federal Anti-Kickback Statute, that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payer, and there are also federal criminal false claims laws.

Separately, there are a number of other fraud and abuse laws that pharmaceutical manufacturers must be mindful of, particularly after a medicine candidate has been approved for marketing in the United States. For example, a federal criminal law enacted as part of, the Health Insurance Portability and Accountability Act of 1996, or HIPAA, prohibits knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payers. The false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. There are also federal civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payers that are false or fraudulent, as well as federal and state consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

Healthcare Privacy and Security Laws. We may be subject to, or our marketing activities may be limited by, HIPAA, as amended by the Health Information Technology and Clinical Health Act and their respective implementing regulations, which established uniform standards for certain "covered entities" (healthcare providers, health plans and healthcare clearinghouses) governing the conduct of certain electronic healthcare transactions and protecting the security and privacy of protected health information. Among other things, HIPAA's privacy and security standards are directly applicable to "business associates" — independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. In addition to possible civil and criminal penalties for violations, state attorneys general are authorized to file civil actions for damages or injunctions in federal courts to enforce HIPAA and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. In the EU/EEA, Directive 95/46/EEC (as amended) or its successor applies to identified or identifiable personal data processed by automated means (for example, a computer database of customers) and data contained in, or intended to be part of, non-automated filing systems (traditional paper files) as well as transfer of such data to a country outside of the EU/EEA.

"Sunshine" and Marketing Disclosure Laws. There are an increasing number of federal and state "sunshine" laws that require pharmaceutical manufacturers to make reports to states on pricing and marketing information. Several states have enacted legislation requiring pharmaceutical companies to, among other things, establish marketing compliance programs, file periodic reports with the state, and make periodic public disclosures on sales and marketing activities, and prohibiting certain other sales and marketing practices. In addition, a similar federal requirement requires manufacturers, including pharmaceutical manufacturers, to track and report to the federal government certain payments and other transfers of value made to physicians and other healthcare professionals and teaching hospitals and ownership or investment interests held by physicians and their immediate family members. The federal government began disclosing the reported information on a publicly available website in 2014. These laws may adversely affect our sales, marketing, and other activities with respect to our medicines in the United States by imposing administrative and compliance burdens on us. If we fail to track and report as required by these laws or otherwise comply with these laws, we could be subject to the penalty provisions of the pertinent state and federal authorities. In the EU/EEA, declaration of transfers of value to healthcare professionals is subject to the requirements under the voluntary industry code of practice. France however has a statutory regime similar to the U.S. Sunshine Act.

Government Price Reporting. For those marketed medicines which are covered in the United States by the Medicaid programs, we have various obligations, including government price reporting and rebate requirements, which generally require medicines be offered at substantial rebates/discounts to Medicaid and certain purchasers (including "covered entities" purchasing under the 340B Drug Discount Program). We are also required to discount such medicines to authorized users of the Federal Supply Schedule of the General Services Administration, under which additional laws and requirements apply. These programs require submission of pricing data and calculation of discounts and rebates pursuant to complex statutory formulas, as well as the entry into government procurement contracts governed by the Federal Acquisition Regulations, and the guidance governing such calculations is not always clear. Compliance with such requirements can require significant investment in personnel, systems and resources, but failure to properly calculate our prices, or offer required discounts or rebates could subject us to substantial penalties. One component of the rebate and discount calculations under the Medicaid and 340B programs, respectively, is the "additional rebate", a complex calculation which is based, in part, on the rate at which a branded drug price increases over time more than the rate of inflation (based on the CPI-U). This comparison is based on the baseline pricing data for the first full quarter of sales associated with a branded drug's NDA, and baseline data cannot generally be reset, even on transfer of the NDA to another manufacturer. This "additional rebate" calculation can, in some cases where price increase have been relatively high versus the first quarter of sales of the NDA, result in Medicaid rebates up to 100 percent of a drug's "average manufacturer price" and 340B prices of one penny. Subject to the control of Directive 89/105/EEC, pricing and reimbursement in the EU/EEA is governed by national rules and policy and may vary from Member State to Member State.

In General. Because of the breadth of these laws and the narrowness of available statutory and regulatory exemptions, it is possible that some of our business activities, in the United States, could be subject to challenge under one or more of such laws. If we or our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including significant civil and criminal penalties, damages, fines, imprisonment, exclusion from participation in U.S. federal or state healthcare programs, additional reporting requirements and/or oversight and the curtailment or restructuring of our operations. To the extent that any medicine we make is sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals. Any penalties, damages, fines, curtailment or restructuring of our operations could materially adversely affect our ability to operate our business and our financial results. Although compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. Moreover, achieving and sustaining compliance with applicable federal and state privacy, security, sunshine, government price reporting, and fraud laws may prove costly.

36

Impact of Healthcare Reform and Recent Public Scrutiny of Specialty Drug Pricing on Coverage, Reimbursement, and Pricing. In the United States and other potentially significant markets for our medicines, government authorities and third-party payers are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative medicines and therapies, which has resulted in lower average selling prices. Further, the increased scrutiny of prescription drug pricing practices and emphasis on managed healthcare in the United States and on country-specific and regional pricing and reimbursement controls in the EU will put additional pressure on medicine pricing, reimbursement and usage, which may adversely affect our future medicine sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical reimbursement policies and pricing in general.

The U.S. and some foreign jurisdictions are considering or have enacted a number of additional legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our medicines profitably. Among policy makers and payers in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs (including a number of proposals pertaining to prescription drugs, specifically), improving quality and/or expanding access. There has been particular and increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices over the course of 2015 and 2016, particularly with respect to drugs that have been subject to relatively large price increases over relatively short time periods. There have been several recent U.S. Congressional inquiries and proposed legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient assistance programs, and reform government program reimbursement methodologies for drugs. In the United States, the pharmaceutical industry has already been significantly affected by major legislative initiatives, including, for example, the ACA. The ACA, among other things, imposes a significant annual fee on companies that manufacture or import branded prescription drug medicines. It also contains substantial provisions intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, and impose additional health policy reforms, any or all of which may affect our business. Since its enactment, there have been judicial and Congressional challenges to numerous provisions of the ACA. In January, Congress voted to adopt a budget resolution for fiscal year 2017, or the Budget Resolution, that authorizes the implementation of legislation that would repeal portions of the ACA. The Budget Resolution is not a law, but it is widely viewed as the first step toward the passage of legislation that would repeal certain aspects of the ACA. Further, on January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. Congress also could consider subsequent legislation to replace elements of the ACA that are repealed. We will continue to evaluate the effect that the ACA and any future measures to repeal or replace the ACA have on our business. The intense public scrutiny of drug pricing in the United States, is likely to continue the downward pressure on pharmaceutical pricing, especially under the Medicare program, and may also increase our regulatory burdens and operating costs.

Other legislative changes have also been proposed and adopted since the ACA was enacted. For example, the Budget Control Act of 2011 resulted in aggregate reductions in Medicare payments to providers of up to two percent per fiscal year, starting in 2013, and the American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Such laws, and others that may affect our business that have been recently enacted or may in the future be enacted, may result in additional reductions in Medicare and other healthcare funding. In the future, there will likely continue to be additional proposals relating to the reform of the U.S. healthcare system, some of which could further limit coverage and reimbursement of medicines, including our medicine candidates. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payers. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our medicines.

Irish Law Matters

As a result of the Vidara Merger, the outstanding shares of the common stock of HPI were canceled and automatically converted into the right to receive our ordinary shares. As we are an Irish-incorporated company, the following matters of Irish law are relevant to the holders of our ordinary shares.

Irish Restrictions on Import and Export of Capital. Except as indicated below, there are no restrictions imposed specifically on non-residents of Ireland dealing in Irish domestic securities, which includes ordinary shares of Irish companies. Dividends and redemption proceeds also continue to be freely transferable to non-resident holders of such securities. The Financial Transfers Act 1992 gives power to the Minister for Finance of Ireland to restrict financial transfers between Ireland and other countries and persons. Financial transfers are broadly defined and include all transfers that would be movements of capital or payments within the meaning of the treaties governing the member states of the EU. The acquisition or disposal of interests in shares issued by an Irish incorporated company and associated payments falls within this definition. In addition, dividends or payments on redemption or purchase of shares and payments on a liquidation of an Irish incorporated company would fall within this definition. The Criminal Justice (Terrorist Offences) Act 2005 also gives the Minister of Finance of Ireland the power to take various measures, including the freezing or seizure of assets, in order to combat terrorism. At present the Financial Transfers Act 1992 and the Criminal Justice (Terrorist Offences) Act 2005 prohibit financial transfers involving the late Slobodan Milosevic and associated persons, Republic of Guinea-Bissau, Myanmar/Burma, Belarus, certain persons indicted by the International Criminal Tribunal for the former Yugoslavia, the late Osama bin Laden, Al-Qaida, the Taliban of Afghanistan, Democratic Republic of Congo, Democratic People's Republic of Korea (North Korea), Iran, Iraq, Côte d'Ivoire, Lebanon, Liberia, Zimbabwe, Sudan, Somalia, Republic of Guinea, Afghanistan, Egypt, Eritrea, Libya, Syria, Tunisia, Burundi, the Central African Republic, Ukraine, Yemen, certain known terrorists and terrorist groups, and countries that harbor certain terrorist groups, without the prior permission of the Central Bank of Ireland or the Minister of Finance (as applicable).

Any transfer of, or payment in respect of, a share or interest in a share involving the government of any country that is currently the subject of United Nations sanctions, any person or body controlled by any of the foregoing, or by any person acting on behalf of the foregoing, may be subject to restrictions pursuant to such sanctions as implemented into Irish law.

Irish Taxes Applicable to U.S. Holders

Withholding Tax on Dividends. While we have no current plans to pay dividends, dividends on our ordinary shares would generally be subject to Irish Dividend Withholding Tax, or DWT, at the standard rate of income tax (currently twenty percent), unless an exemption applies.

Dividends on our ordinary shares that are owned by residents of the United States and held beneficially through the Depositary Trust Company, or DTC, will not be subject to DWT provided that the address of the beneficial owner of the ordinary shares in the records of the broker is in the United States.

Dividends on our ordinary shares that are owned by residents of the United States and held directly (outside of DTC) will not be subject to DWT provided that the shareholder has completed the appropriate Irish DWT form and this form remains valid. Such shareholders must provide the appropriate Irish DWT form to our transfer agent at least seven business days before the record date for the first dividend payment to which they are entitled.

If any shareholder who is resident in the United States receives a dividend subject to DWT, he or she should generally be able to make an application for a refund from the Irish Revenue Commissioners on the prescribed form.

While the U.S./Ireland Double Tax Treaty contains provisions regarding withholding, due to the wide scope of the exemptions from DWT available under Irish domestic law, it would generally be unnecessary for a U.S. resident shareholder to rely on the treaty provisions.

Income Tax on Dividends. A shareholder who is neither resident nor ordinarily resident in Ireland and who is entitled to an exemption from DWT generally has no additional liability to Irish income tax or to the universal social charge on a dividend from us unless that shareholder holds our ordinary shares through a branch or agency in Ireland through which a trade is carried on.

A shareholder who is neither resident nor ordinarily resident in Ireland and who is not entitled to an exemption from DWT generally has no additional liability to Irish income tax or to the universal social charge on a dividend from us. The DWT deducted by us discharges the liability to Irish income tax and to the universal social charge. This however is not the case where the shareholder holds the ordinary shares through a branch or agency in Ireland through which a trade is carried on.

Irish Tax on Capital Gains. A shareholder who is neither resident nor ordinarily resident in Ireland and does not hold our ordinary shares in connection with a trade or business carried on by such shareholder in Ireland through a branch or agency should not be within the charge to Irish tax on capital gains on a disposal of our ordinary shares.

Capital Acquisitions Tax. Irish capital acquisitions tax, or CAT, is composed principally of gift tax and inheritance tax. CAT could apply to a gift or inheritance of our ordinary shares irrespective of the place of residence, ordinary residence or domicile of the parties. This is because our ordinary shares are regarded as property situated in Ireland as our share register must be held in Ireland. The person who receives the gift or inheritance has primary liability for CAT.

CAT is levied at a rate of 33 percent above certain tax-free thresholds. The appropriate tax-free threshold is dependent upon (i) the relationship between the donor and the donee and (ii) the aggregation of the values of previous gifts and inheritances received by the donee from persons within the same category of relationship for CAT purposes. Gifts and inheritances passing between spouses are exempt from CAT. Our shareholders should consult their own tax advisers as to whether CAT is creditable or deductible in computing any domestic tax liabilities.

Stamp Duty. Irish stamp duty (if any) may become payable in respect of ordinary share transfers. However, a transfer of our ordinary shares from a seller who holds shares through DTC to a buyer who holds the acquired shares through DTC will not be subject to Irish stamp duty. A transfer of our ordinary shares (i) by a seller who holds ordinary shares outside of DTC to any buyer, or (ii) by a seller who holds the ordinary shares through DTC to a buyer who holds the acquired ordinary shares outside of DTC, may be subject to Irish stamp duty (currently at the rate of one percent of the price paid or the market value of the ordinary shares acquired, if greater). The person accountable for payment of stamp duty is the buyer or, in the case of a transfer by way of a gift or for less than market value, all parties to the transfer.

A shareholder who holds ordinary shares outside of DTC may transfer those ordinary shares into DTC without giving rise to Irish stamp duty provided that the shareholder would be the beneficial owner of the related book-entry interest in those ordinary shares recorded in the systems of DTC (and in exactly the same proportions) as a result of the transfer and at the time of the transfer into DTC there is no sale of those book-entry interests to a third party being contemplated by the shareholder. Similarly, a shareholder who holds ordinary shares through DTC may transfer those ordinary shares out of DTC without giving rise to Irish stamp duty provided that the shareholder would be the beneficial owner of the ordinary shares (and in exactly the same proportions) as a result of the transfer, and at the time of the transfer out of DTC there is no sale of those ordinary shares to a third party being contemplated by the shareholder. In order for the share registrar to be satisfied as to the application of this Irish stamp duty treatment where relevant, the shareholder must confirm to us that the shareholder would be the beneficial owner of the related book-entry interest in those ordinary shares recorded in the systems of DTC (and in exactly the same proportions) (or vice-versa) as a result of the transfer and there is no agreement for the sale of the related book-entry interest or the ordinary shares or an interest in the ordinary shares, as the case may be, by the shareholder to a third party being contemplated.

Employees

As of December 31, 2016, we had approximately 1,050 full-time employees. Of our employees as of December 31, 2016, approximately 185 were engaged in development, regulatory and manufacturing activities, approximately 650 were engaged in sales and marketing and approximately 215 were engaged in administration, including business development, finance, legal, information systems, facilities and human resources. None of our employees is subject to a collective bargaining agreement. We consider our employee relations to be satisfactory.

Available Information

We make available free of charge on or through our internet website our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and all amendments to those reports as soon as reasonably practicable after such material is electronically filed with or furnished to the Securities and Exchange Commission. We also regularly post copies of our press releases as well as copies of presentations and other updates about our business on our website. Our website address is www.horizonpharma.com. The information contained in or that can be accessed through our website is not part of this report. Information is also available through the Securities and Exchange Commission's website at www.sec.gov or is available at the Securities and Exchange Commission's Public Reference Room located at 100 F Street, NE, Washington DC, 20549. Information on the operation of the Public Reference Room is available by calling the Securities and Exchange Commission at 800-SEC-0330.

Item 1A. Risk Factors

Certain factors may have a material adverse effect on our business, financial condition and results of operations, and you should carefully consider them. Accordingly, in evaluating our business, we encourage you to consider the following discussion of risk factors in its entirety, in addition to other information contained in this report as well as our other public filings with the Securities and Exchange Commission, or SEC.

Risks Related to Our Business and Industry

Our ability to generate revenues from our medicines is subject to attaining significant market acceptance among physicians, patients and healthcare payers.

Our current medicines, and other medicines or medicine candidates that we may develop or acquire, may not attain market acceptance among physicians, patients, healthcare payers or the medical community. We have a limited history of commercializing medicines and most of our medicines have not been on the market for an extensive period of time, which subjects us to numerous risks as we attempt to increase our market share. We believe that the degree of market acceptance and our ability to generate revenues from our medicines will depend on a number of factors, including:

- timing of market introduction of our medicines as well as competitive medicines;
- efficacy and safety of our medicines;
- continued projected growth of the markets in which our medicines compete;
- prevalence and severity of any side effects;
- if and when we are able to obtain regulatory approvals for additional indications for our medicines;
- acceptance by patients, primary care physicians and key specialists;
- availability of coverage and adequate reimbursement and pricing from government and other third-party payers;
- potential or perceived advantages or disadvantages of our medicines over alternative treatments, including cost of treatment and relative convenience and ease of administration;
- strength of sales, marketing and distribution support;
- the price of our medicines, both in absolute terms and relative to alternative treatments;
- impact of past and limitation of future medicine price increases;
- our ability to maintain a continuous supply of medicine for commercial sale;
- the effect of current and future healthcare laws;
- the performance of third-party distribution partners, over which we have limited control; and
- medicine labeling or medicine insert requirements of the U.S. Food and Drug Administration, or FDA, or other regulatory authorities.

With respect to DUEXIS and VIMOVO, studies indicate that physicians do not commonly co-prescribe gastrointestinal, or GI, protective agents to high-risk patients taking nonsteroidal anti-inflammatory drugs, or NSAIDs. We believe this is due in part to a lack of awareness among physicians prescribing NSAIDs regarding the risk of NSAID-induced upper GI ulcers, in addition to the inconvenience of prescribing two separate medications and patient compliance issues associated with multiple prescriptions. If physicians remain unaware of, or do not otherwise believe in, the benefits of combining GI protective agents with NSAIDs, our market opportunity for DUEXIS and VIMOVO will be limited. Some physicians may also be reluctant to prescribe DUEXIS or VIMOVO due to the inability to vary the dose of ibuprofen and naproxen, respectively, or if they believe treatment with NSAIDs or GI protective agents other than those contained in DUEXIS and VIMOVO, including those of its competitors, would be more effective for their patients. With respect to each of DUEXIS, PENNSAID 2% w/w, or PENNSAID 2%, RAYOS/LODOTRA, VIMOVO and BUPHENYL, their higher cost compared to the generic or branded forms of their active ingredients alone may limit adoption by physicians, patients and healthcare payers. With respect to ACTIMMUNE, while it is the only FDA-approved treatment for chronic granulomatous disease, or CGD, and severe, malignant osteopetrosis, or SMO, they are very rare conditions and, as a result, our ability to grow ACTIMMUNE sales will depend on our ability to further penetrate this limited market and obtain marketing approval for additional indications. With respect to RAVICTI, which is also approved to treat a very limited patient population, our ability to grow sales will depend in large part on our ability to transition urea cycle disorder, or UCD, patients from BUPHENYL or generic equivalents, which are comparatively much less expensive, to RAVICTI. With respect to KRYSTEXXA, our ability to grow sales will be affected by the success of our sales and marketing strategies and life cycle management, including studies designed to test reduction of immunogenicity in KRYSTEXXA which could expand the patient population and usage of KRYSTEXXA. With respect to MIGERGOT, our ability to sustain sales will depend on the management of inventory levels and the continued awareness of its benefits among physicians. With respect to PROCYSBI, which is approved to treat a very limited patient population, our ability to grow sales will depend in large part on our ability to transition patients from the first-generation immediate-release cysteamine therapy to PROCYSBI, to identify additional patients with nephropathic cystinosis, and expand commercialization in Europe. Unless QUINSAIR is approved for marketing in additional countries, our ability to drive growth of this medicine will largely depend on expanding its use in Europe and Canada. If our current medicines or any other medicine that we may seek approval for or acquire fail to attain market acceptance, we may not be able to generate significant revenue to achieve or sustain profitability, which would have a material adverse effect on our business, results of operations, financial condition and prospects (including, possibly, the value of our ordinary shares).

Our future prospects are highly dependent on our ability to successfully formulate and execute commercialization strategies for each of our medicines. Failure to do so would adversely impact our financial condition and prospects.

A substantial majority of our resources are focused on the commercialization of our current medicines. Our ability to generate significant medicine revenues and to achieve commercial success in the near-term will initially depend almost entirely on our ability to successfully commercialize these medicines in the United States.

With respect to our orphan business unit medicines, ACTIMMUNE, BUPHENYL, PROCYSBI, QUINSAIR and RAVICTI, and with respect to our rheumatology business unit medicine, KRYSTEXXA, our commercialization strategy includes efforts to increase awareness of the rare conditions that each medicine is designed to treat, enhancing efforts to identify target patients and in certain cases pursue opportunities for label expansion and more effective use through clinical trials. In addition, our strategy with respect to ACTIMMUNE includes pursuing label expansion for additional indications, such as for advanced urothelial carcinoma and renal cell carcinoma, and price increases but we cannot be certain that our pricing strategy will not result in downward pressure on sales or that we or others will be able to successfully complete clinical trials and obtain regulatory approvals in additional indications. With respect to PROCYSBI and RAVICTI, our strategy includes accelerating the transition of patients from first-generation therapies, and increasing the diagnosis of the associated rare conditions through patient and physician outreach. Part of our success in our strategy for RAVICTI will also depend on obtaining approval of RAVICTI for the treatment of UCD in patients less than two years of age. However, we cannot guarantee that on-going studies will be positive or that we will be able to expand the labeling for RAVICTI on our anticipated timeline or at all. Our strategy with respect to

KRYSTEXXA includes the continued enhancement of the marketing campaign with improved immunogenicity data, continued volume growth and pricing optimization.

With respect to our primary care medicines DUEXIS, PENNSAID 2% and VIMOVO, our strategy has more recently included entering into rebate agreements with pharmacy benefit managers, or PBMs, for certain of our primary care medicines where we believe the rebates and costs justify expanded formulary access for patients. However, we cannot guarantee that we will be able to secure additional rebate agreements on commercially reasonable terms or that expected volume growth will sufficiently offset the rebates and fees paid to PBMs or that our existing agreements with PBMs will have the intended impact on formulary access. For each of our primary care medicines, we expect that our commercial success will depend on our sales and marketing efforts in the United States.

Our strategy for RAYOS in the United States is to focus on the rheumatology indications approved for RAYOS, including our collaboration with the Alliance for Lupus Research, or ALR, to study the effect of RAYOS on the fatigue experienced by systemic lupus erythematosus, or SLE, patients.

Our overall commercialization strategy also includes plans to expand sales in Europe and other countries outside the United States directly or through distributors for certain of our orphan and rheumatology medicines. In November 2015, we received approval of the Committee for Medicinal Products for Human Use of the European Medicines Agency, or EMA, for RAVICTI for use as an adjunctive therapy for chronic management of adult and pediatric UCD patients greater than two months of age. This authorizes us to market RAVICTI in all 28 Member States of the European Union, or EU, and will form the basis for recognition by the Member States of the European Economic Area, or EEA, namely Norway, Iceland and Liechtenstein, for the medicine to be placed on the market. In June 2016, we partnered with Clinigen Group plc's Idis managed access division to initiate a managed access program in selected European countries, which agreement will terminate on April 10, 2017 and after which we will partner with Swedish Orphan Biovitrum AB, or SOBI, to continue our managed access program in selected European countries. While we expect to commercially launch RAVICTI in Europe in 2017 through an exclusive distribution agreement with SOBI, we cannot guarantee we will be able to successfully implement our commercial plans for RAVICTI in Europe. With respect to PROCYSBI and QUINSAIR, which are approved for marketing in the EU, we intend to continue evaluating commercial launches in additional EU countries as well as pursuing early access programs. Although LODOTRA is approved for marketing in countries outside the United States, to date it has only been marketed in a limited number of countries.

If any of our commercial strategies are unsuccessful or we fail to successfully modify our strategies over time due to changing market conditions, our ability to increase market share for our medicines, grow revenues and sustain profitability will be harmed.

In order to increase adoption and sales of our medicines, we will need to continue developing our commercial organization as well as recruit and retain qualified sales representatives.

Part of our strategy is to continue to build a biopharmaceutical company to successfully execute the commercialization of our medicines in the U.S. market, and in selected markets outside the United States where we have commercial rights. We may not be able to successfully commercialize our medicines in the United States or in any other territories where we have commercial rights. In order to commercialize any approved medicines, we must continue to build our sales, marketing, distribution, managerial and other non-technical capabilities. Although we had expanded our sales force to approximately 480 sales representatives as of December 31, 2016, consisting of approximately 20 orphan disease sales representatives, 100 rheumatology sales specialists and 360 primary care sales representatives, we currently have limited resources compared to some of our competitors, and the continued development of our own commercial organization to market our medicines and any additional medicines we may acquire will be expensive and time-consuming. We also cannot be certain that we will be able to continue to successfully develop this capability.

As a result of the evolving role of various constituents in the prescription decision making process, we focus on hiring sales representatives for our primary care and rheumatology business units with successful business to business experience. For example, we have faced challenges due to pharmacists increasingly switching a patient's intended prescription from DUEXIS and VIMOVO to a generic or over-the-counter brand of their active ingredients. We have faced similar challenges for RAYOS, BUPHENYL and PENNSAID 2% with respect to generic brands. While we believe the profile of our representatives is better suited for this evolving environment, we cannot be certain that our representatives will be able to successfully protect our market for DUEXIS, PENNSAID 2%, RAYOS, BUPHENYL and VIMOVO or that we will be able to continue attracting and retaining sales representatives with our desired profile and skills. We will also have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train and retain commercial personnel. To the extent we rely on additional third parties to commercialize any approved medicines, we may receive less revenue than if we commercialized these medicines ourselves. In addition, we may have little or no control over the sales efforts of any third parties involved in our commercialization efforts. In the event we are unable to successfully develop and maintain our own commercial organization or collaborate with a third-party sales and marketing organization, we may not be able to commercialize our medicines and medicine candidates and execute on our business plan.

If we are unable to effectively train and equip our sales force, our ability to successfully commercialize our medicines will be harmed.

As we continue to acquire additional medicines through acquisition transactions, the members of our sales force may have limited experience promoting certain of our medicines. To the extent we employ an acquired entity's original sales forces to promote acquired medicines, we may not be successful in continuing to retain these employees and we otherwise will have limited experience marketing these medicines under our commercial organization. As a result, we are required to expend significant time and resources to train our sales force to be credible and persuasive in convincing physicians to prescribe and pharmacists to dispense our medicines. In addition, we must train our sales force to ensure that a consistent and appropriate message about our medicines is being delivered to our potential customers. Our sales representatives may also experience challenges promoting multiple medicines when we call on physicians and their office staff. We have experienced, and may continue to experience, turnover of the sales representatives that we hired or will hire, requiring us to train new sales representatives. If we are unable to effectively train our sales force and equip them with effective materials, including medical and sales literature to help them inform and educate physicians about the benefits of our medicines and their proper administration and label indication, as well as our patient access programs, our efforts to successfully commercialize our medicines could be put in jeopardy, which could have a material adverse effect on our financial condition, share price and operations.

If we cannot successfully implement our patient access programs or increase formulary access and reimbursement for our medicines in the face of increasing pressure to reduce the price of medications, the adoption of our medicines by physicians, patients and payers may decline.

There continues to be immense pressure from healthcare payers and PBMs to use less expensive generics or over-the-counter brands instead of branded medicines. For example, some of the largest PBMs previously placed DUEXIS and VIMOVO on their formulary exclusion lists. Additional healthcare plans, including those that contract with these PBMs but use different formularies, may also choose to exclude our medicines from their formularies or restrict coverage to situations where a generic or over-the-counter medicine has been tried first. Many payers and PBMs also require patients to make co-payments for branded medicines, including many of our medicines, in order to incentivize the use of generic or other lower-priced alternatives instead. Legislation enacted in most states in the United States allows, or in some instances mandates, that a pharmacist dispenses an available generic equivalent when filling a prescription for a branded medicine, in the absence of specific instructions from the prescribing physician. Because our medicines (other than BUPHENYL) do not currently have FDA-approved generic equivalents in the United States, we do not believe our medicines should be subject to mandatory generic substitution laws. However, we understand that some pharmacies may attempt to obtain physician authorization to switch prescriptions for DUEXIS or VIMOVO to prescriptions for multiple generic medicines with similar active pharmaceutical ingredients,

or APIs, to ensure payment for the medicine if the physician's prescription for the branded medicine is not immediately covered by the payer, despite such substitution being off-label in the case of DUEXIS and VIMOVO. If these limitations in coverage and other incentives result in patients refusing to fill prescriptions or being dissatisfied with the out-of-pocket costs of their medications, or if pharmacies otherwise seek and receive physician authorization to switch prescriptions, not only would we lose sales on prescriptions that are ultimately not filled, but physicians may be dissuaded from writing prescriptions for our medicines in the first place in order to avoid potential patient non-compliance or dissatisfaction over medication costs, or to avoid spending the time and effort of responding to pharmacy requests to switch prescriptions.

Part of our commercial strategy to increase adoption and access to our medicines in the face of these incentives to use generic alternatives is to offer physicians the opportunity to have patients fill prescriptions through independent pharmacies participating in our HorizonCares patient access program. Through HorizonCares, financial assistance may be available to reduce eligible patients' out-of-pocket costs for prescriptions filled. Because of this assistance, eligible patients' out-of-pocket cost for our medicines when dispensed through HorizonCares may be significantly lower than such costs when our medicines are dispensed outside of the HorizonCares program. However, to the extent physicians do not direct prescriptions currently filled through traditional pharmacies, including those associated with or controlled by PBMs, to pharmacies participating in our HorizonCares program, we may experience a significant decline in DUEXIS, VIMOVO and PENNSAID 2% prescriptions as a result of formulary exclusions, co-payment requirements or other incentives to use lower-priced alternatives to our medicines. Our ability to increase utilization of our patient access programs will depend on physician and patient awareness and comfort with the programs, and we have limited ability to influence whether physicians use our patient access programs to prescribe our medicines or whether patients will agree to receive our medicines through our HorizonCares program. In addition, the HorizonCares program is not available to federal health care program (such as Medicare and Medicaid) beneficiaries. We have also contracted with certain PBMs and other payers to secure formulary status and reimbursement for certain of our primary care medicines, which generally require us to pay administrative fees and rebates to the PBMs and other payers for qualifying prescriptions. While we recently announced business relationships with two of the largest PBMs, Express Scripts, Inc., or Express Scripts, and CVS Caremark, that have resulted in DUEXIS and VIMOVO being removed from the Express Scripts and CVS Caremark 2017 exclusion lists, as well as a rebate agreement with another PBM, Prime Therapeutics LLC, and we believe these agreements will secure formulary status for certain of our medicines, we cannot guarantee that we will be able to agree to terms with other PBMs and other payers, or that such terms will be commercially reasonable to us. In addition, despite our agreements with PBMs, the extent of formulary status and reimbursement will ultimately depend to a large extent upon individual healthcare plan formulary decisions. If healthcare plans that contract with PBMs with which we have agreements do not adopt formulary changes recommended by the PBMs with respect to our medicines, we may not realize the expected access and reimbursement benefits from these agreements. If we are unable to increase adoption of HorizonCares for filling prescriptions of our medicines or to secure formulary status and reimbursement through arrangements with PBMs and other payers, our ability to maintain or increase prescriptions for our medicines could be impaired.

There has been negative publicity and inquiries from Congress and enforcement authorities regarding the use of specialty pharmacies and drug pricing. Our patient access programs are not involved in the prescribing of medicines and are solely to assist in ensuring that when a physician determines one of our medicines offers a potential clinical benefit to their patients and they prescribe one for an eligible patient, financial assistance may be available to reduce the patient's out-of-pocket costs. In addition, all pharmacies that fill prescriptions for our medicines are fully independent, including those that participate in HorizonCares. We do not own or possess any option to purchase an ownership stake in any pharmacy that distributes our medicines, and our relationship with each pharmacy is non-exclusive and arm's length. All of our sales are processed through pharmacies independent of us. Despite this, the negative publicity and interest from Congress and enforcement authorities regarding specialty pharmacies may result in physicians being less willing to participate in our patient access programs and thereby limit our ability to increase patient access and adoption of our medicines.

We may also encounter difficulty in forming and maintaining relationships with pharmacies that participate in our patient access programs. We currently depend on a limited number of pharmacies participating in HorizonCares to fulfill patient prescriptions under the HorizonCares program. If these HorizonCares participating pharmacies are unable to process and fulfill the volume of patient prescriptions directed to them under the HorizonCares program, our ability to maintain or increase prescriptions for our medicines will be impaired. The commercialization of our medicines and our operating results could be affected should any of the HorizonCares participating pharmacies choose not to continue participation in our HorizonCares program or by any adverse events at any of those HorizonCares participating pharmacies. For example, pharmacies that dispense our medicines could lose contracts that they currently maintain with managed care organizations, or MCOs, including PBMs. Pharmacies often enter into agreements with MCOs. They may be required to abide by certain terms and conditions to maintain access to MCO

networks, including terms and conditions that could limit their ability to participate in patient access programs like ours. Failure to comply with the terms of their agreements with MCOs could result in a variety of penalties, including termination of their agreement, which could negatively impact the ability of those pharmacies to dispense our medicines and collect reimbursement from MCOs for such medicines.

The HorizonCares program may implicate certain state laws related to, among other things, unlawful schemes to defraud, excessive fees for services, tortious interference with patient contracts and statutory or common law fraud. We have a comprehensive compliance program in place to address adherence with various laws and regulations relating to the selling, marketing and manufacturing of our medicines, as well as certain third-party relationships, including pharmacies. Specifically with respect to pharmacies, the compliance program utilizes a variety of methods and tools to monitor and audit pharmacies, including those that participate in the HorizonCares program, to confirm their activities, adjudication and practices are consistent with our compliance policies and guidance. Despite our compliance efforts, to the extent the HorizonCares program is found to be inconsistent with applicable laws or the pharmacies that participate in our patient access programs do not comply with applicable laws, we may be required to restructure or discontinue such programs, terminate our relationship with certain pharmacies, or be subject to other significant penalties. In November 2015, we received a subpoena from the U.S. Attorney's Office for the Southern District of New York requesting documents and information related to our patient access programs and other aspects of our marketing and commercialization activities. We are unable to predict how long this investigation will continue or its outcome, but we have incurred and anticipate that we may continue to incur significant costs in connection with the investigation, regardless of the outcome. We may also become subject to similar investigations by other governmental agencies or Congress. The investigation by the U.S. Attorney's Office and any additional investigations of our patient access programs and sales and marketing activities may result in damages, fines, penalties, exclusion, additional reporting requirements and/or oversight or other administrative sanctions against us.

If the cost of maintaining our patient access programs increases relative to our sales revenues, we could be forced to reduce the amount of patient financial assistance that we offer or otherwise scale back or eliminate such programs, which could in turn have a negative impact on physicians' willingness to prescribe and patients' willingness to fill prescriptions of our medicines. While we believe that our recent arrangements with PBMs will result in broader inclusion of certain of our primary care medicines on healthcare plan formularies, and therefore increase payer reimbursement and lower our cost of providing patient access programs, these arrangements generally require us to pay administrative and rebate payments to the PBMs and/or other payers and their effectiveness will ultimately depend to a large extent upon individual healthcare plan formulary decisions that are beyond the control of the PBMs. If our arrangements with PBMs and other payers do not result in increased prescriptions and reductions in our costs to provide our patient access programs that are sufficient to offset the administrative fees and rebate payments to the PBMs and/or other payers, our financial results may be harmed.

If we are unable to successfully implement our commercial plans and facilitate adoption by patients and physicians of any approved medicines through our sales, marketing and commercialization efforts, then we will not be able to generate sustainable revenues from medicine sales which will have a material adverse effect on our business and prospects.

We are solely dependent on third parties to commercialize certain of our medicines outside the United States. Failure of these third parties or any other third parties to successfully commercialize our medicines and medicine candidates in the applicable jurisdictions could have a material adverse effect on our business.

Mundipharma International Corporation Limited, or Mundipharma, is our exclusive distributor for LODOTRA in Europe, Asia and Latin America. We rely on other third-party distributors for commercialization of BUPHENYL (known as AMMONAPS in certain European countries) in certain territories outside the United States for which we currently have rights. We have limited contractual rights to force these third parties to invest significantly in commercialization of these medicines in our markets. In the event that Mundipharma or our current ex-U.S. distributors for BUPHENYL or any other third-party with any future commercialization rights to any of our medicines or medicine candidates fail to adequately commercialize those medicines or medicine candidates because they lack adequate financial or other resources, decide to focus on other initiatives or otherwise, our ability to successfully commercialize our medicines or medicine candidates in the applicable jurisdictions would be limited, which would adversely affect our business, financial condition, results of operations and prospects. We have had disagreements with Mundipharma under our European agreements and may continue to have disagreements, which could harm

commercialization of LODOTRA in Europe or result in the termination of our agreements with Mundipharma. In addition, our agreements with Mundipharma and our agreements with our current ex-U.S. distributors for BUPHENYL may be terminated by either party in the event of a bankruptcy of the other party or upon an uncured material breach by the other party. If these third parties terminated their agreements, we may not be able to secure an alternative distributor in the applicable territory on a timely basis or at all, in which case our ability to generate revenues from the sale of LODOTRA, QUINSAIR, RAVICTI or BUPHENYL outside the United States would be materially harmed.

Our medicines are subject to extensive regulation, and we may not obtain additional regulatory approvals for our medicines.

The clinical development, manufacturing, labeling, packaging, storage, recordkeeping, advertising, promotion, export, marketing and distribution and other possible activities relating to our medicines and our medicine candidates are, and will be, subject to extensive regulation by the FDA and other regulatory agencies. Failure to comply with FDA and other applicable regulatory requirements may, either before or after medicine approval, subject us to administrative or judicially imposed sanctions.

To market any drugs or biologics outside of the United States, we and current or future collaborators must comply with numerous and varying regulatory and compliance related requirements of other countries. Approval procedures vary among countries and can involve additional medicine testing and additional administrative review periods, including obtaining reimbursement and pricing approval in select markets. The time required to obtain approval in other countries might differ from that required to obtain FDA approval. The regulatory approval process in other countries may include all of the risks associated with FDA approval as well as additional, presently unanticipated, risks. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others.

Applications for regulatory approval, including a marketing authorization application, or MAA, for marketing new drugs in Europe, must be supported by extensive clinical and preclinical data, as well as extensive information regarding chemistry, manufacturing and controls, or CMC, to demonstrate the safety and effectiveness of the applicable medicine candidate. The number and types of preclinical studies and clinical trials that will be required for regulatory approval varies depending on the medicine candidate, the disease or the condition that the medicine candidate is designed to target and the regulations applicable to any particular medicine candidate. Despite the time and expense associated with preclinical and clinical studies, failure can occur at any stage, and we could encounter problems that cause us to repeat or perform additional preclinical studies, CMC studies or clinical trials. Regulatory authorities could delay, limit or deny approval of a medicine candidate for many reasons, including because they:

- may not deem a medicine candidate to be adequately safe and effective;
- may not find the data from preclinical studies, CMC studies and clinical trials to be sufficient to support a claim of safety and efficacy;
- may interpret data from preclinical studies, CMC studies and clinical trials significantly differently than we do;
- may not approve the manufacturing processes or facilities associated with our medicine candidates;
- may conclude that we have not sufficiently demonstrated long-term stability of the formulation for which we are seeking marketing approval;
- may change approval policies (including with respect to our medicine candidates' class of drugs) or adopt new regulations; or
- may not accept a submission due to, among other reasons, the content or formatting of the submission.

Even if we believe that data collected from our preclinical studies, CMC studies and clinical trials of our medicine candidates are promising and that our information and procedures regarding CMC are sufficient, our data may not be sufficient to support marketing approval by regulatory authorities, or regulatory interpretation of these data and procedures may be unfavorable. Even if approved, medicine candidates may not be approved for all indications requested and such approval may be subject to limitations on the indicated uses for which the medicine may be marketed, restricted distribution methods or other limitations. Our business and reputation may be harmed by any failure or significant delay in obtaining regulatory approval for the sale of any of our medicine candidates. We cannot predict when or whether regulatory approval will be obtained for any medicine candidate we develop.

If we are unable to obtain any further approvals for RAVICTI outside the United States, Canada and Europe, or determine that commercializing RAVICTI outside the United States, Canada and Europe is not economically viable, the market potential of RAVICTI may be limited.

46

On July 12, 2016, Raptor Pharmaceutical Corp., or Raptor, received a notice of deficiency, or NOD, from Health Canada, or HC, dated July 11, 2016 relating to the New Drug Submission, or NDS, Raptor submitted for PROCYSBI in January 2016. The NOD outlined specific deficiencies in the NDS that needed to be addressed for HC to complete its review. A complete response was submitted to HC to address the NOD on November 3, 2016. HC completed the screening process and accepted the NOD response for review on December 16, 2016. Based on a 180-day review for priority applications, we anticipate that HC will complete its review of the NDS and decide whether to grant marketing approval for PROCYSBI for the treatment of nephropathic cystinosis by June 14, 2017.

With respect to QUINSAIR, the FDA has indicated in previous written and verbal communications with Raptor and with the drug's previous sponsor that it believes the data submitted in connection with EMA's subsequent approval of QUINSAIR for the management of chronic pulmonary infections due to Pseudomonas aeruginosa in adults with cystic fibrosis does not provide substantial evidence of efficacy and safety to support FDA approval of QUINSAIR for treatment of patients with cystic fibrosis. On October 27, 2016, the FDA expressed its recommendation that an additional clinical trial should be conducted, and noted that if Raptor submits a new drug application, or NDA, without conducting an additional clinical trial, the FDA will review the submission to determine whether it is acceptable for filing. Based upon the FDA's feedback, we have made the decision not to pursue an NDA for U.S. approval of QUINSAIR as a treatment of Pseudomonas aeruginosa in adults with cystic fibrosis.

Prior to our acquisition of Raptor, Raptor planned to pursue the development of QUINSAIR for use in the indication of bronchiectasis, or BE, not associated with cystic fibrosis. On September 8, 2016, Raptor met the Medicines and Healthcare Products Regulatory Agency, or the MHRA, to discuss non-clinical and clinical development aspects of QUINSAIR for the treatment of BE. On September 29, 2016, Raptor received a written response from the MHRA, which included answers to questions on trial design, among other responses. Raptor submitted a protocol to FDA on August 18, 2016 for a Phase 2, placebo-controlled study of QUINSAIR in adults with BE. Feedback from FDA was received on October 17, 2016 requesting additional information and changes to the proposed study protocol. Raptor was also exploring further clinical development of QUINSAIR for the treatment of pulmonary nontuberculous mycobacteria, or NTM, infection, based on third-party data generated pertaining to the susceptibility of certain pathogens to treatment with levofloxacin and other fluoroquinolone molecules. No clinical data has been generated with QUINSAIR in patients with BE or with NTM infections, either by Raptor, by us or by other parties. This creates uncertainty regarding the potential efficacy of QUINSAIR in these indications.

We will evaluate all development opportunities, including all obligations to use commercial reasonable efforts to further develop QUINSAIR. However, we may determine not to pursue such further development.

The ultimate approval and commercial marketing of any of our medicines in additional indications or geographies is subject to substantial uncertainty. Failure to gain additional regulatory approvals would limit the potential revenues and value of our medicines and could cause our share price to decline.

The amount of our medicine sales in the EEA is dependent in part upon the pricing and reimbursement decisions adopted in each of the EEA countries, which may not be at acceptable levels to us.

One or more EEA countries may not support pricing within our target pricing and reimbursement range for our medicines due to budgetary decisions made by regional, national and local health authorities and third-party payers in the EEA, which would negatively affect our revenues. The pricing and reimbursement process in EEA countries can be lengthy, involved and difficult to predict. Failure to timely complete the pricing and reimbursement process in the EEA countries will delay our ability to market PROCYSBI, to bring QUINSAIR to market in the EEA and to derive revenues from those countries.

We may be subject to penalties and litigation and large incremental expenses if we fail to comply with regulatory requirements or experience problems with our medicines.

Even after we achieve regulatory approvals, we are subject to ongoing obligations and continued regulatory review with respect to many operational aspects including our manufacturing processes, labeling, packaging, distribution, storage, adverse event monitoring and reporting, dispensation, advertising, promotion and recordkeeping. These requirements include submissions of safety and other post-marketing information and reports, ongoing maintenance of medicine registration and continued compliance with current good manufacturing practices, or cGMPs, GCPs, good pharmacovigilance practice, good distribution practices and good laboratory practices, or GLPs. If we, our medicines or medicine candidates, or the third-party manufacturing facilities for our medicines or medicine candidates fail to comply with applicable regulatory requirements, a regulatory agency may:

- impose injunctions or restrictions on the marketing, manufacturing or distribution of a medicine, suspend or withdraw medicine approvals, revoke necessary licenses or suspend medicine reimbursement;
- issue warning letters, show cause notices or untitled letters describing alleged violations, which may be publicly available;
- suspend any ongoing clinical trials or delay or prevent the initiation of clinical trials;
- delay or refuse to approve pending applications or supplements to approved applications we have filed;
- refuse to permit drugs or precursor or intermediary chemicals to be imported or exported to or from the United States;
- suspend or impose restrictions or additional requirements on operations, including costly new manufacturing quality or pharmacovigilance requirements;
- seize or detain medicines or require us to initiate a medicine recall; and/or
- commence criminal investigations and prosecutions.

Moreover, existing regulatory approvals and any future regulatory approvals that we obtain will be subject to limitations on the approved indicated uses and patient populations for which our medicines may be marketed, the conditions of approval, requirements for potentially costly, post-market testing and requirements for surveillance to monitor the safety and efficacy of the medicines. In the EEA, the advertising and promotion of pharmaceuticals is strictly regulated. The direct-to-consumer promotion of prescription pharmaceuticals is not permitted, and some countries in the EEA require the notification and/or prior authorization of promotional or advertising materials directed at healthcare professionals. The FDA, EMA and other authorities in the EEA countries strictly regulate the promotional claims that may be made about prescription medicines, and our medicine labeling, advertising and promotion are subject to continuing regulatory review. Physicians nevertheless may prescribe our medicines to their patients in a manner that is inconsistent with the approved label or that is off-label. Positive clinical trial results in any of our medicine development programs increase the risk that approved pharmaceutical forms of the same APIs may be used off-label in those indications. Our investigational medicine candidate RP103 is comprised of the same API as PROCYSBI. If we are found to have improperly promoted off-label uses of approved medicines, we may be subject to significant sanctions, civil and criminal fines and injunctions prohibiting us from engaging in specified promotional conduct.

In addition, engaging in improper promotion of our medicines for off-label uses in the United States can subject us to false claims litigation under federal and state statutes. These false claims statutes in the United States include the federal False Claims Act, which allows any individual to bring a lawsuit against a pharmaceutical company on behalf of the federal government alleging submission of false or fraudulent claims or causing to present such false or fraudulent claims for payment by a federal program such as Medicare or Medicaid. Growth in false claims litigation has increased the risk that a pharmaceutical company will have to defend a false claim action, pay civil money penalties, settlement fines or restitution, agree to comply with burdensome reporting and compliance obligations and be excluded from Medicare, Medicaid and other federal and state healthcare programs.

The regulations, policies or guidance of regulatory agencies may change and new or additional statutes or government regulations may be enacted that could prevent or delay regulatory approval of our medicine candidates or further restrict or regulate post-approval activities. For example, the Food and Drug Administration Safety and Innovation Act requires the FDA to issue new guidance describing its policy regarding internet and social media promotion of regulated medical products, and the FDA may soon specify new restrictions on this type of promotion. In January 2014, the FDA released draft guidance on how drug companies can fulfill their regulatory requirements for post-marketing submission of interactive promotional media, and though the guidance provided insight into how the FDA views a company's responsibility for certain types of social media promotion, there remains a substantial amount of uncertainty. We cannot predict the likelihood, nature or extent of adverse government regulation that may arise from pending or future legislation or administrative action, either in the United States or abroad. If we are unable to achieve and maintain regulatory compliance, we will not be permitted to market our drugs, which would materially adversely affect our business, results of operations and financial condition.

Our limited history of commercial operations makes evaluating our business and future prospects difficult and may increase the risk of any investment in our ordinary shares.

We face considerable risks and difficulties as a company with limited commercial operating history, particularly as a global consolidated entity with operating subsidiaries that also have limited operating histories. If we do not successfully address these risks, our business, prospects, operating results and financial condition will be materially and adversely harmed. Our limited commercial operating history, including our limited history commercializing our current medicines, makes it particularly difficult for us to predict our future operating results and appropriately budget for our expenses. In the event that actual results differ from our estimates or we adjust our estimates in future periods, our operating results and financial position could be materially affected. For example, we may underestimate the resources we will require to successfully integrate recent or future medicine or company acquisitions, or to commercialize our medicines, or not realize the benefits we expect to derive from our recent or future acquisitions. In addition, we have a limited history implementing our commercialization strategy focused on patient access, and we cannot guarantee that we will be able to successfully implement this strategy or that it will represent a viable strategy over the long term.

We have rights to medicines in certain jurisdictions but have no control over third parties that have rights to commercialize those medicines in other jurisdictions, which could adversely affect our commercialization of these medicines.

Boehringer Ingelheim International GmbH, or Boehringer Ingelheim International, currently has certain rights to commercialize interferon gamma 1b, known as IMUKIN, outside the United States, Canada and Japan. On May 18, 2016, we entered into a definitive agreement with Boehringer Ingelheim International to acquire such rights to IMUKIN, or the IMUKIN Acquisition. The transaction is expected to close in 2017 and we are continuing to work with Boehringer Ingelheim International to enable the transfer of applicable marketing authorizations. AstraZeneca AB, or AstraZeneca, has retained its existing rights to VIMOVO in territories outside of the United States, including the right to use the VIMOVO name and related trademark. While we have the worldwide rights to BUPHENYL, the marketing and distribution rights are granted to SOBI. Similarly, Nuvo Research Inc., or Nuvo, has retained its rights to PENNSAID 2% in territories outside of the United States and has announced its intention to seek commercialization partners outside the United States. We have little or no control over Boehringer Ingelheim International's activities with respect to IMUKIN outside the United States, Canada and Japan, over AstraZeneca's activities with respect to VIMOVO outside of the United States, over SOBI's activities with respect to BUPHENYL in Europe, certain Asian, Latin American, Middle Eastern, North African and other countries or over Nuvo's or its future commercial partners' activities with respect to PENNSAID 2% outside of the United States, even though those activities could impact our ability to successfully commercialize these medicines. For example, AstraZeneca or its assignees or Nuvo or its assignees can make statements or use promotional materials with respect to VIMOVO or PENNSAID 2%, respectively, outside of the United States that are inconsistent with our positioning of the medicines in the United States, and could sell VIMOVO or PENNSAID 2%, respectively, in foreign countries, including

Canada, at prices that are dramatically lower than the prices we charge in the United States. These activities and decisions, while occurring outside of the United States, could harm our commercialization strategy in the United States, in particular because AstraZeneca is continuing to market VIMOVO outside the United States under the same VIMOVO brand name that we are using in the United States. In addition, medicine recalls or safety issues with these medicines outside the United States, even if not related to the commercial medicine we sell in the United States, could result in serious damage to the brand in the United States and impair our ability to successfully market them. We also rely on Boehringer Ingelheim International, AstraZeneca, SOBI and Nuvo or their assignees to provide us with timely and accurate safety information regarding the use of these medicines outside of the United States (and outside of Canada and Japan with regards to Boehringer Ingelheim International), as we have or will have limited access to this information ourselves.

We rely on third parties to manufacture commercial supplies of all of our medicines, and we currently intend to rely on third parties to manufacture commercial supplies of any other approved medicines. The commercialization of any of our medicines could be stopped, delayed or made less profitable if those third parties fail to provide us with sufficient quantities of medicine or fail to do so at acceptable quality levels or prices or fail to maintain or achieve satisfactory regulatory compliance.

The facilities used by our third-party manufacturers to manufacture our medicines and medicine candidates must be approved by the applicable regulatory authorities. We do not control the manufacturing processes of third-party manufacturers and are currently completely dependent on our third-party manufacturing partners. In addition, we are required to obtain AstraZeneca's consent prior to engaging any third-party manufacturers for esomeprazole, one of the APIs in VIMOVO, other than the third-party manufacturer(s) used by AstraZeneca or its affiliates or licensees. To the extent such manufacturers are unwilling or unable to manufacture esomeprazole for us on commercially acceptable terms, we cannot guarantee that AstraZeneca would consent to our use of alternate sources of supply.

We rely on an exclusive supply agreement with Boehringer Ingelheim RCV GmbH & Co. KG, or Boehringer Ingelheim, for manufacturing and supply of ACTIMMUNE. However, Boehringer Ingelheim also currently manufactures interferon gamma-1b to supply its own commercial needs in its licensed territory, and this may lead to capacity allocation issues and supply constraints to our company. ACTIMMUNE is manufactured by starting with cells from working cell bank samples which are derived from a master cell bank. We and Boehringer Ingelheim separately store multiple vials of the master cell bank. In the event of catastrophic loss at our or Boehringer Ingelheim's storage facility, it is possible that we could lose multiple cell banks and have the manufacturing capacity of ACTIMMUNE severely impacted by the need to substitute or replace the cell banks. In addition, a key excipient used in PENNSAID 2% as a penetration enhancer is dimethyl sulfoxide, or DMSO. We and Nuvo, our exclusive supplier of PENNSAID 2%, rely on a sole proprietary form of DMSO for which we maintain a substantial safety stock. However, should this supply become inadequate, damaged, destroyed or unusable, we and Nuvo may not be able to qualify a second source. We rely on NOF Corporation, or NOF, as our exclusive supplier of the PEGylation agent that is a critical raw material in the manufacture of KRYSTEXXA. If NOF failed to supply such PEGylation agent, it may lead to KRYSTEXXA supply constraints.

If any of our third-party manufacturers cannot successfully manufacture material that conforms to our specifications and the applicable regulatory authorities' strict regulatory requirements, or pass regulatory inspection, they will not be able to secure or maintain regulatory approval for the manufacturing facilities. For example, Pharmaceutics International, Inc., or PII, our manufacturer of BUPHENYL, was found to be non-compliant for cGMPs by the MHRA, which could restrict PII from supplying BUPHENYL in the EU. However, BUPHENYL was considered to be critical to public health and as a result, the MHRA issued a certificate of cGMP compliance for PII which is valid until June 30, 2017. In addition, we have no control over the ability of third-party manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or any other applicable regulatory authorities do not approve these facilities for the manufacture of our medicines or if they withdraw any such approval in the future, or if our suppliers or third-party manufacturers decide they no longer want to supply our primary active ingredients or manufacture our medicines, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our medicines. To the extent any third-party manufacturers that we engage with respect to our medicines are different from those currently being used for commercial supply in the United States, the FDA will need to approve the facilities of those third-party manufacturers used in the manufacture of our medicines prior to our sale of any medicine using these facilities.

Although we have entered into supply agreements for the manufacture and packaging of our medicines, our manufacturers may not perform as agreed or may terminate their agreements with us. We currently rely on single source suppliers for certain of our medicines. If our manufacturers terminate their agreements with us, we may have to qualify new back-up manufacturers. We rely on safety stock to mitigate the risk of our current suppliers electing to cease producing bulk drug medicine or ceasing to do so at acceptable prices and quality. However, we can provide no assurance that such safety stocks would be sufficient to avoid supply shortfalls in the event we have to identify and

qualify new contract manufacturers.

The manufacture of medicines requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of medicines often encounter difficulties in production, particularly in scaling up and validating initial production. These problems include difficulties with production costs and yields, quality control, including stability of the medicine, quality assurance testing, shortages of qualified personnel, as well as compliance with strictly enforced federal, state and foreign regulations. Furthermore, if microbial, viral or other contaminations are discovered in the medicines or in the manufacturing facilities in which our medicines are made, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the contamination. We cannot assure you that issues relating to the manufacture of any of our medicines will not occur in the future. Additionally, our manufacturers may experience manufacturing difficulties due to resource constraints or as a result of labor disputes or unstable political environments. If our manufacturers were to encounter any of these difficulties, or otherwise fail to comply with their contractual obligations, our ability to commercialize our medicines in the United States or provide any medicine candidates to patients in clinical trials would be jeopardized.

Any delay or interruption in our ability to meet commercial demand for our medicines will result in the loss of potential revenues and could adversely affect our ability to gain market acceptance for these medicines. In addition, any delay or interruption in the supply of clinical trial supplies could delay the completion of clinical trials, increase the costs associated with maintaining clinical trial programs and, depending upon the period of delay, require us to commence new clinical trials at additional expense or terminate clinical trials completely.

Failures or difficulties faced at any level of our supply chain could materially adversely affect our business and delay or impede the development and commercialization of any of our medicines or medicine candidates and could have a material adverse effect on our business, results of operations, financial condition and prospects.

We have experienced recent growth and expanded the size of our organization substantially in connection with our recent acquisition transactions, and we may experience difficulties in managing this growth as well as potential additional growth in connection with future medicine, development program or company acquisitions.

As of December 31, 2010 and prior to the commercial launch of DUEXIS, we employed approximately 40 full-time employees as a consolidated entity. As of December 31, 2016, we employed approximately 1,050 full-time employees, including approximately 480 sales representatives, representing a substantial change to the size of our organization. We have also experienced, and may continue to experience, turnover of the sales representatives that we hired or will hire in connection with the commercialization of our medicines, requiring us to hire and train new sales representatives. Our management, personnel, systems and facilities currently in place may not be adequate to support this recent and anticipated growth, and we may not be able to retain or recruit qualified personnel in the future due to competition for personnel among pharmaceutical businesses.

As our commercialization plans and strategies continue to develop, we will need to continue to recruit and train sales and marketing personnel and expect to need to expand the size of our employee base for managerial, operational, financial and other resources as a result of our recent acquisitions. Our ability to manage any future growth effectively may require us to, among other things:

- continue to manage and expand the sales and marketing efforts for our existing medicines;
- enhance our operational, financial and management controls, reporting systems and procedures;
- expand our international resources;
- successfully identify, recruit, hire, train, maintain, motivate and integrate additional employees;
- establish and increase our access to commercial supplies of our medicines and medicine candidates;
- expand our facilities and equipment; and
- manage our internal development efforts effectively while complying with our contractual obligations to licensors, licensees, contractors, collaborators, distributors and other third parties.

Our recent acquisitions have resulted in many changes, including significant changes in the corporate business and legal entity structure, the integration of other companies and their personnel with us, and changes in systems. We are currently undertaking numerous complex transition activities associated with our recent acquisitions, and we may encounter unexpected difficulties or incur unexpected costs, including:

- difficulties in achieving growth prospects from combining third-party businesses with our business;
- difficulties in the integration of operations and systems;
- difficulties in the assimilation of employees and corporate cultures;
- challenges in preparing financial statements and reporting timely results at both a statutory level for multiple entities and jurisdictions and at a consolidated level for public reporting;
- challenges in keeping existing physician prescribers and patients and increasing adoption of acquired medicines;
- difficulties in achieving anticipated cost savings, synergies, business opportunities and growth prospects from the combination;
- potential unknown liabilities, adverse consequences and unforeseen increased expenses associated with the transaction; and
- challenges in attracting and retaining key personnel.

If any of these factors impair our ability to continue to integrate our operations with those of any companies or businesses we acquire, we may not be able to realize the business opportunities, growth prospects and anticipated tax synergies from combining the businesses. In addition, we may be required to spend additional time or money on integration that otherwise would be spent on the development and expansion of our business.

As a result of our acquisition of Raptor and our plans to launch RAVICTI in Europe, we may continue expanding our operations and add commercial personnel in Europe. We may not be successful in integrating Raptor's existing European operations and personnel with our own or in otherwise growing our commercial operations outside the United States, and could encounter other challenges in growing our commercial presence in Europe, including due to risks associated with political and economic instability, operating under different legal requirements and tax complexities. If we are unable to manage our commercial growth outside of the Unites States, our opportunities to expand sales in other countries will be limited or we may experience greater costs with respect to our ex-U.S. commercial operations.

We are also broadening our acquisition strategy to potentially include development-stage assets or programs, which entails additional risk to us. For example, if we are unable to identify programs that ultimately result in approved medicines, we may spend material amounts of our capital and other resources evaluating, acquiring and developing medicines that ultimately do not provide a return on our investment. We have less experience evaluating development-stage assets and may be at a disadvantage compared to other entities pursuing similar opportunities. Regardless, development-stage programs generally have a high rate of failure and we cannot guarantee that any such programs will ultimately be successful. We will also need to enhance our clinical development and regulatory functions to properly evaluate and develop earlier-stage opportunities, which may include recruiting personnel that are knowledgeable in therapeutic areas we have not yet pursued. If we are unable to acquire promising development-stage assets or eventually obtain marketing approval for them, we may not be able to create a meaningful pipeline of new medicines and eventually realize a return on our investments.

Our management may also have to divert a disproportionate amount of its attention away from day-to-day activities and toward managing these growth and integration activities. Our future financial performance and our ability to execute on our business plan will depend, in part, on our ability to effectively manage any future growth and our failure to effectively manage growth could have a material adverse effect on our business, results of operations, financial condition and prospects.

We face significant competition from other biotechnology and pharmaceutical companies, including those marketing generic medicines and our operating results will suffer if we fail to compete effectively.

The biotechnology and pharmaceutical industries are intensely competitive. We have competitors both in the United States and international markets, including major multinational pharmaceutical companies, biotechnology companies and universities and other research institutions. Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff, experienced marketing and manufacturing organizations and well-established sales forces. Additional consolidations in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors and we will have to find new ways to compete and may have to potentially merge with or acquire other businesses to stay competitive. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or in-licensing on an exclusive basis, medicines that are more effective and/or less costly than our medicines.

DUEXIS and VIMOVO face competition from other NSAIDs, including Celebrex®, which was marketed by Pfizer Inc., and is also a generic medicine known as celecoxib and marketed by other pharmaceutical companies. DUEXIS and VIMOVO also face significant competition from the separate use of NSAIDs for pain relief and GI protective medications to reduce the risk of NSAID-induced upper GI ulcers. Both NSAIDs and GI protective medications are available in generic form and may be less expensive to use separately than DUEXIS or VIMOVO. PENNSAID 2% faces competition from generic versions of diclofenac sodium topical solutions that are priced significantly less than the price we charge for PENNSAID 2%, and Voltaren Gel, marketed by Endo Pharmaceuticals Solutions Inc., which is the market leader in the topical NSAID category. Legislation enacted in most states in the United States allows, or in some instances mandates, that a pharmacist dispense an available generic equivalent when filling a prescription for a branded medicine, in the absence of specific instructions from the prescribing physician. Because pharmacists often have economic and other incentives to prescribe lower-cost generics, if physicians prescribe DUEXIS, PENNSAID 2% or VIMOVO, those prescriptions may not result in sales. If physicians do not complete prescriptions through our HorizonCares program or otherwise provide prescribing instructions prohibiting the substitution of generic ibuprofen and famotidine separately as a substitution for DUEXIS or generic naproxen and branded Nexium® (esomeprazole) as a substitute for VIMOVO or generic diclofenac sodium topical solutions as a substitute for PENNSAID 2%, sales of DUEXIS, PENNSAID 2% and VIMOVO may suffer despite any success we may have in promoting DUEXIS, PENNSAID 2% or VIMOVO to physicians. In addition, other medicine candidates that contain ibuprofen and famotidine in combination or naproxen and esomeprazole in combination, while not currently known or FDA approved, may be developed and compete with DUEXIS or VIMOVO, respectively, in the future. While KRYSTEXXA faces limited direct competition, a number of competitors have drugs in Phase 1 or Phase 2 trials. On December 22, 2015, AstraZeneca secured approval from the FDA for ZURAMPIC (lesinurad) 200mg tablets in combination with a xanthine oxidase inhibitor, or XOI, for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid (sUA) levels with an XOI alone. In April 2016, the U.S. rights to ZURAMPIC were licensed to Ironwood Pharmaceuticals Inc. Although ZURAMPIC is not a direct competitor because it has not been approved for refractory gout, this therapy could be used prior to use of KRYSTEXXA and if effective, could reduce the target patient population for KRYSTEXXA. PROCYSBI faces competition from Cystagon (immediate-release cysteamine bitartrate capsules) for the treatment of cystinosis and Cystaran (cysteamine ophthalmic solution) for treatment of corneal crystal accumulation in patients with cystinosis. QUINSAIR faces competition from Tobramycin solution, which is available as a generic medicine for treatment of chronic Pseudomonas aeruginosa lung infections in patients with cystic fibrosis, TOBI Podhaler, Cayston and colistimethate.

We have also entered into settlement and license agreements that may allow certain of our competitors to sell generic versions of certain of our medicines in the United States, subject to the terms of such agreements. We granted a non-exclusive license (that is only royalty-bearing in some circumstances), to manufacture and commercialize a generic version of DUEXIS in the United States after January 1, 2023, or earlier under certain circumstances. We granted non-exclusive licenses to manufacture and commercialize generic versions of PENNSAID 2% in the United States after January 10, 2029, or earlier under certain circumstances. We granted a non-exclusive license to

manufacture and commercialize a generic version of RAYOS tablets in the United States after December 23, 2022, or earlier under certain circumstances.

Patent litigation is currently pending in the United States District Court for the District of New Jersey against several companies intending to market a generic version of PENNSAID 2% prior to the expiration of certain of our patents listed in the FDA's Orange Book, or the Orange Book. These cases are collectively known as the PENNSAID 2% cases, and involve the following sets of defendants: (i) Actavis Laboratories UT, Inc., formerly known as Watson Laboratories, Inc., Actavis, Inc. and Actavis plc, or collectively Actavis; and (ii) Lupin Limited and Lupin Pharmaceuticals, Inc., or collectively Lupin. These cases arise from Paragraph IV Patent Certification notice letters from each of Actavis and Lupin advising each had filed an Abbreviated New Drug Application, or ANDA, with the FDA seeking approval to market a generic version of PENNSAID 2% before the expiration of the patents-in-suit. In Horizon Pharma Ireland Limited, et al v. Actavis Laboratories UT, Inc., C.A. No. 14-cv-7992-NLH-AMD, a bench trial is scheduled to begin on March 21, 2017. No trial date has been set in any other PENNSAID 2% case.

We received from Actavis a Paragraph IV Patent Certification Notice Letter dated September 27, 2016, against Orange Book listed U.S. Patent No. 9,415,029 advising that Actavis had filed an ANDA with the FDA for a generic version of PENNSAID 2%.

We received from Apotex Inc., or Apotex, three Paragraph IV Patent Certification Notice Letters dated April 1, 2016, June 30, 2016, and September 21, 2016 against Orange Book listed U.S. Patent Nos. 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164, 8,741,956, 8,871,809, 9,066,913, 9,101,591, 9,132,110, 9,168,304, 9,168,305, 9,220,784, 9,339,551, 9,339,552 and 9,415,029, advising that Apotex had filed an ANDA with the FDA for a generic version of PENNSAID 2%.

Patent litigation is currently pending in the United States District Court for the District of New Jersey against several companies intending to market a generic version of VIMOVO before the expiration of certain of our patents listed in the Orange Book. These cases are collectively known as the VIMOVO cases, and involve the following sets of defendants: (i) Dr. Reddy's Laboratories Inc. and Dr. Reddy's Laboratories Ltd., or collectively Dr. Reddy's; (ii) Lupin; and (iii) Mylan Pharmaceuticals Inc., Mylan Laboratories Limited, and Mylan Inc., or collectively Mylan. Patent litigation is currently pending before the Court of Appeals for the Federal Circuit against a fourth generic company, Actavis Laboratories FL., Inc. and Actavis Pharma, Inc., or collectively Actavis Pharma. The cases arise from Paragraph IV Patent Certification notice letters from each of Dr. Reddy's, Lupin and Mylan advising each had filed an ANDA with the FDA seeking approval to market generic versions of VIMOVO before the expiration of the patents-in-suit.

Patent litigation is currently pending in the United States District Court for the Eastern District of Texas against Par Pharmaceutical, Inc., or Par Pharmaceutical, and in the United States District Court for the District of New Jersey against Par Pharmaceutical and against Lupin, who are each intending to market generic versions of RAVICTI prior to the expiration of certain of our patents listed in the Orange Book. These cases are collectively known as the RAVICTI cases and arise from Paragraph IV Patent Certification notice letters from each of Par Pharmaceutical and Lupin advising each had filed an ANDA with the FDA seeking approval to market a generic version of RAVICTI before the expiration of the patents-in-suit.

If we are unsuccessful in any of the VIMOVO cases or PENNSAID 2% cases, we will likely face generic competition with respect to VIMOVO and/or PENNSAID 2% and sales of VIMOVO and/or PENNSAID 2% will be substantially harmed. If we are unsuccessful in any of the RAVICTI cases, RAVICTI would likely face generic competition in the United States when its orphan exclusivity expires (currently scheduled to occur in February 2020), and its sales would likely materially decline.

ACTIMMUNE is the only medicine currently approved by the FDA specifically for the treatment of CGD and SMO. While there are additional or alternative approaches used to treat patients with CGD and SMO, there are currently no medicines on the market that compete directly with ACTIMMUNE. A widely accepted protocol to treat CGD in the United States is the use of concomitant "triple prophylactic therapy" comprising ACTIMMUNE, an oral antibiotic agent and an oral antifungal agent. However, the FDA-approved labeling for ACTIMMUNE does not discuss this "triple prophylactic therapy," and physicians may choose to prescribe one or both of the other modalities in the absence of ACTIMMUNE. Because of the immediate and life-threatening nature of SMO, the preferred treatment option for SMO is often to have the patient undergo a bone marrow transplant which, if successful, will likely obviate the need for further use of ACTIMMUNE in that patient. Likewise, the use of bone marrow transplants in the treatment of patients with CGD is becoming more prevalent, which could have a material adverse effect on sales of ACTIMMUNE and its profitability. We are aware of a number of research programs investigating the potential of gene therapy as a possible cure for CGD. Additionally, other companies may be pursuing the development of medicines and treatments that target the same diseases and conditions which ACTIMMUNE is currently approved to treat. As a result, it is possible that our competitors may develop new medicines that manage CGD or SMO more effectively, cost less or possibly even cure CGD or SMO. In addition, U.S. healthcare legislation passed in March 2010 authorized the FDA to approve biological products, known as biosimilars, that are similar to or interchangeable with previously approved biological products, like ACTIMMUNE, based upon potentially abbreviated data packages. Biosimilars are likely to be sold at substantially lower prices than branded medicines because the biosimilar manufacturer would not have to recoup the research and development and marketing costs associated with the branded medicine. Though we are not currently aware of any biosimilar under development, the development and commercialization of any competing medicines or the discovery of any new alternative treatment for CGD or SMO could have a material adverse effect on sales of ACTIMMUNE and its profitability.

BUPHENYL's composition of matter patent protection and orphan drug exclusivity have expired. Because BUPHENYL has no regulatory exclusivity or listed patents, there is nothing to prevent a competitor from submitting an ANDA for a generic version of BUPHENYL and receiving FDA approval. In November 2011, Ampolgen Pharmaceuticals, LLC received FDA approval for a generic version of NaPBA tablets, which may compete with RAVICTI and BUPHENYL in treating UCD. In March 2013, SigmaPharm Laboratories, LLC received FDA approval for a generic version of NaPBA powder, which competes with BUPHENYL and may compete with RAVICTI in treating UCD. In July 2013, Lucane Pharma, or Lucane, received marketing approval from the EMA for taste-masked NaPBA and has announced a distribution partnership in Canada. In January 2015, Lucane announced it had received marketing approval for its taste-masked NaPBA in Canada. We believe Lucane is also seeking approval via an ANDA in the United States. If this ANDA is approved, this formulation may compete with RAVICTI and BUPHENYL in treating UCD in the United States. Generic versions of BUPHENYL to date have been priced at a discount relative to BUPHENYL or RAVICTI, and physicians, patients, or payers may decide that this less expensive alternative is preferable to BUPHENYL and RAVICTI. If this occurs, sales of BUPHENYL and/or RAVICTI could be materially reduced, but we would nevertheless be required to make royalty payments to Ucyclyd Pharma, Inc., or Ucyclyd, and another external party, at the same royalty rates. While Ucyclyd and its affiliates are generally contractually prohibited from developing or commercializing new medicines, anywhere in the world, for the treatment of UCD or hepatic encephalopathy, or HE, which are chemically similar to RAVICTI, they may still develop and commercialize medicines that compete with RAVICTI. For example, medicines approved for indications other than UCD and HE may still compete with RAVICTI if physicians prescribe such medicines off-label for UCD or HE. We are also aware that Orphan Europe SARL, or Orphan Europe, is conducting a clinical trial of carglumic acid to treat some of the UCD enzyme deficiencies for which RAVICTI was approved. Promethera Biosciences SA has successfully completed Phase I/II trials of its cell-based therapy for the treatment of UCD and plans to conduct a Phase IIb/III clinical trial. Carglumic acid is approved for maintenance therapy for chronic hyperammonemia and to treat hyperammonenic crises in Nacetylglutamate synthase deficiency, a rare UCD subtype, and is sold under the name Carbaglu. If the results of this trial are successful and Orphan Europe is able to complete development and obtain approval of Carbaglu to treat additional UCD enzyme deficiencies, RAVICTI would face additional competition from this compound.

The availability and price of our competitors' medicines could limit the demand, and the price we are able to charge, for our medicines. We will not successfully execute on our business objectives if the market acceptance of our medicines is inhibited by price competition, if physicians are reluctant to switch from existing medicines to our medicines, or if physicians switch to other new medicines or choose to reserve our medicines for use in limited patient populations.

In addition, established pharmaceutical companies may invest heavily to accelerate discovery and development of novel compounds or to acquire novel compounds that could make our medicines obsolete. Our ability to compete successfully with these companies and other potential competitors will depend largely on our ability to leverage our experience in clinical, regulatory and commercial development to:

- develop and acquire medicines that are superior to other medicines in the market;
- attract qualified clinical, regulatory, and sales and marketing personnel;
- obtain patent and/or other proprietary protection for our medicines and technologies;
- obtain required regulatory approvals; and
- successfully collaborate with pharmaceutical companies in the discovery, development and commercialization of new medicine candidates.

If we are unable to maintain or realize the benefits of orphan drug exclusivity, we may face increased competition with respect to certain of our medicines.

Under the Orphan Drug Act of 1983, the FDA may designate a medicine as an orphan drug if it is a drug intended to treat a rare disease or condition affecting fewer than 200,000 people in the United States. A company that first obtains FDA approval for a designated orphan drug for the specified rare disease or condition receives orphan drug marketing exclusivity for that drug for a period of seven years from the date of its approval. RAVICTI, KRYSTEXXA and PROCYSBI have been granted orphan drug exclusivity by the FDA, which we expect will provide orphan drug marketing exclusivity in the United States until February 2020, September 2017 and December 2020, respectively, with exclusivity for PROCYSBI extending to 2022 for patients ages two to six years. However, despite orphan drug exclusivity, the FDA can still approve another drug containing the same active ingredient and used for the same orphan indication if it determines that a subsequent drug is safer, more effective or makes a major contribution to patient care, and orphan exclusivity can be lost if the orphan drug manufacturer is unable to ensure that a sufficient quantity of the orphan drug is available to meet the needs of patients with the rare disease or condition. Orphan drug exclusivity may also be lost if the FDA later determines that the initial request for designation was materially defective. In addition, orphan drug exclusivity does not prevent the FDA from approving competing drugs for the same or similar indication containing a different active ingredient. If orphan drug exclusivity is lost and we were unable to successfully enforce any remaining patents covering RAVICTI, KRYSTEXXA or PROCYSBI, we could be subject to generic competition and revenues from RAVICTI, KRYSTEXXA or PROCYSBI could decrease materially. In addition, if a subsequent drug is approved for marketing for the same or a similar indication as RAVICTI, KRYSTEXXA or PROCYSBI despite orphan drug exclusivity, we may face increased competition and lose market share with respect to these medicines. KRYSTEXXA does not have orphan drug exclusivity in the EU or other regions of the world. RAVICTI will benefit from a period of 10 years of orphan market exclusivity in the EU, concurrently applied to each of the approved six sub-types of the UCDs. This will run concurrently with its marketing exclusivity status. PROCYSBI received marketing authorization in September 2013 from the European Commission for marketing in the EU as an orphan medicine for the management of proven nephropathic cystinosis. PROCYSBI received seven years of market exclusivity, through 2020 for patients six years and older as an orphan drug in the United States and ten years of market exclusivity, through 2023, as an orphan drug in Europe. QUINSAIR received 10 years of market exclusivity in the EU, beginning with its March 2015 marketing authorization. Orphan market exclusivity may be reduced to six years in the EU if the orphan drug designation criteria are no longer met after five years, including where it is shown that the medicine is sufficiently profitable. As in the United States, loss of orphan marketing exclusivity in the EU may result in early generic competition, which could substantially reduce our revenues from EU sales of these medicines.

Our business operations may subject us to numerous commercial disputes, claims and/or lawsuits and such litigation may be costly and time-consuming and could materially and adversely impact our financial position and results of operations.

Operating in the pharmaceutical industry, particularly the commercialization of medicines, involves numerous commercial relationships, complex contractual arrangements, uncertain intellectual property rights, potential product liability and other aspects that create heightened risks of disputes, claims and lawsuits. In particular, we may face claims related to the safety of our medicines, intellectual property matters, employment matters, tax matters, commercial disputes, competition, sales and marketing practices, environmental matters, personal injury, insurance coverage and acquisition or divestiture-related matters. For example, the active ingredient in QUINSAIR, levofloxacin, is currently subject to product liability claims. Any commercial dispute, claim or lawsuit may divert management's attention away from our business, we may incur significant expenses in addressing or defending any commercial dispute, claim or lawsuit, and we may be required to pay damage awards or settlements or become subject to equitable remedies that could adversely affect our operations and financial results.

We are currently in litigation with multiple generic drug manufacturers regarding intellectual property infringement. For example, we are currently involved in Hatch Waxman litigation with generic drug manufacturers related to VIMOVO, PENNSAID 2% and RAVICTI.

Similarly, from time to time we are involved in disputes with distributors, PBMs and licensing partners regarding our rights and performance of obligations under contractual arrangements. For example, we were previously in litigation with Express Scripts, related to alleged breach of contract claims and in which Express Scripts was seeking payment for rebates relating to DUEXIS, RAYOS and VIMOVO. We counterclaimed against Express Scripts, contesting the amount owed and contending Express Scripts had breached the rebate agreement. In September 2016, we entered into a settlement agreement and mutual release with Express Scripts pursuant to which we and Express Scripts were released from any and all claims relating to the litigation without admitting any fault or wrongdoing and we agreed to pay Express Scripts $65.0 million.

Litigation related to these disputes may be costly and time-consuming and could materially and adversely impact our financial position and results of operations if resolved against us.

A variety of risks associated with operating our business and marketing our medicines internationally could materially adversely affect our business.

In addition to our U.S. operations, we have operations in Ireland, Bermuda, the Grand Duchy of Luxembourg, or Luxembourg, the Netherlands, France, Switzerland, Germany, Canada, the Grand Cayman Islands and in Israel (through Andromeda Biotech Ltd). Moreover, Grünenthal S.A. is in the registration process for the commercialization of DUEXIS in Latin America. BUPHENYL is currently marketed in various territories outside the United States by third-party distributors. RAVICTI received marketing authorization from HC in March 2016 and marketing approval in the EU in November 2015. We launched RAVICTI in Canada in November 2016 and plan to begin commercializing RAVICTI in Europe in 2017. PROCYSBI received marketing authorization from the EMA in September 2013 and is marketed in various countries within the EEA. QUINSAIR received marketing authorization from the EMA in March 2015 and is also marketed in several countries within the EEA. QUINSAIR received marketing authorization from HC in June 2015 and we launched QUINSAIR in Canada in December 2016. We face risks associated with our international operations, including possible unfavorable regulatory, pricing and reimbursement, political, tax and labor conditions, which could harm our business. We are subject to numerous risks associated with international business activities, including:

- compliance with differing or unexpected regulatory requirements for our medicines;
- compliance with Irish laws and the maintenance of our Irish tax residency with respect to our overall corporate structure and administrative operations, including the need to generally hold meetings of our board of directors and

make decisions in Ireland, which may make certain corporate actions more cumbersome, costly and time-consuming;

- difficulties in staffing and managing foreign operations;
- in certain circumstances, including with respect to the commercialization of LODOTRA in Europe and certain Asian, Latin American, Middle Eastern and African countries, commercialization of BUPHENYL in select countries throughout Europe, the Middle East, and the Asia-Pacific region, commercialization of RAVICTI in select countries throughout Europe and commercialization of DUEXIS in Latin America, increased dependence on the commercialization efforts and regulatory compliance of third-party distributors or strategic partners;

- compliance with German laws with respect to our Horizon Pharma GmbH subsidiary through which Horizon Pharma Switzerland GmbH conducts most of its European operations;
- foreign government taxes, regulations and permit requirements;
- U.S. and foreign government tariffs, trade restrictions, price and exchange controls and other regulatory requirements;
    - anti-corruption laws, including the Foreign Corrupt Practices Act, or the FCPA;
- economic weakness, including inflation, natural disasters, war, events of terrorism or political instability in particular foreign countries;
- fluctuations in currency exchange rates, which could result in increased operating expenses and reduced revenues, and other obligations related to doing business in another country;
- compliance with tax, employment, immigration and labor laws, regulations and restrictions for employees living or traveling abroad;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad;
- changes in diplomatic and trade relationships; and
- challenges in enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States.

Our business activities outside of the United States are subject to the FCPA and similar anti-bribery or anti-corruption laws, regulations or rules of other countries in which we operate, including the United Kingdom's Bribery Act 2010, or the U.K. Bribery Act. The FCPA and similar anti-corruption laws generally prohibit offering, promising, giving, or authorizing others to give anything of value, either directly or indirectly, to non-U.S. government officials in order to improperly influence any act or decision, secure any other improper advantage, or obtain or retain business. The FCPA also requires public companies to make and keep books and records that accurately and fairly reflect the transactions of the company and to devise and maintain an adequate system of internal accounting controls. The U.K. Bribery Act prohibits giving, offering, or promising bribes to any person, including non-United Kingdom, or U.K., government officials and private persons, as well as requesting, agreeing to receive, or accepting bribes from any person. In addition, under the U.K. Bribery Act, companies which carry on a business or part of a business in the U.K. may be held liable for bribes given, offered or promised to any person, including non-U.K. government officials and private persons, by employees and persons associated with the company in order to obtain or retain business or a business advantage for the company. Liability is strict, with no element of a corrupt state of mind, but a defense of having in place adequate procedures designed to prevent bribery is available. Furthermore, under the U.K. Bribery Act there is no exception for facilitation payments. As described above, our business is heavily regulated and therefore involves significant interaction with public officials, including officials of non-U.S. governments. Additionally, in many other countries, the health care providers who prescribe pharmaceuticals are employed by their government, and the purchasers of pharmaceuticals are government entities; therefore, any dealings with these prescribers and purchasers may be subject to regulation under the FCPA. Recently the SEC and the U.S. Department of Justice have increased their FCPA enforcement activities with respect to pharmaceutical companies. In addition, under the Dodd–Frank Wall Street Reform and Consumer Protection Act, private individuals who report to the SEC original information that leads to successful enforcement actions may be eligible for a monetary award. We are engaged in ongoing efforts that are designed to ensure our compliance with these laws, including due diligence, training, policies, procedures and internal controls. However, there is no certainty that all employees and third-party business partners (including our distributors, wholesalers, agents, contractors, and other partners) will comply with anti-bribery laws. In particular, we do not control the actions of manufacturers and other third-party agents, although we may be liable for their actions. Violation of these laws may result in civil or criminal sanctions, which could include monetary fines, criminal penalties, and disgorgement of past profits, which could have a material adverse impact on our business and financial condition.

These and other risks associated with our international operations may materially adversely affect our business, financial condition and results of operations.

58

If we fail to develop or acquire other medicine candidates or medicines, our business and prospects would be limited.

A key element of our strategy is to develop or acquire and commercialize a portfolio of other medicines or medicine candidates in addition to our current medicines, through business or medicine acquisitions. Because we do not engage in proprietary drug discovery, the success of this strategy depends in large part upon the combination of our regulatory, development and commercial capabilities and expertise and our ability to identify, select and acquire approved or clinically enabled medicine candidates for therapeutic indications that complement or augment our current medicines, or that otherwise fit into our development or strategic plans on terms that are acceptable to us. Identifying, selecting and acquiring promising medicines or medicine candidates requires substantial technical, financial and human resources expertise. Efforts to do so may not result in the actual acquisition or license of a particular medicine or medicine candidate, potentially resulting in a diversion of our management's time and the expenditure of our resources with no resulting benefit. If we are unable to identify, select and acquire suitable medicines or medicine candidates from third parties or acquire businesses at valuations and on other terms acceptable to us, or if we are unable to raise capital required to acquire businesses or new medicines, our business and prospects will be limited.

Moreover, any medicine candidate we acquire may require additional, time-consuming development or regulatory efforts prior to commercial sale or prior to expansion into other indications, including preclinical studies if applicable, and extensive clinical testing and approval by the FDA and applicable foreign regulatory authorities. All medicine candidates are prone to the risk of failure that is inherent in pharmaceutical medicine development, including the possibility that the medicine candidate will not be shown to be sufficiently safe and/or effective for approval by regulatory authorities. In addition, we cannot assure you that any such medicines that are approved will be manufactured or produced economically, successfully commercialized or widely accepted in the marketplace or be more effective or desired than other commercially available alternatives.

In addition, if we fail to successfully commercialize and further develop our medicines, there is a greater likelihood that we will fail to successfully develop a pipeline of other medicine candidates to follow our existing medicines or be able to acquire other medicines to expand our existing portfolio, and our business and prospects would be harmed.

Our recent medicine and company acquisitions and any other strategic transactions that we may pursue in the future could have a variety of negative consequences, and we may not realize the benefits of such transactions or attempts to engage in such transactions.

We have recently completed multiple medicine and company acquisitions and our strategy is to engage in additional strategic transactions with third parties, such as acquisitions of companies or divisions of companies and asset purchases of medicines, medicine candidates or technologies that we believe will complement or augment our existing business. We may also consider a variety of other business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and other investments. Any such transaction may require us to incur non-recurring and other charges, increase our near and long-term expenditures, pose significant integration challenges, create additional tax, legal, accounting and operational complexities in our business, require additional expertise, result in dilution to our existing shareholders and disrupt our management and business, which could harm our operations and financial results. For example, in connection with our acquisition of the U.S. rights to VIMOVO, we assumed primary responsibility for the existing patent infringement litigation with respect to VIMOVO, and have also agreed to reimburse certain legal expenses of Pozen Inc., who subsequently entered into a business combination with Tribute Pharmaceuticals Canada Inc. to become known as Aralez Pharmaceuticals Inc., or Aralez, with respect to its continued involvement in such litigation. We also assumed responsibility for the existing patent infringement litigation with respect to RAVICTI upon the closing of our acquisition of Hyperion Therapeutics Inc., or Hyperion, and have assumed responsibility for completing post-marketing clinical trials of RAVICTI that are required by the FDA and are ongoing. We expect that the RAVICTI litigation will result in substantial on-going expenses and potential distractions to our management team.

59

In connection with our acquisition of Raptor, we assumed Raptor's post-marketing clinical study obligations in the MAA for QUINSAIR and contractual obligations under agreements with Tripex Pharmaceuticals, LLC, or Tripex, and PARI Pharma GmbH, or PARI, related to QUINSAIR. Under the agreement with Tripex, we are required to pursue commercially reasonable efforts to initiate, and subsequently to complete, an additional clinical trial of QUINSAIR in a non-cystic fibrosis patient population within a specified period of time and an obligation to progress toward submitting an NDA for approval of QUINSAIR in the United States for use in all or part of the cystic fibrosis patient population. These obligations are subject to certain exceptions due to, for example, manufacturing delays not under our control, or delays caused by the FDA. If we fail to properly exercise such efforts to initiate and complete an appropriate clinical trial, or fail to submit an NDA for U.S. approval in the cystic fibrosis patient population, during the time periods specified in the agreement, we may be subject to various claims by Tripex and parties affiliated with Tripex. In addition, if we do not spend a minimum amount on QUINSAIR development in each of the three years following our acquisition of Raptor, we may also be obligated to pre-pay a milestone payment related to initiating a clinical trial for QUINSAIR in a non-cystic fibrosis indication. Under the license agreement with PARI, we are required to comply with diligence milestones related to development and commercialization of QUINSAIR in the United States and to spend a specified minimum amount per year on development activities in the United States until submission of the NDA for QUINSAIR in the United States. If we do not comply with these obligations, our licenses to certain intellectual property related to QUINSAIR may become non-exclusive in the United States or could be terminated. We are also now subject to contractual obligations under license agreements with the Regents of the University of California, San Diego, or UCSD, with respect to PROCYSBI, including diligence obligations to develop PROCYSBI for the treatment of non-alcoholic steatohepatitis, or NASH, and Huntington's disease, with which we currently are not in compliance. To the extent that we fail to perform the diligence obligations under the agreement, UCSD may, with respect to such indication, terminate the license or otherwise cause the license to become non-exclusive. If one or more of these licenses was terminated, we would have no further right to use or exploit the related intellectual property, which would limit our ability to develop PROCYSBI or QUINSAIR in other indications, and could impact our ability to continue commercializing PROCYSBI or QUINSAIR in their approved indications.

We face significant competition in seeking appropriate strategic transaction opportunities and the negotiation process for any strategic transaction can be time-consuming and complex. In addition, we may not be successful in our efforts to engage in certain strategic transactions because our financial resources may be insufficient and/or third parties may not view our commercial and development capabilities as being adequate. We may not be able to expand our business or realize our strategic goals if we do not have sufficient funding or cannot borrow or raise additional capital. There is no assurance that following any of our recent acquisition transactions or any other strategic transaction, we will achieve the anticipated revenues, net income, tax or other benefits that we believe justify such transactions. In addition, any failures or delays in entering into strategic transactions anticipated by analysts or the investment community could seriously harm our consolidated business, financial condition, results of operations or cash flow.

Our parent company may not be able to successfully maintain its current advantageous tax status and resulting tax rates, which could adversely affect our business and financial condition, results of operations and growth prospects.

Our parent company is incorporated in Ireland and maintains subsidiaries in multiple jurisdictions, including Ireland, the U.K, the United States, Switzerland, Luxembourg, Germany, France, the Netherlands, Canada and Bermuda. Prior to our merger transaction with Vidara Therapeutics International Public Limited Company, or Vidara, and such transaction, the Vidara Merger, Vidara was able to achieve a favorable tax rate through the performance of certain functions and ownership of certain assets in tax-efficient jurisdictions, including Ireland and Bermuda, together with intra-group service and transfer pricing agreements, each on an arm's length basis. We are continuing a substantially similar structure and arrangements. Taxing authorities, such as the U.S. Internal Revenue Service, or IRS, actively audit and otherwise challenge these types of arrangements, and have done so in the pharmaceutical industry. We expect that these challenges will continue as a result of the recent increase in scrutiny and political attention on corporate tax structures. The IRS may challenge our structure and transfer pricing arrangements through an audit or lawsuit. Responding to or defending such a challenge could be expensive and consume time and other resources, and divert management's time and focus from operating our business. We cannot predict whether taxing authorities will

conduct an audit or file a lawsuit challenging this structure, the cost involved in responding to any such audit or lawsuit, or the outcome. If we are unsuccessful in defending such a challenge, we may be required to pay taxes for prior periods, interest, fines or penalties, and may be obligated to pay increased taxes in the future, any of which could require us to reduce our operating expenses, decrease efforts in support of our medicines or seek to raise additional funds, all of which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

The IRS may not agree with our conclusion that our parent company should be treated as a foreign corporation for U.S. federal income tax purposes following the combination of the businesses of Horizon Pharma, Inc., or HPI, and Vidara.

Although our parent company is incorporated in Ireland, the IRS may assert that it should be treated as a U.S. corporation (and, therefore, a U.S. tax resident) for U.S. federal income tax purposes pursuant to Section 7874 of the Internal Revenue Code of 1986, as amended, or the Code. A corporation is generally considered a tax resident in the jurisdiction of its organization or incorporation for U.S. federal income tax purposes. Because our parent company is an Irish incorporated entity, it would generally be classified as a foreign corporation (and, therefore, a non-U.S. tax resident) under these rules. Section 7874 of the Code provides an exception pursuant to which a foreign incorporated entity may, in certain circumstances, be treated as a U.S. corporation for U.S. federal income tax purposes.

Under Section 7874 of the Code, a foreign corporation will be treated as a U.S. corporation for U.S. federal tax purposes if, due to an acquisition of a U.S. corporation, at least 80 percent of its stock (by vote or value) is held by former stockholders of the acquired U.S. corporation. We believe that we should be treated as a foreign corporation because the former stockholders of HPI owned (within the meaning of Section 7874 of the Code) less than 80 percent (by both vote and value) of the combined entity's stock immediately after the Vidara Merger. However, there can be no assurance that there will not exist in the future a subsequent change in the facts or in law which might cause our parent company to be treated as a domestic corporation for U.S. federal income tax purposes, including with retroactive effect.

Further, there can be no assurance that the IRS will agree with the position that the ownership test was satisfied. There is limited guidance regarding the application of Section 7874 of the Code, including with respect to the provisions regarding the application of the ownership test. If our parent company were unable to be treated as a foreign corporation for U.S. federal income tax purposes, one of our significant strategic reasons for completing the Vidara Merger would be nullified and we may not be able to recoup the significant investment in completing the transaction.

Future changes to U.S. and non-U.S. tax laws could materially adversely affect our company.

Under current law, we expect our parent company to be treated as a foreign corporation for U.S. federal income tax purposes. However, changes to the rules in Section 7874 of the Code or regulations promulgated thereunder or other guidance issued by the U.S. Department of the Treasury, or the U.S. Treasury, or the IRS could adversely affect our parent company's status as a foreign corporation for U.S. federal income tax purposes, and any such changes could have prospective or retroactive application. If our parent company is treated as a domestic corporation, more of our income will be taxed by the United States which may substantially increase our effective tax rate.

On April 4, 2016, the U.S. Treasury and the IRS issued temporary regulations that expand the scope of transactions subject to the rules designed to eliminate the U.S. tax benefits of inversions. Under the temporary regulations, the former stockholders of U.S. corporations acquired by a foreign corporation within 36 months of the signing date of the last such acquisition are aggregated for the purpose of determining whether the foreign corporation will be treated as a domestic corporation for U.S. federal tax purposes because at least 80 percent of the stock of the foreign corporation is held by former stockholders of a U.S. corporation. The requirement to aggregate the stockholders in such acquisitions for the purpose of determining whether the 80 percent threshold is met may limit our ability to use our stock to acquire U.S. corporations or their assets in the future.

The U.S. Treasury and the IRS also issued proposed regulations on April 4, 2016 that address whether an interest in a related corporation is debt or equity. The proposed regulations would treat certain inter-company debt issued on or after that date as equity including, subject to certain exceptions, inter-company debt issued in certain distributions, acquisitions of related party stock and asset reorganizations. As drafted, the proposed regulations would limit the ability of our U.S. group to deduct interest on such new inter-company debt. The proposed regulations could also result in recharacterization of inter-company debt to equity for inter-company debt incurred to provide funding for an

acquisition by the U.S. group if, and to the extent of, certain cash or property transfers by our U.S. group to the foreign affiliates within 36 months before or after these inter-company borrowings. These limitations could result in more of our future income being taxed by the United States and thereby increase our effective tax rate.

In July 2015, the International Tax Bipartisan Tax Working Group of the United States Senate Committee on Finance, or the Finance Committee, issued its report on international tax reform. The Finance Committee's co-chairs concluded that it will be necessary to limit earnings stripping by foreign multinationals through interest deductions on inter-company debt in order to eliminate a competitive advantage that foreign multinationals would otherwise have over domestic multinational companies. The status of the recommendations from the International Tax Bipartisan Tax Working Group, including regulations aimed at curbing earnings stripping, as well as the status of United States tax reform in general, is subject to significant uncertainty as the White House and both houses of Congress are considering several material tax reform proposals. These proposals include, among other items, a significant reduction to the United States corporate tax rate and a possible "border adjustment tax" that would effectively increase the economic cost of imports. At this point in time it is not possible to determine all of the possible consequences to us of the various tax reform proposals that are under consideration. However, any tax reform could significantly impact our United States and worldwide tax liabilities.

In addition, the Organization for Economic Co-operation and Development released its Base Erosion and Profit Shifting project final report on October 5, 2015. This report provides the basis for international standards for corporate taxation that are designed to prevent, among other things, the artificial shifting of income to tax havens and low-tax jurisdictions, the erosion of the tax base through interest deductions on inter-company debt and the artificial avoidance of permanent establishments (i.e., tax nexus with a jurisdiction). Legislation to adopt these standards has been enacted or is currently under consideration in a number of jurisdictions. As a result, our income may be taxed in jurisdictions where it is not currently taxed and at higher rates of tax than it is currently taxed, which may substantially increase our effective tax rate.

The U.S. federal government has called for substantial changes to U.S. tax policy and laws. We do not currently have sufficient information that would allow us to predict what U.S. tax reform, if any, may be enacted in the future or what impact any such changes would have on our business. Changes to U.S. tax laws could significantly impact our business, financial condition, results of operations, or cash flows.

If we are not successful in attracting and retaining highly qualified personnel, we may not be able to successfully implement our business strategy.

Our ability to compete in the highly competitive biotechnology and pharmaceuticals industries depends upon our ability to attract and retain highly qualified managerial, scientific and medical personnel. We are highly dependent on our management, sales and marketing and scientific and medical personnel, including our executive committee composed of our Chairman, President and Chief Executive Officer, Timothy P. Walbert; our Executive Vice President, Chief Business Officer, Robert F. Carey; our Executive Vice President, Chief Financial Officer, Paul W. Hoelscher; our Executive Vice President, Chief Administrative Officer, Barry J. Moze; our Executive Vice President, Research and Development and Chief Medical Officer, Jeffrey W. Sherman, M.D., FACP; our Executive Vice President, General Counsel, Brian K. Beeler; our Executive Vice President, Primary Care Business Unit, George Hampton; our Executive Vice President, Orphan Business Unit, Dave Happel; our Executive Vice President, Technical Operations, Michael A. DesJardin and our Senior Vice President, Rheumatology Business Unit, Vikram Karnani. In order to retain valuable employees at our company, in addition to salary and cash incentives, we provide performance stock units, or PSUs, and stock options and restricted stock units that vest over time. The value to employees of PSUs, stock options and restricted stock units will be significantly affected by movements in our share price that are beyond our control, and may at any time be insufficient to counteract more lucrative offers from other companies.

Despite our efforts to retain valuable employees, members of our management, sales and marketing, regulatory affairs, clinical development, medical affairs and development teams may terminate their employment with us on short notice. Although we have written employment arrangements with all of our employees, these employment arrangements generally provide for at-will employment, which means that our employees can leave our employment at any time, with or without notice. The loss of the services of any of our executive officers or other key employees and our

inability to find suitable replacements could potentially harm our business, financial condition and prospects. We do not maintain “key man” insurance policies on the lives of these individuals or the lives of any of our other employees. Our success also depends on our ability to continue to attract, retain and motivate highly skilled junior, mid-level, and senior managers as well as junior, mid-level, and senior sales and marketing and scientific and medical personnel.

Many of the other biotechnology and pharmaceutical companies with whom we compete for qualified personnel have greater financial and other resources, different risk profiles and longer histories in the industry than we do. They also may provide more diverse opportunities and better chances for career advancement. Some of these characteristics may be more appealing to high quality candidates than that which we have to offer. If we are unable to continue to attract and retain high quality personnel, the rate and success at which we can develop and commercialize medicines and medicine candidates will be limited.

We are, with respect to our current medicines, and will be, with respect to any other medicine or medicine candidate for which we obtain FDA or EMA approval or which we acquire, subject to ongoing FDA or the EMA obligations and continued regulatory review, which may result in significant additional expense. Additionally, any other medicine candidate, if approved by the FDA or the EMA, could be subject to labeling and other restrictions and market withdrawal, and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our medicines.

Any regulatory approvals that we obtain for our medicine candidates may also be subject to limitations on the approved indicated uses for which the medicine may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials and surveillance to monitor the safety and efficacy of the medicine candidate. In addition, with respect to our current FDA-approved medicines (and with respect to our medicine candidates, if approved), the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for the medicine are subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMPs, GCPs, international conference on harmonization regulations, or ICH regulations, and GLPs, which are regulations and guidelines enforced by the FDA for all of our medicines in clinical development, for any clinical trials that we conduct post-approval. With respect to RAVICTI, the FDA imposed several post-marketing requirements and a post-marketing commitment, which include remaining obligations to conduct studies in UCD patients during the first two months of life and from two months to two years of age, including a study of the pharmacokinetics in both age groups, and a randomized study to determine the safety and efficacy in UCD patients who are treatment naïve to phenylbutyrate treatment. Although we are committed to carrying out these commitments, there are challenges in conducting studies in pediatric patients including availability of study sites, patients, and obtaining parental informed consent. On June 29, 2016, we submitted a supplemental new drug application, or sNDA, to the FDA for RAVICTI to expand the age range for chronic management of UCDs from two years of age and older to two months of age and older. Subject to positive data from on-going studies, we have targeted an sNDA submission in the first quarter of 2018 in relation to UCD patients during the first two months of life. In connection with our acquisition of Crealta Holdings LLC, or Crealta, in January 2016, we assumed responsibility for an observational study related to KRYSTEXXA. Thus far in this study there have been no new safety signals and the reported safety results parallel those in the KRYSTEXXA product label. We are continuing to screen and enroll patients in the near term. With respect to QUINSAIR, we are required to conduct post-marketing clinical studies in cystic fibrosis patients pursuant to obligations in the MAA for QUINSAIR and submit data to the EMA regularly regarding observed clinical medicine profile and safety assessment.

In addition, the FDA closely regulates the marketing and promotion of drugs and biologics. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, restrict manufacturers' promotional communications. A significant number of pharmaceutical companies have been the target of inquiries and investigations by various U.S. federal and state regulatory, investigative, prosecutorial and administrative entities in connection with the promotion of medicines for off-label uses and other sales practices. These investigations have alleged violations of various U.S. federal and state laws and regulations, including claims asserting antitrust violations, violations of the Food, Drug and Cosmetic Act, false claims laws, the Prescription Drug Marketing Act, anti-kickback laws, and other alleged violations in connection with the promotion of medicines for unapproved uses, pricing and Medicare and/or Medicaid reimbursement.

Later discovery of previously unknown problems with a medicine, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on the marketing or manufacturing of the medicine, withdrawal of the medicine from the market, or voluntary or mandatory medicine recalls;
- fines, warning letters or holds on clinical trials;
- refusal by the FDA to approve pending applications or supplements to approved applications filed by us or our strategic partners, or suspension or revocation of medicine license approvals;

- medicine seizure or detention, or refusal to permit the import or export of medicines; and
- injunctions, the imposition of civil or criminal penalties, or exclusion, debarment or suspension from government healthcare programs.

If we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would have a material adverse effect on our business, results of operations, financial condition and prospects.

Coverage and reimbursement may not be available, or reimbursement may be available at only limited levels, for our medicines, which could make it difficult for us to sell our medicines profitably or to successfully execute planned medicine price increases.

Market acceptance and sales of our medicines will depend in large part on global coverage and reimbursement policies and may be affected by future healthcare reform measures, both in the United States and other key international markets. Successful commercialization of our medicines will depend in part on the availability of governmental and third-party payer reimbursement for the cost of our medicines. Government health administration authorities, private health insurers and other organizations generally provide reimbursement for healthcare. In particular, in the United States, private health insurers and other third-party payers often provide reimbursement for medicines and services based on the level at which the government (through the Medicare or Medicaid programs) provides reimbursement for such treatments. In the United States, the EU and other significant or potentially significant markets for our medicines and medicine candidates, government authorities and third-party payers are increasingly attempting to limit or regulate the price of medicines and services, particularly for new and innovative medicines and therapies, which has resulted in lower average selling prices. Further, the increased scrutiny of prescription drug pricing practices and emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the EU will put additional pressure on medicine pricing, reimbursement and usage, which may adversely affect our medicine sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical reimbursement policies and pricing in general. These pressures may create negative reactions to any medicine price increases, or limit the amount by which we may be able to increase our medicine prices, which may adversely affect our medicine sales and results of operations.

Patients are unlikely to use our medicines unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our medicines. Third-party payers may limit coverage to specific medicines on an approved list, also known as a formulary, which might not include all of the FDA-approved medicines for a particular indication. Moreover, a third-party payer’s decision to provide coverage for a medicine does not imply that an adequate reimbursement rate will be approved. Additionally, one third-party payer’s decision to cover a particular medicine does not ensure that other payers will also provide coverage for the medicine, or will provide coverage at an adequate reimbursement rate. Even though we have contracts with some PBMs in the United States, that does not guarantee that they will perform in accordance with the contracts, nor does that preclude them from taking adverse actions against us, which could materially adversely affect our operating results. In addition, the existence of such PBM contracts does not guarantee coverage by such PBM’s contracted health plans or adequate reimbursement to their respective providers for our medicines. For example, two significant PBMs placed DUEXIS and VIMOVO on their exclusion lists beginning in 2015, which has resulted in a loss of coverage for patients whose healthcare plans have adopted these PBM lists. While DUEXIS and VIMOVO were removed from the Express Scripts and CVS Caremark 2017 exclusion lists, we cannot guarantee that Express Scripts or CVS Caremark will not later add these medicines back to their exclusion lists or that we will be able to otherwise expand formulary access for DUEXIS and VIMOVO under health plans that contract with Express Scripts and/or CVS Caremark. Additional healthcare plan formularies may also exclude our medicines from coverage due to the actions of certain PBMs, future price increases we may implement, our use of the HorizonCares program or any other co-pay programs, or other reasons. If our strategies to mitigate formulary exclusions are not effective, these events may reduce the likelihood that physicians prescribe our medicines and increase the likelihood that prescriptions for our medicines are not filled.

64

Outside of the United States, the success of our medicines, including BUPHENYL, LODOTRA, PROCYSBI, QUINSAIR, RAVICTI and, following the IMUKIN Acquisition, interferon gamma-1b (currently commercialized under the trade names IMUKIN, IMUKINE, IMMUKIN and IMMUKINE), will depend largely on obtaining and maintaining government coverage, because in many countries patients are unlikely to use prescription drugs that are not covered by their government healthcare programs. The majority of LODOTRA sales are in Germany and Italy where reimbursement has been approved. BUPHENYL is marketed in select countries throughout Europe, the Middle East and the Asia-Pacific region. We launched RAVICTI in Canada in November 2016 and we expect to begin commercializing RAVICTI in Europe in 2017. PROCYSBI is marketed in select countries in Europe and QUINSAIR was recently launched in certain countries in Europe and in Canada, but we cannot be certain that existing reimbursement in EU countries will be maintained or that we will be able to secure reimbursement in additional countries. Negotiating coverage and reimbursement with governmental authorities can delay commercialization by 12 months or more. Coverage and reimbursement policies may adversely affect our ability to sell our medicines on a profitable basis. In many international markets, governments control the prices of prescription pharmaceuticals, including through the implementation of reference pricing, price cuts, rebates, revenue-related taxes and profit control, and we expect prices of prescription pharmaceuticals to decline over the life of the medicine or as volumes increase. Many countries in the EU have increased the amount of discounts required on medicines, and we expect these discounts to continue as countries attempt to manage healthcare expenditures, especially in light of current economic conditions. As a result of these pricing practices, it may become difficult to achieve or sustain profitability or expected rates of growth in revenue or results of operations. Any shortfalls in revenue could adversely affect our business, financial condition and results of operations.

In light of such policies and the uncertainty surrounding proposed regulations and changes in the coverage and reimbursement policies of governments and third-party payers, we cannot be sure that coverage and reimbursement will be available for any of our medicines in any additional markets or for any other medicine candidates that we may develop. Also, we cannot be sure that reimbursement amounts will not reduce the demand for, or the price of, our medicines. If coverage and reimbursement are not available or are available only at limited levels, we may not be able to successfully commercialize our medicines.

We expect to experience pricing pressures in connection with the sale of our medicines due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative proposals relating to outcomes and quality. For example, the ACA increased the mandated Medicaid rebate from 15.1% to 23.1%, expanded the rebate to Medicaid managed care utilization and increased the types of entities eligible for the federal 340B drug discount program. On January 30, 2017, the White House Office of Management and Budget withdrew the draft August 2015 Omnibus Guidance document that was issued by the Department of Health and Human Services Health Resources and Services Administration, or HRSA, that addressed a broad range of topics including, among other items, the definition of a patient’s eligibility for 340B drug pricing. However, as concerns over drug pricing have not abated, there remains the possibility that HRSA will propose a similar regulation or that Congress will explore changes to the program through legislation. Also, in March 2016, the Centers for Medicare & Medicaid Services, or CMS, announced a Proposed Rule that would test new payment models for Medicare Part B prescription drugs, and provider services incident to, or otherwise related to, such drugs. Generally, the Proposed Rule included payment models designed on quality and value propositions and incentives to drive utilization of efficient therapies and payments based on clinical outcomes. The Proposed Rule greatly differs from the current reimbursement methodology for Medicare Part B drugs and was subject to significant discussion among stakeholders including Congress, industry, payers, healthcare providers and other interested organizations. Although the Proposed Rule was withdrawn by CMS in December, we will continue to monitor for legislative developments and new regulatory proposals.

There may be additional pressure by payers, healthcare providers, and Congress, to use generic drugs that contain the active ingredients found in our medicines or any other medicine candidates that we may develop or acquire. If we fail to successfully secure and maintain coverage and adequate reimbursement for our medicines or are significantly delayed in doing so, we will have difficulty achieving market acceptance of our medicines and expected revenue and

profitability which would have a material adverse effect on our business, results of operations, financial condition and prospects.

We may also experience pressure from payers concerning certain promotional approaches that we may implement such as our HorizonCares program or any other co-pay or free medicine programs whereby we assist qualified patients with certain out-of-pocket expenditures for our medicine. If we are unsuccessful with our HorizonCares program or any other co-pay initiatives or free medicine programs, or we alternatively are unable to secure expanded formulary access through additional arrangements with PBMs or other payers, we would be at a competitive disadvantage in terms of pricing versus preferred branded and generic competitors. We may also experience financial pressure in the future which would make it difficult to support investment levels in areas such as managed care contract rebates, HorizonCares and other access tools.

We are subject to federal, state and foreign healthcare laws and regulations and implementation or changes to such healthcare laws and regulations could adversely affect our business and results of operations.

The United States and some foreign jurisdictions are considering or have enacted a number of legislative and regulatory proposals to regulate and to change the healthcare system in ways that could affect our ability to sell our medicines profitably. In the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs (including a number of proposals pertaining to prescription drugs, specifically), improving quality and/or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives.

If we are found to be in violation of any of these laws or any other federal or state regulations, we may be subject to civil and/or criminal penalties, damages, fines, exclusion, additional reporting requirements and/or oversight from federal health care programs and the restructuring of our operations. Any of these could have a material adverse effect on our business and financial results. Since many of these laws have not been fully interpreted by the courts, there is an increased risk that we may be found in violation of one or more of their provisions. Any action against us for violation of these laws, even if we ultimately are successful in our defense, will cause us to incur significant legal expenses and divert our management's attention away from the operation of our business.

In January 2017, the United States House of Representatives and Senate passed legislation, the concurrent budget resolution for fiscal year 2017, which initiates actions that would repeal certain aspects of the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the ACA. Further, on January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA, to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. Congress also could consider subsequent legislation to replace elements of the ACA that are repealed.

Moreover, certain politicians, including President Trump, have called for federal legislation to regulate the prices of medicines. The majority of our medicines are purchased by private payers, and we do not believe that any such legislation, if enacted, would have a material effect on us or our business. However, we cannot know what form any such legislation may take, the likelihood it would be signed into law or the market's perception of how such legislation would affect us. Any reduction in reimbursement from government programs may result in a similar reduction in payments from private payers. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our current medicines and/or those for which we may receive regulatory approval in the future.

We are subject, directly or indirectly, to federal and state healthcare fraud and abuse and false claims laws and regulations. Prosecutions under such laws have increased in recent years and we may become subject to such litigation. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

In the United States, we are subject directly, or indirectly through our customers, to various state and federal fraud and abuse laws, including, without limitation, the federal Anti-Kickback Statute, the federal False Claims Act, civil monetary penalty statutes prohibiting beneficiary inducements, and similar state laws, federal and state privacy and security laws, sunshine laws, government price reporting laws, and other fraud laws. These laws may impact, among other things, our current and proposed sales, marketing and educational programs, as well as other possible relationships with customers, pharmacies, physicians, payers, and patients.

Compliance with these laws, including the development of a comprehensive compliance program, is difficult, costly and time consuming. Because of the breadth of these laws and the narrowness of available statutory and regulatory exemptions, it is possible that some of our business activities could be subject to challenge under one or more of such laws. These risks may be increased where there are evolving interpretations of applicable regulatory requirements, such as those applicable to manufacturer co-pay initiatives. Pharmaceutical manufacturer co-pay initiatives and free medicine programs are the subject of ongoing litigation (involving other manufacturers and to which we are not a party) and evolving interpretations of applicable regulatory requirements and certain state laws, and any change in the regulatory or enforcement environment regarding such programs could impact our ability to offer such programs. If we are unsuccessful with our HorizonCares programs, any other co-pay initiatives or free medicine programs, we would be at a competitive disadvantage in terms of pricing versus preferred branded and generic competitors, or be subject to significant penalties. We are engaged in various business arrangements with current and potential customers, and we can give no assurance that such arrangements would not be subject to scrutiny under such laws, despite our efforts to properly structure such arrangements. Even if we structure our programs with the intent of compliance with such laws, there can be no certainty that we would not need to defend our business activities against enforcement or litigation. Further, we cannot give any assurances that prior business activities or arrangements of other companies that we acquire will not be scrutinized or subject to enforcement or litigation.

There has also been a trend of increased federal and state regulation of payments made to physicians and other healthcare providers. The ACA, among other things, imposed reporting requirements on drug manufacturers for payments made by them to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit required information may result in significant civil monetary penalties.

We are unable to predict whether we could be subject to actions under any of these or other healthcare laws, or the impact of such actions. If we are found to be in violation of, or to encourage or assist the violation by third parties of any of the laws described above or other applicable state and federal fraud and abuse laws, we may be subject to penalties, including administrative, civil and criminal penalties, damages, fines, withdrawal of regulatory approval, imprisonment, exclusion from government healthcare reimbursement programs, contractual damages, reputational harm, diminished profits and future earnings, injunctions and other associated remedies, or private “qui tam” actions brought by individual whistleblowers in the name of the government, and the curtailment or restructuring of our operations, all of which could have a material adverse effect on our business and results of operations. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management’s attention from the operation of our business.

Our medicines or any other medicine candidate that we develop may cause undesirable side effects or have other properties that could delay or prevent regulatory approval or commercialization, result in medicine re-labeling or withdrawal from the market or have a significant impact on customer demand.

Undesirable side effects caused by any medicine candidate that we develop could result in the denial of regulatory approval by the FDA or other regulatory authorities for any or all targeted indications, or cause us to evaluate the future of our development programs. In our two Phase 3 clinical trials with DUEXIS, the most commonly reported treatment-emergent adverse events were nausea, dyspepsia, diarrhea, constipation and upper respiratory tract infection. In Phase 3 endoscopic registration clinical trials with VIMOVO, the most commonly reported treatment-emergent adverse events were erosive gastritis, dyspepsia, gastritis, diarrhea, gastric ulcer, upper abdominal pain, nausea and upper respiratory tract infection. The most common side effects observed in pivotal trials for ACTIMMUNE were “flu-like” or constitutional symptoms such as fever, headache, chills, myalgia and fatigue. The most commonly reported treatment-emergent adverse events in the Phase 3 clinical trials with RAYOS/LODOTRA included flare in rheumatoid arthritis related symptoms, abdominal pain, nasopharyngitis, headache, flushing, upper respiratory tract infection, back pain and weight gain. The most common adverse events reported in a Phase 2 clinical trial of PENNSAID 2% were application site reactions, such as dryness, exfoliation, erythema, pruritus, pain, induration, rash and scabbing. With respect to BUPHENYL, the most common side effects are change in the frequency of breathing, lack of or irregular menstruation, lower back, side, or stomach pain, mood or mental changes, muscle pain or twitching, nausea or vomiting, nervousness or restlessness, swelling of the feet or lower legs, unpleasant taste and unusual tiredness or weakness. With respect to RAVICTI, the most common side effects are diarrhea, nausea, decreased appetite, gas, vomiting, high blood levels of ammonia, headache, tiredness and dizziness. With respect to KRYSTEXXA, the most commonly reported serious adverse reactions in the pivotal trial were gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis, exacerbation of pre-existing congestive heart failure and vomiting. With respect to MIGERGOT, the most commonly reported adverse reactions are ischemia, cyanosis, absence of pulse, cold extremities, gangrene, precordial distress and pain, electrocardiogram change, muscle pain, nausea and vomiting, rectal or anal ulcer, parathesias, numbness weakness, vertigo, localized edemas and itching. With respect to PROCYSBI, the most common side effects include vomiting, nausea, abdominal pain, breath odor, diarrhea, skin odor, fatigue, rash and headache. With respect to QUINSAIR, the most common side effects include itching, wheezing, hives, rash, swelling, pale skin color, fast heartbeat and faintness.

The FDA or other regulatory authorities may also require, or we may undertake, additional clinical trials to support the safety profile of our medicines or medicine candidates.

In addition, if we or others identify undesirable side effects caused by our medicines or any other medicine candidate that we may develop that receives marketing approval, or if there is a perception that the medicine is associated with undesirable side effects:

- regulatory authorities may require the addition of labeling statements, such as a “black box” warning or a contraindication;
- regulatory authorities may withdraw their approval of the medicine or place restrictions on the way it is prescribed;
- we may be required to change the way the medicine is administered, conduct additional clinical trials or change the labeling of the medicine or implement a risk evaluation and mitigation strategy; and
- we may be subject to increased exposure to product liability and/or personal injury claims.

If any of these events occurred with respect to our medicines, our ability to generate significant revenues from the sale of these medicines would be significantly harmed.

We rely on third parties to conduct our preclinical and clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines or if they experience regulatory compliance issues, we may not be able to obtain regulatory approval for or commercialize our medicine candidates and our business could be substantially harmed.

We have agreements with third-party contract research organizations, or CROs, to conduct our clinical programs, including those required for post-marketing commitments, and we expect to continue to rely on CROs for the completion of on-going and planned clinical trials. We may also have the need to enter into other such agreements in the future if we were to develop other medicine candidates or conduct clinical trials in additional indications for our existing medicines. In connection with the investigator-initiated study to evaluate ACTIMMUNE in combination with PD-1/PD-L1 inhibitors in various forms of cancer including advanced urothelial carcinoma (bladder cancer) and renal cell carcinoma, we are collaborating with Fox Chase Cancer Center. In connection with our ongoing study to evaluate RAYOS/LODOTRA on the fatigue experienced by SLE patients, we are collaborating with the ALR. We rely heavily on these parties for the execution of our clinical studies and control only certain aspects of their activities. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol. We, our CROs and our academic research organizations are required to comply with current GCP or ICH regulations. The FDA enforces these GCP or ICH regulations through periodic inspections of trial sponsors, principal investigators and trial sites. If we or our CROs or collaborators fail to comply with applicable GCP or ICH regulations, the data generated in our clinical trials may be deemed unreliable and our submission of marketing applications may be delayed or the FDA may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that, upon inspection, the FDA will determine that any of our clinical trials comply or complied with GCP or ICH regulations. In addition, our clinical trials must be conducted with medicine produced under cGMP regulations, and may require a large number of test subjects. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. Moreover, our business may be implicated if any of our CROs or collaborators violates federal or state fraud and abuse or false claims laws and regulations or healthcare privacy and security laws. We must also obtain certain third-party institutional review board, or IRB, and ethics committee approvals in order to conduct our clinical trials. Delays by IRBs and ethics committees in providing such approvals may delay our clinical trials.

If any of our relationships with these third-party CROs or collaborators terminate, we may not be able to enter into similar arrangements on commercially reasonable terms, or at all. If CROs or collaborators do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our medicines and medicine candidates. As a result, our results of operations and the commercial prospects for our medicines and medicine candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed.

Switching or adding additional CROs or collaborators can involve substantial cost and require extensive management time and focus. In addition, there is a natural transition period when a new CRO or collaborator commences work. As a result, delays may occur, which can materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our CROs and collaborators, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition or prospects.

Clinical development of drugs and biologics involves a lengthy and expensive process with an uncertain outcome, and results of earlier studies and trials may not be predictive of future trial results.

Clinical testing is expensive and can take many years to complete, and its outcome is uncertain. Failure can occur at any time during the clinical trial process. The results of preclinical studies and early clinical trials of potential medicine candidates may not be predictive of the results of later-stage clinical trials. Medicine candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through preclinical studies and initial clinical testing. For example, Raptor announced in September 2015, based on information then available, that it would not advance its program for the treatment of pediatric NASH with PROCYSBI after a Phase 2b trial failed achieve its primary endpoints. Also, on December 8, 2016, we announced that the Phase 3 trial, Safety, Tolerability and Efficacy of ACTIMMUNE Dose Escalation in Friedreich's Ataxia study evaluating ACTIMMUNE for the treatment of Friedreich's ataxia, or FA, did not meet its primary endpoint of a statistically significant change from baseline in the modified Friedreich's Ataxia Rating Scale at twenty-six weeks versus treatment with placebo. In addition, the secondary endpoints did not meet statistical significance. We, in conjunction with the independent Data Safety Monitoring Board, the principal investigator and the Friedreich's Ataxia Research Alliance Collaborative Clinical Research Network in FA, determined that, based on the trial results, the STEADFAST program would be discontinued, including the twenty-six week extension study and the long-term safety study.

With respect to the investigator-initiated study to evaluate ACTIMMUNE in combination with OPDIVO® (nivolumab) in advanced solid tumors and to the extent that we are required to conduct additional clinical development of any of our existing or later acquired medicines or we conduct clinical development of earlier stage medicine candidates or for other additional indications for RAYOS/LODOTRA, we may experience delays in these clinical trials or investigator-initiated studies. We do not know whether any additional clinical trials will be initiated in the future, begin on time, need to be redesigned, enroll patients on time or be completed on schedule, if at all. Clinical trials can be delayed for a variety of reasons, including delays related to:

- obtaining regulatory approval to commence a trial;
- reaching agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- obtaining IRB or ethics committee approval at each site;
- recruiting suitable patients to participate in a trial;
- having patients complete a trial or return for post-treatment follow-up;
- clinical sites dropping out of a trial;
- adding new sites; or
- manufacturing sufficient quantities of medicine candidates for use in clinical trials.

Patient enrollment, a significant factor in the timing of clinical trials, is affected by many factors including the size and nature of the patient population, the proximity of patients to clinical sites, the eligibility criteria for the trial, the design of the clinical trial, competing clinical trials and clinicians' and patients' perceptions as to the potential advantages of the medicine candidate being studied in relation to other available therapies, including any new drugs or biologics that may be approved for the indications we are investigating. Furthermore, we rely and expect to rely on CROs and clinical trial sites to ensure the proper and timely conduct of our future clinical trials and while we have and intend to have agreements governing their committed activities, we will have limited influence over their actual performance.

We could encounter delays if prescribing physicians encounter unresolved ethical issues associated with enrolling patients in clinical trials of our medicine candidates in lieu of prescribing existing treatments that have established safety and efficacy profiles. Further, a clinical trial may be suspended or terminated by us, our collaborators, the FDA or other regulatory authorities due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a medicine candidate, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. If we experience delays in the completion of, or if we terminate, any clinical trial of our medicine candidates, the commercial prospects of our medicine candidates will be harmed, and our ability to generate medicine revenues from any of these medicine candidates will be delayed. In addition, any delays in completing our clinical trials will increase our costs, slow down our medicine development and approval process and jeopardize our ability to commence medicine sales and generate revenues.

Moreover, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and receive compensation in connection with such services. Under certain circumstances, we may be required to report some of these relationships to the FDA. The FDA may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected interpretation of the study. The FDA may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing applications by the FDA and may ultimately lead to the denial of marketing approval of one or more of our medicine candidates.

Any of these occurrences may harm our business, financial condition, results of operations and prospects significantly. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our medicine candidates.

Business interruptions could seriously harm our future revenue and financial condition and increase our costs and expenses.

Our operations could be subject to earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics and other natural or man-made disasters or business interruptions. While we carry insurance for certain of these events and have implemented disaster management plans and contingencies, the occurrence of any of these business interruptions could seriously harm our business and financial condition and increase our costs and expenses. We conduct significant management operations at both our global headquarters located in Dublin, Ireland and our U.S. office located in Lake Forest, Illinois. If our Dublin or Lake Forest offices were affected by a natural or man-made disaster or other business interruption, our ability to manage our domestic and foreign operations could be impaired, which could materially and adversely affect our results of operations and financial condition. We currently rely, and intend to rely in the future, on third-party manufacturers and suppliers to produce our medicines and third-party logistics partners to ship our medicines. Our ability to obtain commercial supplies of our medicines could be disrupted and our results of operations and financial condition could be materially and adversely affected if the operations of these third-party suppliers or logistics partners were affected by a man-made or natural disaster or other business interruption. The ultimate impact of such events on us, our significant suppliers and our general infrastructure is unknown.

We are dependent on information technology systems, infrastructure and data, which exposes us to data security risks.

We are dependent upon information technology systems, infrastructure and data, including mobile technologies, to operate our business. The multitude and complexity of our computer systems make them inherently vulnerable to service interruption or destruction, malicious intrusion and random attack. Likewise, data privacy or security breaches by employees or others may pose a risk that sensitive data, including our intellectual property, trade secrets or personal information of our employees, patients, customers or other business partners may be exposed to unauthorized persons or to the public. Cyber-attacks are increasing in their frequency, sophistication and intensity. Cyber-attacks could include the deployment of harmful malware, denial-of-service, social engineering and other means to affect service reliability and threaten data confidentiality, integrity and availability. Our business partners face similar risks and any security breach of their systems could adversely affect our security posture. A security breach or privacy violation that leads to disclosure or modification of or prevents access to patient information, including personally identifiable information or protected health information, could harm our reputation, compel us to comply with federal and/or state breach notification laws and foreign law equivalents, subject us to mandatory corrective action, require us to verify the correctness of database contents and otherwise subject us to liability under laws and regulations that protect personal data, any of which could disrupt our business and/or result in increased costs or loss of revenue. Moreover, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information, trade secrets or other intellectual property. While we have invested, and continue to invest, in the protection of our data and information technology infrastructure, there can be no assurance that our efforts will prevent service interruptions, or identify breaches in our systems, that could adversely affect our business and operations and/or result in the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm to us. In addition, our liability insurance may not be sufficient in type or amount to cover us against claims related to security breaches, cyber-attacks and other related breaches.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our medicines.

We face an inherent risk of product liability claims as a result of the commercial sales of our medicines and the clinical testing of our medicine candidates. For example, we may be sued if any of our medicines or medicine candidates allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the medicine, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our medicines and medicine candidates. Even a successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for our medicines or medicine candidates that we may develop;
- injury to our reputation;
- withdrawal of clinical trial participants;
- initiation of investigations by regulators;
- costs to defend the related litigation;
- a diversion of management’s time and resources;
- substantial monetary awards to trial participants or patients;
- medicine recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- exhaustion of any available insurance and our capital resources; and
- the inability to commercialize our medicines or medicine candidates.

Our inability to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of medicines we develop. We currently carry product liability insurance covering our clinical studies and commercial medicine sales in the amount of $75 million in the aggregate. Although we maintain such insurance, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. If we determine that it is prudent to increase our product liability coverage due to the on-going commercialization of our current medicines in the United States, and/or the potential commercial launches of any of our medicines in additional markets or for additional indications, we may be unable to obtain such increased coverage on acceptable terms or at all. Our insurance policies also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We will have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts.

Our business involves the use of hazardous materials, and we and our third-party manufacturers must comply with environmental laws and regulations, which can be expensive and restrict how we do business.

Our third-party manufacturers' activities involve the controlled storage, use and disposal of hazardous materials owned by us, including the components of our medicine candidates and other hazardous compounds. We and our manufacturers are subject to federal, state and local as well as foreign laws and regulations governing the use, manufacture, storage, handling and disposal of these hazardous materials. Although we believe that the safety procedures utilized by our third-party manufacturers for handling and disposing of these materials comply with the standards prescribed by these laws and regulations, we cannot eliminate the risk of accidental contamination or injury from these materials. In the event of an accident, state, federal or foreign authorities may curtail the use of these materials and interrupt our business operations. We do not currently maintain hazardous materials insurance coverage. If we are subject to any liability as a result of our third-party manufacturers' activities involving hazardous materials, our business and financial condition may be adversely affected. In the future we may seek to establish longer-term third-party manufacturing arrangements, pursuant to which we would seek to obtain contractual indemnification protection from such third-party manufacturers potentially limiting this liability exposure.

Our employees, independent contractors, principal investigators, consultants, vendors, distributors and CROs may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk that our employees, independent contractors, principal investigators, consultants, vendors, distributors and CROs may engage in fraudulent or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct or unauthorized activities that violate FDA regulations, including those laws that require the reporting of true, complete and accurate information to the FDA, manufacturing standards, federal and state healthcare fraud and abuse laws and regulations, and laws that require the true, complete and accurate reporting of financial information or data. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Misconduct by our employees and other third parties may also include the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. We have adopted a Code of Business Conduct and Ethics, but it is not always possible to identify and deter misconduct by our employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare

programs and imprisonment.

Risks Related to our Financial Position and Capital Requirements

In the past we have incurred significant operating losses.

We have a limited operating history and even less history operating as a combined organization following the acquisitions of Vidara, Hyperion, Crealta and Raptor. We have financed our operations primarily through equity and debt financings and have incurred significant operating losses in the past. We had an operating loss of $147.2 million for the year ended December 31, 2016, operating income of $55.4 million for the year ended December 31, 2015 and an operating loss of $8.5 million for the year ended December 31, 2014. We had a net loss of $166.8 million and a net income of $39.5 million for the years ended December 31, 2016 and 2015, respectively, and a net loss of $263.6 million for the year ended December 31, 2014. As of December 31, 2016, we had an accumulated deficit of $848.0 million. Our prior losses have resulted principally from costs incurred in our development activities for our medicines and medicine candidates, commercialization activities related to our medicines, costs associated with our acquisition transactions and costs associated with derivative liability accounting. Our prior losses, combined with possible future losses, have had and will continue to have an adverse effect on our shareholders' deficit and working capital. While we anticipate that we will continue to generate operating profits in the future, whether we can sustain this will depend on the revenues we generate from the sale of our medicines being sufficient to cover our operating expenses.

We have limited sources of revenues and significant expenses. We cannot be certain that we will sustain profitability, which would depress the market price of our ordinary shares and could cause our investors to lose all or a part of their investment.

Our ability to sustain profitability depends upon our ability to generate sales of our medicines. We have a limited history of commercializing our medicines as a company, and commercialization has been primarily in the United States. We may never be able to successfully commercialize our medicines or develop or commercialize other medicines in the United States or in the EU, which we believe represents our most significant commercial opportunity. Our ability to generate future revenues depends heavily on our success in:

- continued commercialization of our existing medicines and any other medicine candidates for which we obtain approval;
- obtaining FDA approvals for additional indications for ACTIMMUNE and RAVICTI;
- securing additional foreign regulatory approvals for our medicines in territories where we have commercial rights; and
- developing, acquiring and commercializing a portfolio of other medicines or medicine candidates in addition to our current medicines.

Even if we do generate additional medicine sales, we may not be able to sustain profitability on a quarterly or annual basis. Our failure to remain profitable would depress the market price of our ordinary shares and could impair our ability to raise capital, expand our business, diversify our medicine offerings or continue our operations.

We may need to obtain additional financing to fund additional acquisitions.

Our operations have consumed substantial amounts of cash since inception. We expect to continue to spend substantial amounts to:

- commercialize our existing medicines in the United States, including the substantial expansion of our sales force in recent years;
- complete the regulatory approval process, and any future required clinical development related thereto, for our medicines and medicine candidates;
- potentially acquire other businesses or additional complementary medicines or medicines that augment our current medicine portfolio, including costs associated with refinancing debt of acquired companies; and
-

conduct clinical trials with respect to potential additional indications, as well as conduct post-marketing requirements and commitments, with respect to our medicines and medicines we acquire.

While we believe that our existing cash and cash equivalents will be sufficient to fund our operations based on our current expectations of continued revenue growth, we may need to raise additional funds if we choose to expand our commercialization or development efforts more rapidly than presently anticipated, if we develop or acquire additional medicines or acquire companies, or if our revenue does not meet expectations.

We cannot be certain that additional funding will be available on acceptable terms, or at all. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of one or more of our medicines or medicine candidates or one or more of our other research and development initiatives, or delay, cut back or abandon our plans to grow the business through acquisition. We also could be required to:

- seek collaborators for one or more of our current or future medicine candidates at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available; or
- relinquish or license on unfavorable terms our rights to technologies or medicine candidates that we would otherwise seek to develop or commercialize ourselves.

In addition, if we are unable to secure financing to support future acquisitions, our ability to execute on a key aspect of our overall growth strategy would be impaired.

Any of the above events could significantly harm our business, financial condition and prospects.

We have incurred a substantial amount of debt, which could adversely affect our business, including by restricting our ability to engage in additional transactions or incur additional indebtedness, and prevent us from meeting our debt obligations.

As of December 31, 2016, we had $1,807.5 million book value, or $1,944.0 million principal amount, of indebtedness, including $769.0 million in secured indebtedness. In connection with the acquisition of Hyperion, we issued $475.0 million aggregate principal amount of 6.625% Senior Notes due 2023, or the 2023 Senior Notes, in April 2015 and borrowed $400.0 million in principal amount of secured loans pursuant to a credit agreement we entered into in May 2015 with Citibank, N.A., as administrative and collateral agent, and the lenders from time to time party thereto providing for (i) the six-year $400.0 million term loan facility; (ii) an uncommitted accordion facility subject to the satisfaction of certain financial and other conditions; and (iii) one or more uncommitted refinancing loan facilities with respect to loans thereunder, or the 2015 Senior Secured Credit Facility. We repaid $1.0 million in principal amount from this facility quarterly from the third quarter of 2015 to the fourth quarter of 2016. In connection with the acquisition of Raptor, we issued $300.0 million aggregate principal amount of 8.75% Senior Notes due 2024, or the 2024 Senior Notes, in October 2016 and borrowed $375.0 million in principal amount of secured loans, or the 2016 Incremental Loan Facility, pursuant to an amendment to our credit agreement, or as amended, the credit agreement. Accordingly, we have a significant amount of debt outstanding on a consolidated basis.

This substantial level of debt could have important consequences to our business, including, but not limited to:

- reducing the benefits we expect to receive from our recent and any future acquisition transactions;
- making it more difficult for us to satisfy our obligations;
- requiring a substantial portion of our cash flows from operations to be dedicated to the payment of principal and interest on our indebtedness, therefore reducing our ability to use our cash flows to fund acquisitions, capital expenditures, and future business opportunities;
- exposing us to the risk of increased interest rates to the extent of any future borrowings, including borrowings under our credit agreement, at variable rates of interest;
- making it more difficult for us to satisfy our obligations with respect to our indebtedness, including our outstanding notes, our credit agreement, and any failure to comply with the obligations of any of our debt instruments, including restrictive covenants and borrowing conditions, could result in an event of default under the agreements governing such indebtedness;

- increasing our vulnerability to, and reducing our flexibility to respond to, changes in our business or general adverse economic and industry conditions;

- limiting our ability to obtain additional financing for working capital, capital expenditures, debt service requirements, acquisitions, and general corporate or other purposes and increasing the cost of any such financing;
- limiting our flexibility in planning for, or reacting to, changes in our business and the industry in which we operate; and placing us at a competitive disadvantage as compared to our competitors, to the extent they are not as highly leveraged and who, therefore, may be able to take advantage of opportunities that our leverage may prevent us from exploiting; and
- restricting us from pursuing certain business opportunities.

The credit agreement and the indentures governing the 2024 Senior Notes and the 2023 Senior Notes impose, and the terms of any future indebtedness may impose, various covenants that limit our ability and/or the ability of our restricted subsidiaries' (as designated under such agreements) to, among other things, pay dividends or distributions, repurchase equity, prepay junior debt and make certain investments, incur additional debt and issue certain preferred stock, incur liens on assets, engage in certain asset sales, consolidate with or merge or sell all or substantially all of our assets, enter into transactions with affiliates, designate subsidiaries as unrestricted subsidiaries, and allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to us.

Our ability to obtain future financing and engage in other transactions may be restricted by these covenants. In addition, any credit ratings will impact the cost and availability of future borrowings and our cost of capital. Our ratings at any time will reflect each rating organization's then opinion of our financial strength, operating performance and ability to meet our debt obligations. There can be no assurance that we will achieve a particular rating or maintain a particular rating in the future. A reduction in our credit ratings may limit our ability to borrow at acceptable interest rates. If our credit ratings were downgraded or put on watch for a potential downgrade, we may not be able to sell additional debt securities or borrow money in the amounts, at the times or interest rates or upon the more favorable terms and conditions that might otherwise be available. Any impairment of our ability to obtain future financing on favorable terms could have an adverse effect on our ability to refinance any of our then-existing debt and may severely restrict our ability to execute on our business strategy, which includes the continued acquisition of additional medicines or businesses.

We may not be able to generate sufficient cash to service all of our indebtedness and may be forced to take other actions to satisfy our obligations under our indebtedness, which may not be successful.

Our ability to make scheduled payments under or to refinance our debt obligations depends on our financial condition and operating performance, which is subject to prevailing economic, industry and competitive conditions and to certain financial, business and other factors beyond our control. Our ability to generate cash flow to meet our payment obligations under our debt may also depend on the successful implementation of our operating and growth strategies. Any refinancing of our debt could be at higher interest rates and may require us to comply with more onerous covenants, which could further restrict our business operations. We cannot assure you that we will maintain a level of cash flows from operating activities sufficient to pay the principal, premium, if any, and interest on our indebtedness.

If our cash flows and capital resources are insufficient to fund our debt service obligations, we may be forced to reduce or delay capital expenditures, sell assets or business operations, seek additional capital or restructure or refinance our indebtedness. We cannot ensure that we would be able to take any of these actions, that these actions would be successful and permit us to meet our scheduled debt service obligations or that these actions would be permitted under the terms of existing or future debt agreements, including the indentures that govern the 2024 Senior Notes and the 2023 Senior Notes and the credit agreement. In addition, any failure to make payments of interest and principal on our outstanding indebtedness on a timely basis would likely result in a reduction of our credit rating, which could harm our ability to incur additional indebtedness.

If we cannot make scheduled payments on our debt, we will be in default and, as a result:

- our debt holders could declare all outstanding principal and interest to be due and payable;
-

the administrative agent and/or the lenders under the credit agreement could foreclose against the assets securing the borrowings then outstanding; and

- we could be forced into bankruptcy or liquidation, which could result in you losing your investment.

We generally have broad discretion in the use of our cash and may not use it effectively.

Our management has broad discretion in the application of our cash, and investors will be relying on the judgment of our management regarding the use of our cash. Our management may not apply our cash in ways that ultimately increase the value of any investment in our securities. We expect to use our existing cash to fund commercialization activities for our medicines, to potentially fund additional medicine or business acquisitions, to potentially fund additional regulatory approvals of certain of our medicines, to potentially fund development, life cycle management or manufacturing activities of our medicines for other indications, to potentially fund share repurchases, and for working capital, capital expenditures and general corporate purposes. We may also invest our cash in short-term, investment-grade, interest-bearing securities. These investments may not yield a favorable return to our shareholders. If we do not invest or apply our cash in ways that enhance shareholder value, we may fail to achieve expected financial results, which could cause the price of our ordinary shares to decline.

Our ability to use net operating loss carryforwards and certain other tax attributes may be limited.

Under Sections 382 and 383 of the Code, if a corporation undergoes an “ownership change” (generally defined as a greater than 50 percent change (by value) in its equity ownership over a three-year period), the corporation’s ability to use pre-change net operating loss carryforwards and other pre-change tax attributes to offset post-change income may be limited. We continue to carry forward our annual limitation resulting from an ownership change date of August 2, 2012. The limitation on pre-change net operating losses incurred prior to the August 2, 2012 change date is approximately $14.7 million for 2017 and $7.7 million for 2018 through 2028. During the third quarter of 2016, we also recognized additional net operating losses and federal and state tax credits as a result of our acquisition of Raptor on October 25, 2016 in the amount of approximately $97.3 million of federal net operating losses, state operating losses of approximately $177.5 million and approximately $22.4 million of federal and state tax credits. We continue to carry forward the annual limitation related to Hyperion of $50 million resulting from the last ownership change date in 2014. The net operating loss carryforward limitation is cumulative such that any use of the carryforwards below the limitations in one year will result in a corresponding increase in the limitations for the subsequent tax year.

Following certain acquisitions of a U.S. corporation by a foreign corporation, Section 7874 of the Code limits the ability of the acquired U.S. corporation and its U.S. affiliates to utilize U.S. tax attributes such as net operating losses to offset U.S. taxable income resulting from certain transactions. Based on the limited guidance available, we expect this limitation is applicable following the Vidara Merger. As a result, it is not currently expected that we or our other U.S. affiliates will be able to utilize their U.S. tax attributes to offset their U.S. taxable income, if any, resulting from certain taxable transactions following the Vidara Merger. Notwithstanding this limitation, we expect that we will be able to fully use our U.S. net operating losses prior to their expiration. As a result of this limitation, however, it may take HPI longer to use its net operating losses. Moreover, contrary to these expectations, it is possible that the limitation under Section 7874 of the Code on the utilization of U.S. tax attributes could prevent us from fully utilizing our U.S. tax attributes prior to their expiration if we do not generate sufficient taxable income.

Any limitation on our ability to use our net operating loss and tax credit carryforwards, including the carryforwards of companies that we acquire, will likely increase the taxes we would otherwise pay in future years if we were not subject to such limitations.

Unstable market and economic conditions may have serious adverse consequences on our business, financial condition and share price.

As widely reported, global credit and financial markets have experienced extreme disruptions in the past several years, including severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates, and uncertainty about economic stability. While there has been some recent improvement in some of these financial metrics, there can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions will not occur. Our general business strategy may be

adversely affected by any such economic downturn, volatile business environment and continued unpredictable and unstable market conditions. If the current equity and credit markets deteriorate again, or do not improve, it may make any necessary debt or equity financing more difficult to complete, more costly, and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and share price and could require us to delay or abandon commercialization or development plans. There is a risk that one or more of our current service providers, manufacturers and other partners may not survive these difficult economic times, which could directly affect our ability to attain our operating goals on schedule and on budget.

The U.K.'s referendum to leave the EU or "Brexit," has and may continue to cause disruptions to capital and currency markets worldwide. The full impact of the Brexit decision, however, remains uncertain. A process of negotiation will determine the future terms of the U.K.'s relationship with the EU. During this period of negotiation, our results of operations and access to capital may be negatively affected by interest rate, exchange rate and other market and economic volatility, as well as regulatory and political uncertainty. Brexit may also have a detrimental effect on our customers, distributors and suppliers, which would, in turn, adversely affect our revenues and financial condition.

At December 31, 2016, we had $509.1 million of cash and cash equivalents consisting of cash and money market funds. While we are not aware of any downgrades, material losses, or other significant deterioration in the fair value of our cash equivalents since December 31, 2016, no assurance can be given that further deterioration in conditions of the global credit and financial markets would not negatively impact our current portfolio of cash equivalents or our ability to meet our financing objectives. Further dislocations in the credit market may adversely impact the value and/or liquidity of marketable securities owned by us.

Changes in accounting rules or policies may affect our financial position and results of operations.

Accounting principles generally accepted in the United States, or GAAP, and related implementation guidelines and interpretations can be highly complex and involve subjective judgments. Changes in these rules or their interpretation, the adoption of new guidance or the application of existing guidance to changes in our business could significantly affect our financial position and results of operations. In addition, our operation as an Irish company with multiple subsidiaries in different jurisdictions adds additional complexity to the application of GAAP and this complexity will be exacerbated further if we complete additional strategic transactions. Changes in the application of existing rules or guidance applicable to us or our wholly owned subsidiaries could significantly affect our consolidated financial position and results of operations.

Covenants under the indentures governing our 2024 Senior Notes and 2023 Senior Notes and the credit agreement may restrict our business and operations in many ways, and if we do not effectively manage our covenants, our financial conditions and results of operations could be adversely affected.

The indentures governing the 2024 Senior Notes and the 2023 Senior Notes and the credit agreement impose various covenants that limit our ability and/or our restricted subsidiaries' ability to, among other things:

- pay dividends or distributions, repurchase equity, prepay, redeem or repurchase certain debt and make certain investments;
- incur additional debt and issue certain preferred stock;
- provide guarantees in respect of obligations of other persons;
- incur liens on assets;
- engage in certain asset sales;
- merge, consolidate with or sell all or substantially all of our assets to another person;
- enter into transactions with affiliates;
- sell assets and capital stock of our subsidiaries;
- enter into agreements that restrict distributions from our subsidiaries;
- designate subsidiaries as unrestricted subsidiaries; and
- allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to us.

These covenants may:

- limit our ability to borrow additional funds for working capital, capital expenditures, acquisitions or other general business purposes;
- limit our ability to use our cash flow or obtain additional financing for future working capital, capital expenditures, acquisitions or other general business purposes;

- require us to use a substantial portion of our cash flow from operations to make debt service payments;

- limit our flexibility to plan for, or react to, changes in our business and industry;
- place us at a competitive disadvantage compared to less leveraged competitors; and
- increase our vulnerability to the impact of adverse economic and industry conditions.

If we are unable to successfully manage the limitations and decreased flexibility on our business due to our significant debt obligations, we may not be able to capitalize on strategic opportunities or grow our business to the extent we would be able to without these limitations.

Our failure to comply with any of the covenants could result in a default under the credit agreement or the indentures governing the 2024 Senior Notes or the 2023 Senior Notes, which could permit the administrative agent or the trustee, as applicable, or permit the lenders or the holders of the 2024 Senior Notes or the 2023 Senior Notes to cause the administrative agent or the trustee, as applicable, to declare all or part of any outstanding senior secured term loans, the 2023 Senior Notes or the 2024 Senior Notes to be immediately due and payable or to exercise any remedies provided to the administrative agent or the trustee, including, in the case of the credit agreement proceeding against the collateral granted to secure our obligations under the credit agreement. An event of default under the credit agreement or the indentures governing the 2024 Senior Notes or the 2023 Senior Notes could also lead to an event of default under the terms of the other agreements and the indenture governing our 2.50% Exchangeable Senior Notes due 2022, or the Exchangeable Senior Notes. Any such event of default or any exercise of rights and remedies by our creditors could seriously harm our business.

If intangible assets that we have recorded in connection with our acquisition transactions become impaired, we could have to take significant charges against earnings.

In connection with the accounting for our various acquisition transactions, we have recorded significant amounts of intangible assets. Under GAAP, we must assess, at least annually and potentially more frequently, whether the value of goodwill and other indefinite-lived intangible assets has been impaired. Amortizing intangible assets will be assessed for impairment in the event of an impairment indicator. Any reduction or impairment of the value of goodwill or other intangible assets will result in a charge against earnings, which could materially adversely affect our results of operations and shareholders' equity in future periods.

Risks Related to Our Intellectual Property

If we are unable to obtain or protect intellectual property rights related to our medicines and medicine candidates, we may not be able to compete effectively in our markets.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our medicines and medicine candidates. The strength of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions and can be uncertain. The patent applications that we own may fail to result in issued patents with claims that cover our medicines in the United States or in other foreign countries. If this were to occur, early generic competition could be expected against our current medicines and other medicine candidates in development. There is no assurance that all potentially relevant prior art relating to our patents and patent applications has been found, which prior art can invalidate a patent or prevent a patent from issuing based on a pending patent application. In particular, because the APIs in DUEXIS, VIMOVO and RAYOS/LODOTRA have been on the market as separate medicines for many years, it is possible that these medicines have previously been used off-label in such a manner that such prior usage would affect the validity of our patents or our ability to obtain patents based on our patent applications. In addition, claims directed to dosing and dose adjustment may be substantially less likely to issue in light of the Supreme Court decision in Mayo Collaborative Services v. Prometheus Laboratories, Inc., where the court held that claims directed to methods of determining whether to adjust drug dosing levels based on drug metabolite levels in the red blood cells were not patent eligible because they were directed to a law of nature. This decision may have wide-ranging implications on the validity and scope of pharmaceutical method claims.

Even if patents do successfully issue, third parties may challenge their validity, enforceability or scope, which may result in such patents being narrowed or invalidated.

Patent litigation is currently pending in the United States District Court for the District of New Jersey against several companies intending to market a generic version of VIMOVO before the expiration of certain of our patents listed in the Orange Book. These cases are collectively known as the VIMOVO cases, and involve the following sets of defendants: (i) Dr. Reddy's; (ii) Lupin; and (iii) Mylan. Patent litigation against a fourth generic company, Actavis, is currently pending in the Court of Appeals for the Federal Circuit. Patent litigation against a fourth generic company, Actavis, is currently pending in the Court of Appeals for the Federal Circuit. The cases arise from Paragraph IV Patent Certification notice letters from each of Dr. Reddy's, Lupin, Mylan and Actavis advising each had filed an ANDA with the FDA seeking approval to market generic versions of VIMOVO before the expiration of the patents-in-suit.

On January 12, 2017, a six-day bench trial commenced against defendants Dr. Reddy's and Mylan before the Honorable Judge Mary Cooper in the District of New Jersey. The patents at issue in this trial included two Orange Book listed patents: U.S. Patent Nos. 6,926,907 and 8,557,285. Defendant Lupin formerly entered into a stay pending entry of judgment in this consolidated action. Currently, closing arguments and post-trial filings are not scheduled.

On August 19, 2015, Lupin filed Petitions for inter partes review, or IPR, of U.S. Patent No. 8,858,996, or the '996 patent, and U.S. Patent Nos. 8,852,636 and 8,865,190, or the '190 patent, all patents in litigation in the above referenced VIMOVO cases. On March 1, 2016, the Patent Trial and Appeal Board, or the PTAB, issued decisions to institute the IPRs for the '996 patent and the '190 patent. The PTAB must issue a final written decision on the IPRs of the '996 patent and the '190 patent no later than March 1, 2017. Also on March 1, 2016, the PTAB denied the Petition for IPR for U.S. Patent No. 8,852,636. The PTAB hearings for the '996 and '190 patents were both held on November 29, 2016. The PTAB must issue final written decision on the IPRs of the '996 and '190 patents no later than March 1, 2017.

Patent litigation is currently pending in the United States District Court for the District of New Jersey against several companies intending to market a generic version of PENNSAID 2% prior to the expiration of certain of our patents listed in the Orange Book. These cases are collectively known as the PENNSAID 2% cases, and involve the following sets of defendants: (i) Actavis and (ii) Lupin. These cases arise from Paragraph IV Patent Certification notice letters from each of Actavis and Lupin advising each had filed an ANDA with the FDA seeking approval to market a generic version of PENNSAID 2% before the expiration of the patents-in-suit. The status of these cases is as set forth below.

We received from Actavis a Paragraph IV Patent Certification Notice Letter dated September 27, 2016, against Orange Book listed U.S. Patent No. 9,415,029, advising that Actavis had filed an ANDA with the FDA for a generic version of PENNSAID 2%.

We have received from Apotex three Paragraph IV Patent Certification Notice Letters dated April 1, 2016, June 30, 2016, and September 21, 2016 against Orange Book listed U.S. Patent Nos. 8,217,078, 8,252,838, 8,546,450, 8,563,613, 8,618,164, 8,741,956, 8,871,809, 9,066,913, 9,101,591, 9,132,110, 9,168,304, 9,168,305, 9,220,784, 9,339,551, 9,339,552 and 9,415,029, advising that Apotex had filed an ANDA with the FDA for a generic version of PENNSAID 2%.

Patent litigation is currently pending in the United States District Court for the Eastern District of Texas against Par Pharmaceutical and in the United States District Court for the District of New Jersey against Lupin and against Par Pharmaceutical, who are each intending to market generic versions of RAVICTI prior to the expiration of certain of our patents listed in the Orange Book. These cases are collectively known as the RAVICTI cases, and arise from Paragraph IV Patent Certification notice letters from each of Par Pharmaceutical and Lupin advising each had filed an ANDA with the FDA seeking approval to market a generic version of RAVICTI before the expiration of the patents-in-suit.

On April 29, 2015, Par Pharmaceutical filed Petitions for IPR of U.S. Patent No. 8,404,215 and U.S. Patent No. 8,642,012, two of the patents involved in the above mentioned RAVICTI cases. On November 4, 2015, the PTAB issued decisions instituting such IPRs and on December 14, 2015, the District Court Judge Roy Payne issued a stay

pending a final written decision from the PTAB with respect to such IPRs. On September 29, 2016, the PTAB found all of the claims in U.S. Patent No. 8,404,215 to be unpatentable. Horizon has not appealed the PTAB's final written decision with respect to U.S. Patent No. 8,404,215. On November 3, 2016, the PTAB issued a final written decision holding all of the claims of U.S. Patent No. 8,642,012 patentable. On December 29, 2016, Par filed a notice of appeal with the Federal Circuit to appeal the final written decision of the PTAB concerning the patentability of U.S. Patent No. 8,642,012.

On April 1, 2016, Lupin filed a Petition for IPR of U.S. Patent No. 9,095,559, a patent currently at issue in the Lupin RAVICTI case. On September 30, 2016, the PTAB issued a decision instituting the IPR. The PTAB must issue a final written decision on the IPR no later than September 30, 2017.

We intend to vigorously defend our intellectual property rights relating to our medicines, but we cannot predict the outcome of the VIMOVO cases, the PENNSAID 2% cases, the RAVICTI cases or the IPRs. Any adverse outcome in these matters or any new generic challenges that may arise could result in one or more generic versions of our medicines being launched before the expiration of the listed patents, which could adversely affect our ability to successfully execute our business strategy to increase sales of our medicines, and would negatively impact our financial condition and results of operations, including causing a significant decrease in our revenues and cash flows.

Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property or prevent others from designing around our claims. If the patent applications we hold with respect to our medicines fail to issue or if their breadth or strength of protection is threatened, it could dissuade companies from collaborating with us to develop them and threaten our ability to commercialize our medicines. We cannot offer any assurances about which, if any, patents will issue or whether any issued patents will be found not invalid and not unenforceable or will go unthreatened by third parties. Since patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we were the first to file any patent application related to our medicines or any other medicine candidates. Furthermore, if third parties have filed such patent applications, an interference proceeding in the United States can be provoked by a third-party or instituted by us to determine which party was the first to invent any of the subject matter covered by the patent claims of our applications.

With respect to RAVICTI, the composition of matter patent we hold would have expired in the United States in February 2015 without term extension. However, Hyperion applied for a term extension for this patent under the Drug Price Competition and Patent Term Restoration Act and received notice that the United States Patent and Trademark Office, or the U.S. PTO, extended the expiration date of the patent to July 28, 2018. We cannot guarantee that pending patent applications related to RAVICTI will result in additional patents or that other existing and future patents related to RAVICTI will be held valid and enforceable or will be sufficient to deter generic competition in the United States. Therefore, it is possible that upon expiration of the RAVICTI composition of matter patent, we would need to rely on forms of regulatory exclusivity, to the extent available, to protect against generic competition.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable, processes for which patents are difficult to enforce and any other elements of our drug discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. Although we expect all of our employees to assign their inventions to us, and all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques.

Our ability to obtain patents is highly uncertain because, to date, some legal principles remain unresolved, there has not been a consistent policy regarding the breadth or interpretation of claims allowed in patents in the United States and the specific content of patents and patent applications that are necessary to support and interpret patent claims is highly uncertain due to the complex nature of the relevant legal, scientific and factual issues. Changes in either patent laws or interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property or narrow the scope of our patent protection. For example, on September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. The U.S. PTO has developed new and untested regulations and procedures to govern the full implementation of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, only became effective in March 2013. The Leahy-Smith Act has also introduced procedures making it easier for third-parties to challenge issued patents, as well as to intervene in the prosecution of patent applications. Finally, the Leahy-Smith Act contains new

statutory provisions that still require the U.S. PTO to issue new regulations for their implementation and it may take the courts years to interpret the provisions of the new statute. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. In addition, the ACA allows applicants seeking approval of biosimilar or interchangeable versions of biological products such as ACTIMMUNE to initiate a process for challenging some or all of the patents covering the innovator biological product used as the reference product. This process is complicated and could result in the limitation or loss of certain patent rights. An inability to obtain, enforce and defend patents covering our proprietary technologies would materially and adversely affect our business prospects and financial condition.

Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. For example, if the issuance, in a given country, of a patent to us, covering an invention, is not followed by the issuance, in other countries, of patents covering the same invention, or if any judicial interpretation of the validity, enforceability, or scope of the claims in, or the written description or enablement in, a patent issued in one country is not similar to the interpretation given to the corresponding patent issued in another country, our ability to protect our intellectual property in those countries may be limited. Changes in either patent laws or in interpretations of patent laws in the United States and other countries may materially diminish the value of our intellectual property or narrow the scope of our patent protection. If we are unable to prevent material disclosure of the non-patented intellectual property related to our technologies to third parties, and there is no guarantee that we will have any such enforceable trade secret protection, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, results of operations and financial condition.

Third-party claims of intellectual property infringement may prevent or delay our development and commercialization efforts.

Our commercial success depends in part on us avoiding infringement of the patents and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions and inter party reexamination proceedings before the U.S. PTO. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which our collaborators are developing medicine candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our medicine candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our medicines and/or any other medicine candidates. Because patent applications can take many years to issue, there may be currently pending patent applications, which may later result in issued patents that our medicine candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our medicine candidates, any molecules formed during the manufacturing process or any final medicine itself, the holders of any such patents may be able to block our ability to commercialize such medicine candidate unless we obtained a license under the applicable patents, or until such patents expire. Similarly, if any third-party patent were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or methods of use, including combination therapy, the holders of any such patent may be able to block our ability to develop and commercialize the applicable medicine candidate unless we obtained a license or until such patent expires. In either case, such a license may not be available on commercially reasonable terms or at all.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our medicine candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties or redesign our infringing medicines, which may be impossible or require substantial time and monetary expenditure. We cannot predict whether any such license would be available at all or whether it would be available on commercially reasonable terms. Furthermore, even in the absence of litigation, we may need to obtain licenses from third parties to advance our research or allow commercialization of our medicine candidates, and we have done so from time to time. We may fail to obtain any of these licenses at a reasonable cost or

on reasonable terms, if at all. In that event, we would be unable to further develop and commercialize one or more of our medicine candidates, which could harm our business significantly. We cannot provide any assurances that third-party patents do not exist which might be enforced against our medicines, resulting in either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties.

If we fail to comply with our obligations in the agreements under which we license rights to technology from third parties, we could lose license rights that are important to our business.

We are party to a number of technology licenses that are important to our business and expect to enter into additional licenses in the future. For example, we hold an exclusive license to Vectura Group plc's, or Vectura, proprietary technology and know-how covering the delayed-release of corticosteroids relating to RAYOS/LODOTRA. If we fail to comply with our obligations under our agreement with Vectura or our other license agreements, or if we are subject to a bankruptcy, the licensor may have the right to terminate the license, in which event we would not be able to market medicines covered by the license, including RAYOS/ LODOTRA.

In connection with our November 2013 acquisition of the U.S. rights to VIMOVO, we (i) received the benefit of a covenant not to sue under AstraZeneca's patent portfolio with respect to Nexium (which shall automatically become a license under such patent portfolio if and when AstraZeneca reacquires control of such patent portfolio from Merck Sharp & Dohme Corp. and certain of its affiliates), (ii) were assigned AstraZeneca's amended and restated collaboration and license agreement for the United States with Aralez, under which AstraZeneca has in-licensed exclusive rights under certain of Aralez's patents with respect to VIMOVO, and (iii) acquired AstraZeneca's co-ownership rights with Aralez with respect to certain joint patents covering VIMOVO, all for the commercialization of VIMOVO in the United States. If we fail to comply with our obligations under our agreements with AstraZeneca or if we fail to comply with our obligations under our agreements with Aralez, our rights to commercialize VIMOVO in the United States may be adversely affected or terminated by AstraZeneca or Aralez.

We also license rights to patents, know-how and trademarks for ACTIMMUNE from Genentech Inc., or Genentech, under an agreement that remains in effect for so long as we continue to commercialize and sell ACTIMMUNE. However, Genentech may terminate the agreement upon our material default, if not cured within a specified period of time. Genentech may also terminate the agreement in the event of our bankruptcy or insolvency. Upon such a termination of the agreement, all intellectual property rights conveyed to us under the agreement, including the rights to the ACTIMMUNE trademark, revert to Genentech. If we fail to comply with our obligations under this agreement, we could lose the ability to market and distribute ACTIMMUNE, which would have a material adverse effect on our business, financial condition and results of operations.

We rely on a license from Ucyclyd with respect to technology developed by Ucyclyd in connection with the manufacturing of RAVICTI. The purchase agreement under which Hyperion purchased the worldwide rights to RAVICTI contains obligations to pay Ucyclyd regulatory and sales milestone payments relating to RAVICTI, as well as royalties on the net sales of RAVICTI. On May 31, 2013, when Hyperion acquired BUPHENYL under a restated collaboration agreement with Ucyclyd, Hyperion received a license to use some of the manufacturing technology developed by Ucyclyd in connection with the manufacturing of BUPHENYL. The restated collaboration agreement also contains obligations to pay Ucyclyd regulatory and sales milestone payments, as well as royalties on net sales of BUPHENYL. If we fail to make a required payment to Ucyclyd and do not cure the failure within the required time period, Ucyclyd may be able to terminate the license to use its manufacturing technology for RAVICTI and BUPHENYL. If we lose access to the Ucyclyd manufacturing technology, we cannot guarantee that an acceptable alternative method of manufacture could be developed or acquired. Even if alternative technology could be developed or acquired, the loss of the Ucyclyd technology could still result in substantial costs and potential periods where we would not be able to market and sell RAVICTI and/or BUPHENYL. We also license intellectual property necessary for commercialization of RAVICTI from an external party. This party may be entitled to terminate the license if we breach the agreement, including failure to pay required royalties on net sales of RAVICTI, or we do not meet specified diligence obligations in our development and commercialization of RAVICTI, and we do not cure the failure within the required time period. If the license is terminated, it may be difficult or impossible for us to continue to commercialize RAVICTI, which would have a material adverse effect on our business, financial condition and results of operations.

We also hold an exclusive license to patents and technology from Duke University, or Duke, and Mountain View Pharmaceuticals, Inc., or MVP, covering KRYSTEXXA. Duke and MVP may terminate the license if we commit fraud or for our willful misconduct or illegal conduct. Duke and MVP may also terminate the license upon our material breach of the agreement, if not cured within a specified period of time, or upon written notice if we have committed two or more material breaches under the agreement. Duke and MVP may also terminate the license in the event of our bankruptcy or insolvency. If the license is terminated, it may be impossible for us to continue to commercialize KRYSTEXXA, which would have a material adverse effect on our business, financial condition and results of operations.

In addition, we are subject to contractual obligations under our agreements with Tripex and PARI related to QUINSAIR. Under the agreement with Tripex, we are required to pursue commercially reasonable efforts to initiate, and subsequently to complete, an additional clinical trial of QUINSAIR in a non-cystic fibrosis patient population within a specified period of time and an obligation to progress toward submitting an NDA for approval of QUINSAIR in the United States for use in all or part of the cystic fibrosis patient population. These obligations are subject to certain exceptions due to, for example, manufacturing delays not under our control, or delays caused by the FDA. If we fail to properly exercise such efforts to initiate and complete an appropriate clinical trial, or fail to submit an NDA for U.S. approval in the cystic fibrosis patient population, during the time periods specified in the agreement, we may be subject to various claims by Tripex and parties affiliated with Tripex. In addition, if we do not spend a minimum amount on QUINSAIR development in each of the three years following our acquisition of Raptor, we may also be obligated to pre-pay a milestone payment related to initiating a clinical trial for QUINSAIR in a non-cystic fibrosis indication. Under the license agreement with PARI, we are required to comply with diligence milestones related to development and commercialization of QUINSAIR in the United States and to spend a specified minimum amount per year on development activities in the United States until submission of the NDA for QUINSAIR in the United States. If we do not comply with these obligations, our licenses to certain intellectual property related to QUINSAIR may become non-exclusive in the United States or could be terminated. We are also subject to contractual obligations under our license agreements with the UCSD with respect to PROCYSBI, including diligence obligations to develop PROCYSBI for the treatment of NASH and Huntington's disease, with which we currently are not in compliance. To the extent that we fail to perform the diligence obligations under the agreement, UCSD may, with respect to such indication, terminate the license or otherwise cause the license to become non-exclusive. If one or more of these licenses was terminated, we would have no further right to use or exploit the related intellectual property, which would limit our ability to develop PROCYSBI or QUINSAIR in other indications, and could impact our ability to continue commercializing PROCYSBI or QUINSAIR in their approved indications.

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our patents or the patents of our licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that one of our patents, or a patent of one of our licensors, is not valid or is unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing.

There are numerous post grant review proceedings available at the U.S. PTO (including IPR, post-grant review and ex-parte reexamination) and similar proceedings in other countries of the world that could be initiated by a third-party that could potentially negatively impact our issued patents.

Interference proceedings provoked by third parties or brought by us may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our collaborators or licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim

proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our ordinary shares.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees on any issued patent are due to be paid to the U.S. PTO and foreign patent agencies in several stages over the lifetime of the patent. The U.S. PTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we or licensors that control the prosecution and maintenance of our licensed patents fail to maintain the patents and patent applications covering our medicine candidates, our competitors might be able to enter the market, which would have a material adverse effect on our business.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties.

We employ individuals who were previously employed at other biotechnology or pharmaceutical companies. We may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed confidential information of our employees' former employers or other third parties. We may also be subject to claims that former employers or other third parties have an ownership interest in our patents. Litigation may be necessary to defend against these claims. There is no guarantee of success in defending these claims, and even if we are successful, litigation could result in substantial cost and be a distraction to our management and other employees.

Risks Related to Ownership of Our Ordinary Shares

The market price of our ordinary shares historically has been volatile and is likely to continue to be volatile, and you could lose all or part of any investment in our ordinary shares.

The trading price of our ordinary shares has been volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. In addition to the factors discussed in this "Risk Factors" section and elsewhere in this report, these factors include:

- our failure to successfully execute our commercialization strategy with respect to our approved medicines, particularly our commercialization of our medicines in the United States;
- actions or announcements by third-party or government payers with respect to coverage and reimbursement of our medicines;
- disputes or other developments relating to intellectual property and other proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our medicines and medicine candidates;
- unanticipated serious safety concerns related to the use of our medicines;
- adverse regulatory decisions;
- changes in laws or regulations applicable to our business, medicines or medicine candidates, including but not limited to clinical trial requirements for approvals or tax laws;
- inability to comply with our debt covenants and to make payments as they become due;
- inability to obtain adequate commercial supply for any approved medicine or inability to do so at acceptable prices;
- developments concerning our commercial partners, including but not limited to those with our sources of manufacturing supply;

- our decision to initiate a clinical trial, not to initiate a clinical trial or to terminate an existing clinical trial;
- adverse results or delays in clinical trials;

- our failure to successfully develop and/or acquire additional medicine candidates or obtain approvals for additional indications for our existing medicine candidates;
- introduction of new medicines or services offered by us or our competitors;
- overall performance of the equity markets, including the pharmaceutical sector, and general political and economic conditions;
- failure to meet or exceed revenue and financial projections that we may provide to the public;
- actual or anticipated variations in quarterly operating results;
- failure to meet or exceed the estimates and projections of the investment community;
- inaccurate or significant adverse media coverage;
- publication of research reports about us or our industry or positive or negative recommendations or withdrawal of research coverage by securities analysts;
- our inability to successfully enter new markets;
- the termination of a collaboration or the inability to establish additional collaborations;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us or our competitors;
- our inability to maintain an adequate rate of growth;
- ineffectiveness of our internal controls or our inability to otherwise comply with financial reporting requirements;
- adverse U.S. and foreign tax exposure;
- additions or departures of key management, commercial or regulatory personnel;
- issuances of debt or equity securities;
- significant lawsuits, including patent or shareholder litigation;
- changes in the market valuations of similar companies to us;
- sales of our ordinary shares by us or our shareholders in the future;
- trading volume of our ordinary shares;
- effects of natural or man-made catastrophic events or other business interruptions; and
- other events or factors, many of which are beyond our control.

In addition, the stock market in general, and The NASDAQ Global Select Market and the stock of biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may adversely affect the market price of our ordinary shares, regardless of our actual operating performance.

We have never declared or paid dividends on our share capital and we do not anticipate paying dividends in the foreseeable future.

We have never declared or paid any cash dividends on our ordinary shares. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future, including due to limitations that are currently imposed by the 2015 Senior Secured Credit Facility, the 2016 Incremental Loan Facility, the 2024 Senior Notes and the 2023 Senior Notes. Any return to shareholders will therefore be limited to the increase, if any, of our ordinary share price.

We have incurred and will continue to incur significant increased costs as a result of operating as a public company and our management will be required to devote substantial time to compliance initiatives.

As a public company, we have incurred and will continue to incur significant legal, accounting and other expenses that we did not incur as a private company. In particular, the Sarbanes-Oxley Act of 2000, or the Sarbanes-Oxley Act, as well as rules subsequently implemented by the SEC and the NASDAQ Stock Market, Inc., or NASDAQ, impose significant requirements on public companies, including requiring establishment and maintenance of effective disclosure and financial controls and changes in corporate governance practices. These rules and regulations have substantially increased our legal and financial compliance costs and have made some activities more time-consuming and costly. These effects are exacerbated by our transition to an Irish company and the integration of numerous acquired businesses and operations into our historical business and operating structure. If these requirements divert the attention of our management and personnel from other business concerns, they could have a material adverse effect on our business, financial condition and results of operations. The increased costs will continue to decrease our net income or increase our net loss, and may require us to reduce costs in other areas of our business or increase the prices of our medicines or services. For example, these rules and regulations make it more difficult and more expensive for us to obtain and maintain director and officer liability insurance. We cannot predict or estimate the amount or timing of additional costs that we may incur to respond to these requirements. The impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers. If we fail to comply with the continued listing requirements of NASDAQ, our ordinary shares could be delisted from The NASDAQ Global Select Market, which would adversely affect the liquidity of our ordinary shares and our ability to obtain future financing.

The Sarbanes-Oxley Act requires, among other things, that we maintain effective internal controls for financial reporting and disclosure controls and procedures. In particular, we are required to perform annual system and process evaluation and testing of our internal controls over financial reporting to allow management to report on the effectiveness of our internal controls over financial reporting, as required by Section 404 of the Sarbanes-Oxley Act, or Section 404. Our independent registered public accounting firm is also required to deliver a report on the effectiveness of our internal control over financial reporting. Our testing, or the testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses. Our compliance with Section 404 requires that we incur substantial expense and expend significant management efforts, particularly because of our Irish parent company structure and international operations. If we are not able to comply with the requirements of Section 404 or if we or our independent registered public accounting firm identify deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses, the market price of our ordinary shares could decline and we could be subject to sanctions or investigations by NASDAQ, the SEC or other regulatory authorities, which would require additional financial and management resources.

New laws and regulations as well as changes to existing laws and regulations affecting public companies, including the provisions of the Sarbanes-Oxley Act and rules adopted by the SEC and by NASDAQ, would likely result in increased costs as we respond to their requirements.

Sales of a substantial number of our ordinary shares in the public market could cause our share price to decline.

If our existing shareholders sell, or indicate an intention to sell, substantial amounts of our ordinary shares in the public market, the trading price of such ordinary shares could decline. In addition, our ordinary shares that are either subject to outstanding options or reserved for future issuance under our employee benefit plans are or may become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules and Rule 144 and Rule 701 under the Securities Act of 1933, as amended, or the Securities Act. If these additional ordinary shares are sold, or if it is perceived that they will be sold, in the public market, the trading price of our ordinary shares could decline.

Certain holders of our ordinary shares are entitled to rights with respect to the registration of their shares under the Securities Act. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act, except for shares purchased by our affiliates. For example, we are subject to a registration rights agreement with certain former Vidara shareholders that acquired our ordinary shares in connection with our acquisition of Vidara. Pursuant to this agreement, we filed and are required to maintain a registration statement covering the resale of ordinary shares held by these shareholders and in certain circumstances, these holders can require us to participate in an underwritten public offering of their ordinary shares. Any sales of securities by these shareholders or a public announcement of such sales could have a material adverse effect on the trading price of our ordinary shares.

In addition, any conversion or exchange of our Exchangeable Senior Notes, whether pursuant to their terms or pursuant to privately negotiated transactions between the issuer and/or us and a holder of such securities, could depress the market price for our ordinary shares.

Future sales and issuances of our ordinary shares, securities convertible into our ordinary shares or rights to purchase ordinary shares or convertible securities could result in additional dilution of the percentage ownership of our shareholders and could cause our share price to decline.

Additional capital may be needed in the future to continue our planned operations. To the extent we raise additional capital by issuing equity securities or securities convertible into or exchangeable for ordinary shares, our shareholders may experience substantial dilution. We may sell ordinary shares, and we may sell convertible or exchangeable securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell such ordinary shares, convertible or exchangeable securities or other equity securities in subsequent transactions, existing shareholders may be materially diluted. New investors in such subsequent transactions could gain rights, preferences and privileges senior to those of holders of ordinary shares. We also maintain equity incentive plans, including our Amended and Restated 2014 Equity Incentive Plan, 2014 Non-Employee Equity Plan and 2014 Employee Share Purchase Plan, and intend to grant additional ordinary share awards under these and future plans, which will result in additional dilution to our existing shareholders.

Irish law differs from the laws in effect in the United States and may afford less protection to holders of our securities.

It may not be possible to enforce court judgments obtained in the United States against us in Ireland based on the civil liability provisions of the U.S. federal or state securities laws. In addition, there is some uncertainty as to whether the courts of Ireland would recognize or enforce judgments of U.S. courts obtained against us or our directors or officers based on the civil liabilities provisions of the U.S. federal or state securities laws or hear actions against us or those persons based on those laws. We have been advised that the U.S. currently does not have a treaty with Ireland providing for the reciprocal recognition and enforcement of judgments in civil and commercial matters. Therefore, a final judgment for the payment of money rendered by any U.S. federal or state court based on civil liability, whether or not based solely on U.S. federal or state securities laws, would not automatically be enforceable in Ireland.

As an Irish company, we are governed by the Irish Companies Acts, which differ in some material respects from laws generally applicable to U.S. corporations and shareholders, including, among others, differences relating to interested director and officer transactions and shareholder lawsuits. Likewise, the duties of directors and officers of an Irish company generally are owed to the company only. Shareholders of Irish companies generally do not have a personal right of action against directors or officers of the company and may exercise such rights of action on behalf of the company only in limited circumstances. Accordingly, holders of our securities may have more difficulty protecting their interests than would holders of securities of a corporation incorporated in a jurisdiction of the United States.

Provisions of our articles of association could delay or prevent a takeover of us by a third-party.

Our articles of association could delay, defer or prevent a third-party from acquiring us, despite the possible benefit to our shareholders, or otherwise adversely affect the price of our ordinary shares. For example, our articles of association:

- impose advance notice requirements for shareholder proposals and nominations of directors to be considered at shareholder meetings;
- stagger the terms of our board of directors into three classes; and
- require the approval of a supermajority of the voting power of the shares of our share capital entitled to vote generally at a meeting of shareholders to amend or repeal our articles of association.

In addition, several mandatory provisions of Irish law could prevent or delay an acquisition of us. For example, Irish law does not permit shareholders of an Irish public limited company to take action by written consent with less than

unanimous consent. We are also subject to various provisions of Irish law relating to mandatory bids, voluntary bids, requirements to make a cash offer and minimum price requirements, as well as substantial acquisition rules and rules requiring the disclosure of interests in our ordinary shares in certain circumstances.

These provisions may discourage potential takeover attempts, discourage bids for our ordinary shares at a premium over the market price or adversely affect the market price of, and the voting and other rights of the holders of, our ordinary shares. These provisions could also discourage proxy contests and make it more difficult for you and our other shareholders to elect directors other than the candidates nominated by our board of directors, and could depress the market price of our ordinary shares.

A transfer of our ordinary shares may be subject to Irish stamp duty.

In certain circumstances, the transfer of shares in an Irish incorporated company will be subject to Irish stamp duty, which is a legal obligation of the buyer. This duty is currently charged at the rate of 1.0 percent of the price paid or the market value of the shares acquired, if higher. Because our ordinary shares are traded on a recognized stock exchange in the United States, an exemption from this stamp duty is available to transfers by shareholders who hold ordinary shares beneficially through brokers which in turn hold those shares through the Depositary Trust Company, or DTC, to holders who also hold through DTC. However, a transfer by or to a record holder who holds ordinary shares directly in his, her or its own name could be subject to this stamp duty. We, in our absolute discretion and insofar as the Companies Acts or any other applicable law permit, may, or may provide that one of our subsidiaries will pay Irish stamp duty arising on a transfer of our ordinary shares on behalf of the transferee of such ordinary shares. If stamp duty resulting from the transfer of ordinary shares which would otherwise be payable by the transferee is paid by us or any of our subsidiaries on behalf of the transferee, then in those circumstances, we will, on our behalf or on behalf of such subsidiary (as the case may be), be entitled to (i) seek reimbursement of the stamp duty from the transferee, (ii) set-off the stamp duty against any dividends payable to the transferee of those ordinary shares and (iii) claim a first and permanent lien on the ordinary shares on which stamp duty has been paid by us or such subsidiary for the amount of stamp duty paid. Our lien shall extend to all dividends paid on those ordinary shares.

Dividends paid by us may be subject to Irish dividend withholding tax.

In certain circumstances, as an Irish tax resident company, we will be required to deduct Irish dividend withholding tax (currently at the rate of 20%) from dividends paid to our shareholders. Shareholders that are resident in the United States, EU countries (other than Ireland) or other countries with which Ireland has signed a tax treaty (whether the treaty has been ratified or not) generally should not be subject to Irish withholding tax so long as the shareholder has provided its broker, for onward transmission to our qualifying intermediary or other designated agent (in the case of shares held beneficially), or our or its transfer agent (in the case of shares held directly), with all the necessary documentation by the appropriate due date prior to payment of the dividend. However, some shareholders may be subject to withholding tax, which could adversely affect the price of our ordinary shares.

If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, our share price and trading volume could decline.

The trading market for our ordinary shares will depend in part on the research and reports that securities or industry analysts publish about us or our business. If one or more of the analysts who cover us downgrade our rating or publish inaccurate or unfavorable research about our business, our share price could decline. If one or more of these analysts cease coverage of our company or fail to publish reports on our company regularly, demand for our ordinary shares could decrease, which might cause our share price and trading volume to decline.

Securities class action litigation could divert our management's attention and harm our business and could subject us to significant liabilities.

The stock markets have from time to time experienced significant price and volume fluctuations that have affected the market prices for the equity securities of pharmaceutical companies. These broad market fluctuations may cause the market price of our ordinary shares to decline. In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology and biopharmaceutical companies have experienced significant stock price volatility in recent years. For example, following declines in our stock price, two federal securities class action lawsuits were filed in March 2016 against us and certain of our current and former officers alleging violations of the Securities Exchange Act of 1934, as amended. Subsequently, the two actions were consolidated, and plaintiff added claims under the Securities Act and named additional defendants. This consolidated class action (captioned Schaffer v. Horizon Pharma plc, et al., Case No. 1:16-cv-01763) is currently pending in the United States District Court for the Southern District of New York. In November 2016, defendants filed motions to dismiss plaintiffs' consolidated amended complaint, which are fully briefed but have not yet been decided by the court. Even if we are successful in defending against this action or any similar claims that may be brought in the future, such litigation could result in substantial costs and may be a distraction to our management, and may lead to an unfavorable outcome that could adversely impact our financial condition and prospects.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Location	Approximate Square Footage	Lease Expiry Date
Dublin, Ireland	18,900	November 3, 2029
Lake Forest, Illinois	160,000	March 31, 2024
Novato, California	61,000	August 31, 2021
Deerfield, Illinois (1)	53,500	June 30, 2018
Brisbane, California	20,100	November 30, 2019
Mannheim, Germany	14,300	December 31, 2018
Chicago, Illinois	6,500	December 31, 2018
Utrecht, the Netherlands	5,400	October 31, 2019
Reinach, Switzerland	3,500	May 31, 2020

(1) We vacated the premises in Deerfield, Illinois, and began occupying the premises in Lake Forest, Illinois, in January 2016.

Item 3. Legal Proceedings

For a description of our legal proceedings, see Note 16 of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K.

Item 4. Mine Safety Disclosures

None.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Information

Our ordinary shares trade on The NASDAQ Global Select Market under the trading symbol "HZNP".

The following table sets forth the high and low sales prices per share of our ordinary shares as reported on The NASDAQ Global Select Market for the periods indicated.

	High	Low
2016		
First quarter	$22.02	$13.36
Second quarter	19.45	13.05
Third quarter	23.44	16.18
Fourth quarter	21.98	14.16

	High	Low
2015		
First quarter	$26.46	$12.64
Second quarter	34.99	25.26
Third quarter	39.49	16.22
Fourth quarter	23.70	12.86

Holders of Record

The closing price of our ordinary shares on February 22, 2017 was $17.04. As of February 22, 2017, there were approximately thirteen holders of record of our ordinary shares.

Performance Graph

The following graph shows a comparison from December 31, 2011 through December 31, 2016 of the cumulative total return for (i) our ordinary shares, (ii) the NASDAQ U.S. Benchmark TR Index and (iii) NASDAQ Pharmaceuticals.

Information set forth in the graph below represents the performance of the Horizon Pharma, Inc. common stock from December 31, 2011 until September 18, 2014, the day before the consummation of the Vidara Merger, and the performance of our ordinary shares from September 19, 2014 through December 31, 2016. Our ordinary shares trade on the same exchange, the NASDAQ Global Select Market, and under the same trading symbol, “HZNP”, as the Horizon Pharma, Inc. common stock prior to the Vidara Merger. The graph assumes an initial investment of $100 on December 31, 2011. The comparisons in the graph are required by the Securities and Exchange Commission and are not intended to forecast or be indicative of possible future performance of our ordinary shares.

	12/31/2011	12/31/2012	12/31/2013	12/31/2014	12/31/2015	12/31/2016
Cumulative Returns						
Horizon Pharma plc	$ 100.00	$ 58.25	$ 190.50	$ 322.25	$ 541.75	$ 404.50
NASDAQ Pharmaceuticals	100.00	114.32	155.11	188.95	199.22	197.05
NASDAQ U.S. Benchmark TR Index	100.00	116.43	155.41	174.78	175.62	198.47

The foregoing graph and table are furnished solely with this report, and are not filed with this report, and shall not be deemed incorporated by reference into any other filing under the Securities Act of 1933, as amended, or the Securities Act, or the Securities Exchange Act of 1934, as amended, whether made by us before or after the date hereof, regardless of any general incorporation language in any such filing, except to the extent we specifically incorporate this material by reference into any such filing.

Dividend Policy

We have never declared or paid cash dividends on our common equity. We currently intend to retain all available funds and any future earnings to support operations and finance the growth and development of our business and do not intend to pay cash dividends on our ordinary shares for the foreseeable future. Under Irish law, dividends may only be paid, and share repurchases and redemptions must generally be funded only out of, “distributable reserves.” In addition, our ability to pay cash dividends is currently prohibited by the terms of our credit agreement we entered into in May 2015 with Citibank, N.A., as administrative and collateral agent, as amended, $475.0 million aggregate principal amount of 6.625% Senior Notes due 2023 and the $300.0 million aggregate principal amount of 8.75% Senior Notes due 2024, subject to customary exceptions. Any future determination as to the payment of dividends will, subject to Irish legal requirements, be at the sole discretion of our board of directors and will depend on our financial condition, results of operations, capital requirements and other factors our board of directors deems relevant.

Securities Authorized for Issuance under Equity Compensation Plans

See Item 12 of Part III of this Annual Report on Form 10-K regarding information about securities authorized for issuance under our equity compensation plans.

Recent Sales of Unregistered Securities

We completed the following issuances of unregistered securities during the year ended December 31, 2016 which were not previously reported in a Quarterly Report on Form 10-Q or in a Current Report on Form 8-K:

- In December 2016, we issued an aggregate of 500 ordinary shares to Peter Orlando upon the cash exercise of warrants and we received proceeds of $2,285 representing the aggregate exercise price of such warrants.
- In December 2016, we issued an aggregate of 500 ordinary shares to Troon Capital upon the cash exercise of warrants and we received proceeds of $2,285 representing the aggregate exercise price of such warrants.
- In December 2016, we issued an aggregate of 750 ordinary shares to Foster Equities LP upon the cash exercise of warrants and we received proceeds of $3,428 representing the aggregate exercise price of such warrants.

The offers, sales and issuances of the securities described above were deemed to be exempt from registration under the Securities Act of 1933, as amended, in reliance on Rule 506 of Regulation D in that each issuance of securities was to an accredited investor under Rule 501 of Regulation D and did not involve a public offering. The recipients of securities in each of these transactions acquired the securities for investment only and not with a view to or for sale in connection with any distribution thereof and where appropriate, legends were affixed to the securities issued in these transactions.

Issuer Repurchases of Equity Securities

None.

Irish Law Matters

See Irish Law Matters included in Item 1 of Part I of this Annual Report on Form 10-K.

Item 6. Selected Financial Data

The selected statement of comprehensive (loss) income data and selected statement of cash flows data for the years ended December 31, 2016, 2015 and 2014, and the balance sheet data as of December 31, 2016 and 2015 have been derived from our audited financial statements included elsewhere in this Annual Report on Form 10-K. The selected statements of comprehensive loss data and selected statement of cash flows data for the years ended December 31, 2013 and 2012, and the balance sheet data as of December 31, 2014, 2013 and 2012 have been derived from audited financial statements which are not included in this Annual Report on Form 10-K.

Our historical results are not necessarily indicative of future results. The selected financial data should be read in conjunction with “Management’s Discussion and Analysis of Financial Condition and Results of Operations” and our financial statements and related notes included elsewhere in this Annual Report on Form 10-K. The selected financial data for periods prior to the year ended December 31, 2014 is that of Horizon Pharma, Inc., our predecessor, while the selected financial data for the years ended December 31, 2016, 2015 and 2014 is that of Horizon Pharma plc.

	As of December 31,				
	2016	2015	2014	2013	2012
	(in thousands)				
Selected Balance Sheet Data					
Cash and cash equivalents	$509,055	$859,616	$218,807	$80,480	$104,087
Working capital	440,430	748,595	106,024	67,455	79,983
Total assets (1)	4,292,059	3,058,588	1,102,842	246,328	190,789
Total debt, net (1)	1,807,493	1,136,756	334,012	104,494	45,606
Accumulated deficit	(848,021)	(681,187)	(720,719)	(457,116)	(308,111)
Total shareholders' equity (deficit)	1,263,779	1,313,145	540,204	(49,082)	105,978

	For the Years Ended December 31,				
	2016	2015	2014	2013	2012
	(in thousands, except per share data)				
Selected Statement of Comprehensive (Loss) Income Data					
Net sales	$981,120	$757,044	$296,955	$74,016	$18,844
Cost of goods sold	393,272	219,502	78,753	14,625	11,875
Gross profit	587,848	537,542	218,202	59,391	6,969
Loss before benefit for income taxes	(228,085)	(132,712)	(269,687)	(150,126)	(92,965)
Net (loss) income	(166,834)	39,532	(263,603)	(149,005)	(87,794)
Net (loss) income per ordinary share - basic	(1.04)	0.27	(3.15)	(2.34)	(2.26)
Net (loss) income per ordinary share - diluted	(1.04)	0.25	(3.15)	(2.34)	(2.26)
Selected Statement of Cash Flows Data					
Net cash provided by (used in) operating activities	$369,456	$194,166	$27,549	$(54,287)	$(76,641)
Net cash used in investing activities	(1,375,881)	(995,048)	(227,720)	(36,135)	(1,386)
Net cash provided by financing activities	657,074	1,442,481	338,285	66,716	164,308
Payments for acquisitions, net of cash acquired	(1,356,271)	(1,022,361)	(224,220)	(35,000)	—
Net proceeds from the issuance of common stock	4,884	500,454	41,934	6,637	128,518
Net proceeds from the issuance of debt	656,190	1,241,027	286,966	143,598	55,578
Repayment of debt	(4,000)	(299,000)	—	(64,884)	(19,788)

(1) In 2016, we retrospectively adopted Accounting Standards Update No. 2015-03, Interest-Imputation of Interest (Subtopic 835-30): Simplifying the Presentation of Debt Issuance Costs, simplifying the presentation of debt issuance costs. As a result, deferred financing costs of $11.5 million, $6.3 million and $3.2 million that were classified within “total assets” at December 31, 2014, December 31, 2013 and December 31, 2012, respectively, were reclassified to “total debt, net” in the above table to conform prior-period classifications as a result of the new guidance.

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and the related notes appearing at the end of this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. You should read the "Risk Factors" section of this Annual Report on Form 10-K for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

The discussion below contains "forward-looking statements," as defined in Section 21E of the Securities Exchange Act of 1934, as amended, that reflect our current expectations regarding our future growth, results of operations, cash flows, performance and business prospects and opportunities, as well as assumptions made by, and information currently available to, our management. We have tried to identify forward-looking statements by using words such as "anticipate," "believe," "plan," "expect," "intend," "will," and similar expressions, but these words are not the exclusive means identifying forward-looking statements. These statements are based on information currently available to us and are subject to various risks, uncertainties, and other factors, including, but not limited to, those matters discussed in Item 1A. "Risk Factors" in Part I of this Annual Report on Form 10-K, that could cause our actual growth, results of operations, cash flows, performance and business prospects and opportunities to differ materially from those expressed in, or implied by, these statements. Except as expressly required by the federal securities laws, we undertake no obligation to update such factors or to publicly announce the results of any of the forward-looking statements contained herein to reflect future events, developments, or changed circumstances, or for any other reason.

OVERVIEW

Unless otherwise indicated or the context otherwise requires, references to the "Company", "we", "us" and "our" refer to Horizon Pharma plc and its consolidated subsidiaries, including its predecessor, Horizon Pharma, Inc., or HPI. All references to "Vidara" are references to Horizon Pharma plc (formerly known as Vidara Therapeutics International Public Limited Company) and its consolidated subsidiaries prior to the effective time of the merger of the businesses of HPI and Vidara on September 19, 2014, or the Vidara Merger. The disclosures in this report relating to the pre-Vidara Merger business of Horizon Pharma plc, unless noted as being the business of Vidara prior to the Vidara Merger, pertain to the business of HPI prior to the Vidara Merger.

Our Business

We are a biopharmaceutical company focused on improving patients' lives by identifying, developing, acquiring and commercializing differentiated and accessible medicines that address unmet medical needs. We market eleven medicines through our orphan, rheumatology and primary care business units. Our marketed medicines are ACTIMMUNE® (interferon gamma-1b), BUPHENYL® (sodium phenylbutyrate) Tablets and Powder, DUEXIS® (ibuprofen/famotidine), KRYSTEXXA® (pegloticase), MIGERGOT® (ergotamine tartrate & caffeine suppositories), PENNSAID® (diclofenac sodium topical solution) 2% w/w, or PENNSAID 2%, PROCYSBI® (cysteamine bitartrate) delayed-release capsules, QUINSAIR™ (aerosolized form of levofloxacin), RAVICTI® (glycerol phenylbutyrate) Oral Liquid, RAYOS® (prednisone) delayed-release tablets and VIMOVO® (naproxen/esomeprazole magnesium).

We developed DUEXIS and RAYOS, known as LODOTRA® outside the United States, acquired the U.S. rights to VIMOVO from AstraZeneca AB, or AstraZeneca, in November 2013, acquired certain rights to ACTIMMUNE as a result of the Vidara Merger in September 2014, acquired the U.S. rights to PENNSAID 2% from Nuvo Research Inc., or Nuvo, in October 2014, acquired RAVICTI and BUPHENYL, known as AMMONAPS® in certain European countries, as a result of our acquisition of Hyperion Therapeutics Inc., or Hyperion, in May 2015, acquired KRYSTEXXA and the U.S. rights to MIGERGOT as a result of our acquisition of Crealta Holdings LLC., or Crealta,

in January 2016 and acquired PROCYSBI and QUINSAIR as a result of our acquisition of Raptor Pharmaceutical Corp., or Raptor, in October 2016.

On January 13, 2016, we completed our acquisition of Crealta for approximately $539.7 million, including cash acquired of $24.9 million. Following completion of the acquisition, Crealta became our wholly owned subsidiary and was renamed Horizon Pharma Rheumatology LLC.

On May 18, 2016, we entered into a definitive agreement with Boehringer Ingelheim International GmbH, or Boehringer Ingelheim International, to acquire certain rights to interferon gamma-1b, which Boehringer Ingelheim International currently commercializes under the trade names IMUKIN®, IMUKINE®, IMMUKIN® and IMMUKINE® in an estimated thirty countries primarily in Europe and the Middle East. Under the terms of the agreement, we paid Boehringer Ingelheim International €5.0 million ($5.6 million when converted using a Euro-to-Dollar exchange rate at date of payment of 1.1132) upon signing and will pay €20.0 million upon closing, for certain rights for interferon gamma-1b in all territories outside of the United States, Canada and Japan, as we currently hold marketing rights to interferon gamma-1b in these territories. We currently market interferon gamma-1b as ACTIMMUNE in the United States. The transaction is expected to close in 2017 and we are continuing to work with Boehringer Ingelheim International to enable the transfer of applicable marketing authorizations. We recorded an impairment charge of €5.0 million ($5.3 million when converted using a Euro-to-Dollar exchange rate at date of impairment of 1.052) during the three months ended December 31, 2016 to fully write off the value of the initial payment on our consolidated balance sheet, and upon closing we expect to record the additional €20.0 million payment as an expense in our consolidated statement of comprehensive (loss) income. See “Results from Phase 3 Study of ACTIMMUNE (interferon gamma-1b) in Friedreich's Ataxia” section below for further details.

On October 25, 2016, we completed our acquisition of Raptor in which we acquired all of the issued and outstanding shares of Raptor’s common stock for $9.00 per share in cash. The total consideration was $860.8 million, including cash acquired of $24.9 million and $56.0 million to repay Raptor’s outstanding debt. Following completion of the acquisition, Raptor became our wholly owned subsidiary and converted to a limited liability company, changing its name to Horizon Pharmaceutical LLC. We financed the transaction through $300.0 million aggregate principal amount of 8.75% Senior Notes due 2024, or the 2024 Senior Notes, $375.0 million aggregate principal amount of loans pursuant to an amendment to our existing credit agreement and cash on hand.

Part of our commercial strategy for RAYOS and our primary care medicines is to offer physicians the opportunity to have their patients fill prescriptions through pharmacies participating in our HorizonCares patient access program. For commercial patients who are prescribed our primary care medicines or RAYOS, the HorizonCares program offers co-pay assistance when a third-party commercial payer covers a prescription but requires an eligible patient to pay a co-pay or deductible, and offers full subsidization when a third-party commercial payer rejects coverage for an eligible patient. During 2016, we entered into business arrangements with pharmacy benefit managers, or PBMs, and other payers to secure formulary status and reimbursement of our medicines, such as our arrangements with Express Scripts, Inc., or Express Scripts, CVS Caremark and Prime Therapeutics LLC. While we believe that this strategy will result in broader inclusion of certain of our primary care medicines on healthcare plan formularies, and therefore increase payer reimbursement and lower our cost of providing patient access programs, these arrangements generally require us to pay administrative and rebate payments to the PBMs and/or other payers.

We market our medicines in the United States through our field sales force, which numbered approximately 480 representatives as of December 31, 2016. Our strategy is to continue to build a well-balanced, diversified, high-growth biopharmaceutical company. We are executing this through the successful commercialization of our existing medicines, a strong commitment to patient access and support and business development efforts focused on transformative acquisitions to accelerate our rare disease leadership as well as on-market and development-stage medicines to fill out our pipeline.

We are building a sustainable biopharmaceutical company by helping ensure that patients have access to their medicines and support services, and by investing in the further development of medicines for patients with rare or underserved diseases. Our growing business is diversified across three business units: orphan, rheumatology and primary care, and is driven by a successful commercial model that focuses on differentiated, long-life medicines, innovative patient access programs and a disciplined business development strategy.

96

Results from Phase 3 Study of ACTIMMUNE (interferon gamma-1b) in Friedreich's Ataxia

On December 8, 2016, we announced that the Phase 3 trial, Safety, Tolerability and Efficacy of ACTIMMUNE Dose Escalation in Friedreich's Ataxia study, or STEADFAST, evaluating ACTIMMUNE for the treatment of Friedreich's ataxia, or FA, did not meet its primary endpoint of a statistically significant change from baseline in the modified Friedreich's Ataxia Rating Scale, or FARS-mNeuro, at twenty-six weeks versus treatment with placebo and that the secondary endpoints did not meet statistical significance, or the FA announcement. No new safety findings were identified on initial review of data other than those already noted in the ACTIMMUNE prescribing information for approved indications. We, in conjunction with the independent Data Safety Monitoring Board, the principal investigator and the Friedreich's Ataxia Research Alliance, or FARA, Collaborative Clinical Research Network in FA, determined that, based on the trial results, the STEADFAST program would be discontinued, including the twenty-six week extension study and the long-term safety study.

Following the FA announcement, we recorded the following amounts in our consolidated statement of comprehensive loss during the year ended December 31, 2016 (in thousands):

Description	Financial Statement Line Item	Amount Loss/(Gain)	Note
Impairment of in-process research and development	Impairment of in-process research and development	$ 66,000	1
Impairment of non-current asset	General and administrative expenses	5,260	2
Loss on inventory purchase commitments	Cost of goods sold	14,287	3
Remeasurement of contingent royalty liabilities	Cost of goods sold	(2,480)	4
Clinical trial wind-down costs	Research and development expenses	3,966	5
Total		$ 87,033	

Note 1 In-process research and development, or IPR&D, related to the research and development project to evaluate ACTIMMUNE in the treatment of FA, which we acquired in the Vidara Merger. At the time of the Vidara Merger, IPR&D was considered separable from the business as the project could be sold to a third party, and we assigned a fair value of $66.0 million to the intangible asset using an income approach in our purchase accounting. Following the FA announcement, we determined that the IPR&D has no alternative use or economic value, and we recorded an impairment charge during the three months ended December 31, 2016 to fully write off the value of the asset on our consolidated balance sheet.

Note 2 As described above, on May 18, 2016, we entered into a definitive agreement with Boehringer Ingelheim International to acquire certain rights to interferon gamma-1b, and we paid Boehringer Ingelheim International €5.0 million upon signing. The purchase price was determined with the expectation that the STEADFAST study would be successful. Following the FA announcement, we determined that this payment, which was recorded in "other assets" on our consolidated balance sheet was impaired, and we recorded an impairment charge during the three months ended December 31, 2016 to fully write off the value of the asset ($5.3 million when converted using a Euro-to-Dollar exchange rate at date of impairment of 1.052). Upon closing, we will pay Boehringer Ingelheim International an additional €20.0 million and we expect to record this payment as an expense in our consolidated statement of comprehensive (loss) income.

Note 3 During the year ended December 31, 2016, we committed to purchase additional units of ACTIMMUNE from Boehringer Ingelheim RCV GmbH & Co KG, or Boehringer Ingelheim. These additional units of ACTIMMUNE were intended to cover anticipated demand if the results of the STEADFAST study of ACTIMMUNE for the treatment of FA had been successful. Following the FA announcement, we recorded a loss of $14.3 million for firm, non-cancellable and unconditional purchase commitments for quantities in excess of our current forecasts for future demand. During the year ended December 31, 2016, we also committed to incur an additional $14.9 million for

the harmonization of the drug substance manufacturing process with Boehringer Ingelheim. These additional costs have not been included in our consolidated statement of comprehensive loss or our consolidated balance sheet at December 31, 2016.

Note 4 At the time of the Vidara Merger, we assigned a fair value to a contingent liability for royalties potentially payable under previously existing royalty and licensing agreements related to ACTIMMUNE, which included an amount of $2.5 million for estimated future sales of ACTIMMUNE for FA. Following the FA announcement, we recorded an adjustment to reduce the contingent royalty liability for ACTIMMUNE by $2.5 million as we do not anticipate future sales of ACTIMMUNE for FA.

Note 5 Following the FA announcement, we recorded an amount of $4.0 million at December 31, 2016 related to costs anticipated to be incurred to discontinue the STEADFAST study. These costs will be incurred without economic benefit to us, and represent costs to us to wind down the study under U.S. Food and Drug Administration, or FDA, protocol.

RESULTS OF OPERATIONS

Year Ended December 31, 2016 Compared to Year Ended December 31, 2015

	For the Years Ended December 31,		Increase / (Decrease)	Change %
	2016	2015		
	(in thousands)			
Net sales	$981,120	$757,044	$224,076	30 %
Cost of goods sold	393,272	219,502	173,770	79 %
Gross profit	587,848	537,542	50,306	9 %
Operating expenses				
Research and development	60,707	41,865	18,842	45 %
Sales and marketing	320,366	220,444	99,922	45 %
General and administrative	287,942	219,861	68,081	31 %
Impairment of in-process research and development	66,000	—	66,000	*
Total operating expenses	735,015	482,170	252,845	52 %
Operating (loss) income	(147,167)	55,372	(202,539)	(366)%
Other income (expense), net:				
Interest expense, net	(86,610)	(69,900)	(16,710)	24 %
Foreign exchange loss	(1,005)	(1,237)	232	(19)%
Loss on induced conversion of debt and debt extinguishment	—	(77,624)	77,624	*
Loss on sale of long-term investments	—	(29,032)	29,032	*
Other income (expense), net	6,697	(10,291)	16,988	(165)%
Total other expense, net	(80,918)	(188,084)	107,166	(57)%
Loss before benefit for income taxes	(228,085)	(132,712)	(95,373)	72 %
Benefit for income taxes	(61,251)	(172,244)	110,993	(64)%
Net (loss) income	$(166,834)	$39,532	$(206,366)	(522)%

*Percentage change is not meaningful.

Net sales. Net sales increased $224.1 million, or 30%, to $981.1 million during the year ended December 31, 2016, from $757.0 million during the year ended December 31, 2015.

The following table presents a summary of total net sales attributed to geographic sources for the years ended December 31, 2016 and 2015 (in thousands):

Year Ended December 31, 2016 Year Ended December 31, 2015

		% of Total Net Sales			% of Total Net Sales	
	Amount			Amount		
United States	$ 964,041	98	%	$ 744,036	98	%
Rest of world	17,079	2	%	13,008	2	%
Total net sales	$ 981,120			$ 757,044		

The following table reflects the components of net sales for the years ended December 31, 2016 and 2015 (in thousands):

	Year Ended December 31,		Change	Change
	2016	2015	$	%
PENNSAID 2%	$304,433	$147,010	$157,423	107 %
DUEXIS	173,728	190,357	(16,629)	-9 %
RAVICTI	151,532	86,875	64,657	74 %
VIMOVO	121,315	166,672	(45,357)	-27 %
ACTIMMUNE	104,624	107,444	(2,820)	-3 %
KRYSTEXXA	91,102	—	91,102	*
RAYOS	47,356	40,329	7,027	17 %
PROCYSBI	25,268	—	25,268	*
BUPHENYL	16,879	13,458	3,421	25 %
MIGERGOT	4,651	—	4,651	*
LODOTRA	4,193	4,899	(706)	-14 %
QUINSAIR	1,039	—	1,039	*
Litigation settlement	(65,000)	—	(65,000)	*
Total net sales	$981,120	$757,044	$224,076	30 %

*Percentage change is not meaningful.

The increase in net sales during the year ended December 31, 2016 was primarily due to the growth in net sales of PENNSAID 2%, the full-period recognition of RAVICTI sales in 2016, compared to a partial period recognition in 2015 following the acquisition of Hyperion in May 2015, the recognition of KRYSTEXXA sales following the acquisition of Crealta in January 2016 and the recognition of PROCYSBI sales following the acquisition of Raptor in October 2016, offset by the $65.0 million litigation settlement with Express Scripts along with lower net sales of VIMOVO and DUEXIS.

PENNSAID 2%. Net sales increased $157.4 million, or 107%, to $304.4 million during the year ended December 31, 2016, from $147.0 million during the year ended December 31, 2015. Net sales increased by approximately $87.5 million due to higher net pricing and $69.9 million resulting from prescription volume growth.

DUEXIS. Net sales decreased $16.6 million, or 9%, to $173.7 million during the year ended December 31, 2016, from $190.3 million during the year ended December 31, 2015. Net sales decreased by approximately $50.4 million due to lower net pricing resulting from higher co-pay and other patient assistance, offset by an increase of approximately $33.8 million resulting from prescription volume growth.

RAVICTI. Net sales increased $64.7 million, or 74%, to $151.5 million during the year ended December 31, 2016, from $86.8 million during the year ended December 31, 2015. Net sales increased by approximately $55.7 million resulting from prescription volume growth and $9.0 million due to higher net pricing. We began recognizing RAVICTI sales following the acquisition of Hyperion in May 2015, therefore only a partial period of RAVICTI sales were recognized during the year ended December 31, 2015, compared with full-period recognition of sales during the year ended December 31, 2016.

VIMOVO. Net sales decreased $45.4 million, or 27%, to $121.3 million during the year ended December 31, 2016, from $166.7 million during the year ended December 31, 2015. Net sales decreased by approximately $35.9 million due to lower net pricing resulting from higher co-pay and other patient assistance and approximately $9.5 million

resulting from lower prescription volumes.

ACTIMMUNE. Net sales decreased $2.8 million, or 3%, to $104.6 million during the year ended December 31, 2016, from $107.4 million during the year ended December 31, 2015. Net sales decreased by approximately $8.8 million resulting from prescription volume decreases, offset by an increase of approximately $6.0 million due to higher net pricing.

KRYSTEXXA. Net sales were $91.1 million during the year ended December 31, 2016. We began recognizing KRYSTEXXA sales following the acquisition of Crealta in January 2016.

RAYOS. Net sales increased $7.0 million, or 17%, to $47.4 million during the year ended December 31, 2016, from $40.4 million during the year ended December 31, 2015. Net sales increased by approximately $8.4 million resulting from prescription volume growth, offset by a decrease of approximately $1.4 million due to lower net pricing.

PROCYSBI. Net sales were $25.3 million during the year ended December 31, 2016. We began recognizing PROCYSBI sales following the acquisition of Raptor in October 2016.

BUPHENYL. Net sales increased $3.4 million, or 25%, to $16.9 million during the year ended December 31, 2016, from $13.5 million during the year ended December 31, 2015. We began recognizing BUPHENYL sales following the acquisition of Hyperion in May 2015, therefore only a partial period of BUPHENYL sales were recognized during the year ended December 31, 2015, compared with full-period recognition of sales during the year ended December 31, 2016.

MIGERGOT. Net sales were $4.7 million during the year ended December 31, 2016. We began recognizing MIGERGOT sales following the acquisition of Crealta in January 2016.

LODOTRA. Net sales decreased $0.7 million, or 14%, to $4.2 million during the year ended December 31, 2016, from $4.9 million during the year ended December 31, 2015. The decrease was due to fewer shipments to our European distribution partner, Mundipharma International Corporation Limited, or Mundipharma. LODOTRA sales to Mundipharma occur at the time we ship, based on Mundipharma's estimated requirements. Accordingly, LODOTRA sales are not linear or directly tied to Mundipharma's in-market sales and can therefore fluctuate significantly.

QUINSAIR. Net sales were $1.0 million during the year ended December 31, 2016. We began recognizing QUINSAIR sales following the acquisition of Raptor in October 2016.

In September 2016, we entered into a settlement agreement and mutual release with Express Scripts pursuant to which we and Express Scripts were released from any and all claims relating to our then ongoing litigation without admitting any fault or wrongdoing and we agreed to pay Express Scripts $65.0 million. This settlement has been accounted for as a reduction of "net sales" in the consolidated statement of comprehensive loss for the year ended December 31, 2016.

The table below reconciles our gross sales to net sales for the years ended December 31, 2016 and 2015 (in millions):

	Year Ended December 31, 2016		Year Ended December 31, 2015	
	Amount	% of Gross Sales	Amount	% of Gross Sales
Gross sales	$3,234.2	100.0%	$2,057.3	100.0%
Adjustments to gross sales:				
Prompt pay discounts	(64.0)	(2.0)%	(41.3)	(2.0)%
Medicine returns	(17.1)	(0.5)%	(14.4)	(0.7)%
Co-pay and other patient assistance	(1,701.3)	(52.6)%	(1,020.2)	(49.6)%
Wholesaler fees and commercial rebates	(133.7)	(4.2)%	(66.1)	(3.2)%
Government rebates and chargebacks	(272.0)	(8.4)%	(158.3)	(7.7)%
Litigation settlement	(65.0)	(2.0)%	—	—

Total adjustments	(2,253.1)	(69.7)%	(1,300.3)	(63.2)%
Net sales	$981.1	30.3 %	$757.0	36.8 %

During the year ended December 31, 2016, co-pay and other patient assistance, as a percentage of gross sales, increased to 52.6% from 49.6% during the year ended December 31, 2015. The increase was primarily due to the expansion of our HorizonCares program during 2016.

On a quarter-to-quarter basis, our net sales have traditionally been lower in first half of the year, particularly in the first quarter, with the second half of the year representing a greater share of overall net sales each year. This is due to annual managed care plan changes and the re-setting of patient deductibles at the beginning of each year, resulting in higher co-pay and other patient assistance costs as patients meet their annual deductibles during the first and second quarters, and higher net sales in the second half of the year after patients meet their deductibles and healthcare plans reimburse a greater portion of the total cost of our medicines.

Cost of Goods Sold. Cost of goods sold increased $173.8 million to $393.3 million during the year ended December 31, 2016, from $219.5 million during the year ended December 31, 2015. As a percentage of net sales, cost of goods sold was 40.0% during the year ended December 31, 2016, compared to 29.0% during the year ended December 31, 2015. The large increase in costs of goods sold as a percentage of net sales was due to the one-time reduction in net sales in the year ended December 31, 2016 as a result of the litigation settlement with Express Scripts and an increase in cost of goods sold in the year ended December 31, 2016. The increase in cost of goods sold was primarily a result of higher intangible amortization expense of $84.0 million and increased inventory step-up expense of $59.6 million. Other factors that caused cost of goods sold to increase during the year included a $14.3 million expense related to a loss on inventory purchase commitments, higher royalty accretion expense of $20.5 million and a $16.2 million increase in direct and indirect costs associated with higher sales, offset by a $20.8 million decrease in charges relating to the remeasurement of contingent royalty liabilities.

The increase in intangible amortization of $84.0 million during the year ended December 31, 2016 compared to the prior year was due to a $33.9 million increase in amortization expense related to RAVICTI and BUPHENYL intangible assets (acquired in May 2015), $35.9 million amortization of developed technology related to KRYSTEXXA and MIGERGOT (acquired in January 2016), $14.0 million amortization of developed technology related to PROCYSBI (acquired in October 2016) and $0.2 million increase in amortization related to ACTIMMUNE.

Because inventory step-up expense is acquisition-related, will not continue indefinitely and has a significant effect on our gross profit, gross margin percentage and net income (loss) for all affected periods, we disclose balance sheet and income statement amounts related to inventory step-up within the notes to the consolidated financial statements. The increase in inventory step-up expense of $59.6 million during the year ended December 31, 2016 compared to the prior year was due to $48.8 million recorded during the year ended December 31, 2016 related to KRYSTEXXA and MIGERGOT inventory step-up (acquired in January 2016) and $22.4 million related to PROCYSBI and QUINSAIR inventory step-up (acquired in October 2016), compared to $8.4 million recorded during the year ended December 31, 2015 related to RAVICTI and BUPHENYL inventory step-up (acquired in May 2015) and $3.2 million related to ACTIMMUNE inventory step-up (acquired in September 2014).

Research and Development Expenses. Research and development expenses increased $18.8 million to $60.7 million during the year ended December 31, 2016, from $41.9 million during the year ended December 31, 2015. The increase in research and development expenses during the year ended December 31, 2016 was primarily attributable to $2.8 million of higher share-based compensation, an increase of $5.5 million in other employee costs resulting from growth in our headcount following the Hyperion, Crealta and Raptor acquisitions, $4.0 million related to costs to be incurred in the winding down of the STEADFAST study, an increase of $3.0 million in general research and development costs, a $2.0 million upfront fee paid for a license of a patent and an increase of $1.5 million in regulatory submission fees.

Sales and Marketing Expenses. Sales and marketing expenses increased $99.9 million to $320.4 million during the year ended December 31, 2016, from $220.5 million during the year ended December 31, 2015. The increase in sales and marketing expenses was in line with the significant growth in gross sales and an increase in the number of sales representatives over the same period, which primarily contributed to an increase of $52.2 million in employee costs resulting from increased staffing of our field sales force and an increase of $47.7 million in marketing and commercialization expenses following the Hyperion, Crealta and Raptor acquisitions.

General and Administrative Expenses. General and administrative expenses increased $68.1 million to $287.9 million during the year ended December 31, 2016, from $219.8 million during the year ended December 31, 2015. The increase was attributable to $22.4 million of higher share-based compensation, $10.2 million in other employee costs resulting from growth in our headcount following the Hyperion, Crealta and Raptor acquisitions, an increase of $36.8 million in costs following the Hyperion, Crealta and Raptor acquisitions and $5.3 million due to the impairment of the initial amount paid to Boehringer Ingelheim International for certain rights to interferon gamma-1b, offset by a decrease of $6.6 million in acquisition-related general and administrative expenses.

Impairment of In-Process Research and Development. At the time of the Vidara Merger, IPR&D was considered separable from the business as the project could be sold to a third party, and we assigned a fair value of $66.0 million to the intangible asset. Following the FA announcement, we determined that the IPR&D has no alternative use or economic value, and we recorded an impairment charge during the three months ended December 31, 2016 to fully write off the value of the asset on our consolidated balance sheet.

Interest Expense, Net. Interest expense, net, increased $16.7 million to $86.6 million during the year ended December 31, 2016, from $69.9 million during the year ended December 31, 2015. The increased interest expense, net, was primarily due to full-period recognition during the year ended December 31, 2016 of the interest on higher borrowings to fund the acquisition of Hyperion in May 2015, including our $475.0 million aggregate principal amount of 6.625% Senior Notes due 2023, or the 2023 Senior Notes, six-year $400.0 million term loan facility, or the 2015 Term Loan Facility, and $400.0 million aggregate principal amount of 2.50% Exchangeable Senior Notes due 2022, or the Exchangeable Senior Notes, as compared to partial period recognition of the interest on these borrowings during the year ended December 31, 2015 and our lower prior year borrowings under our prior five-year $300.0 million term loan facility, or 2014 Term Loan Facility. We also incurred additional interest expense following our borrowings to fund the acquisition of Raptor in October 2016, including our additional $375.0 million additional borrowings under the 2015 Term Loan Facility, or the 2016 Incremental Loan Facility, and the 2024 Senior Notes.

Foreign Exchange Loss. During the year ended December 31, 2016, we reported a foreign exchange loss of $1.0 million.

Loss on Induced Conversion of Debt and Debt Extinguishment. The loss on induced conversion of debt and debt extinguishment during the year ended December 31, 2015 of $77.6 million was composed of $20.7 million related to the induced conversions of our 5.00% Convertible Senior Notes due 2018, or Convertible Senior Notes, including $10.0 million for cash inducement payments, a $10.1 million charge for the extinguishment of debt and $0.6 million of expenses, and $56.9 million related to the extinguishment of the 2014 Term Loan Facility, consisting of a $45.4 million early redemption premium and a $11.5 million charge for the extinguishment of debt. The number of shares issued equaled the number of shares based on the underlying conversion option. The aggregate cash payments to the holders for additional exchange consideration were recorded as part of the extinguishment loss. There were no induced conversions in 2016.

Loss on Sale of Long-Term Investments. The loss on sale of long-term investments during the year ended December 31, 2015 was $29.0 million. During the third quarter of 2015, we purchased 2,250,000 shares of common stock of Depomed, Inc., or Depomed, representing 3.75% of Depomed's then outstanding common stock. The shares were acquired at a cost of $71.8 million. During the fourth quarter of 2015, following our decision to withdraw our offer to acquire Depomed, we sold all of our shares in Depomed, receiving sales proceeds of $42.8 million and recognized a realized loss of $29.0 million. There were no sales of long-term investments in 2016.

Other Income (Expense) net. Other income, net during the year ended December 31, 2016 was primarily related to the release of a contingent liability of $6.9 million which was assumed as part of the Crealta acquisition. In December 2015, Crealta considered it probable that the manufacture of the active pharmaceutical ingredient, or API, for KRYSTEXXA would be moved out of Israel based on a notice of termination provided by its contract manufacturer, therefore triggering a repayment obligation to Israel's Office of the Chief Scientist. As a result, Crealta established a $6.9 million contingent liability reserve in its December 31, 2015 financial statements. As of the date of our acquisition of Crealta, the $6.9 million repayment obligation was still probable. Therefore, it was recorded as an assumed liability in "other long-term liabilities" as part of the acquisition accounting for Crealta. During the third quarter of 2016, Horizon management negotiated a new amendment to the manufacturing agreement and it was determined that the manufacture of the KRYSTEXXA API would not be moved outside of Israel and thus the repayment of the $6.9 million would not be triggered. The contingent liability was released to "other income (expense)" during the year ended December 31, 2016 as it was a reversal of an assumed liability and therefore did not represent income from operations. Other expense, net, during the year ended December 31, 2015 totaled $10.3 million, which primarily included the fees related to the Hyperion acquisition financing commitment.

Benefit for Income Taxes. During the year ended December 31, 2016, we recorded an income tax benefit of $61.3 million compared to $172.2 million during the year ended December 31, 2015. The recognition of income tax benefit during the year ended December 31, 2016 was primarily attributable to the mix of income and losses amongst jurisdictions, a notional interest deduction and the change in our U.S. state effective tax rate. The recognition of an

income tax benefit during the year ended December 31, 2015 was primarily attributable to the release of $103.1 million in valuation allowances in the U.S. tax consolidation group due to the recognition of significant deferred tax liabilities as a result of the Hyperion acquisition as well as the ability to recognize a tax benefit on losses incurred in the United States.

Year Ended December 31, 2015 Compared to Year Ended December 31, 2014

	For the Years Ended December 31,		Increase / (Decrease)	Change %
	2015	2014		
	(in thousands)			
Net sales	$757,044	$296,955	$460,089	155 %
Cost of goods sold	219,502	78,753	140,749	179 %
Gross profit	537,542	218,202	319,340	146 %
Operating expenses				
Research and development	41,865	17,460	24,405	140 %
Sales and marketing	220,444	120,276	100,168	83 %
General and administrative	219,861	88,957	130,904	147 %
Total operating expenses	482,170	226,693	255,477	113 %
Operating income (loss)	55,372	(8,491)	63,863	752 %
Other income (expense), net:				
Interest expense, net	(69,900)	(23,826)	46,074	193 %
Foreign exchange loss	(1,237)	(3,905)	(2,668)	(68)%
Loss on derivative fair value	—	(214,995)	(214,995)	(100)%
Loss on induced conversion and debt extinguishment	(77,624)	(29,390)	48,234	164 %
Loss on sale of long-term investments	(29,032)	—	29,032	100 %
Bargain purchase gain	—	22,171	22,171	100 %
Other expense	(10,291)	(11,251)	(960)	(9)%
Total other expense, net	(188,084)	(261,196)	(73,112)	28 %
Loss before benefit for income taxes	(132,712)	(269,687)	(136,975)	(51)%
Benefit for income taxes	(172,244)	(6,084)	166,160	2,731 %
Net income (loss)	$39,532	$(263,603)	$303,135	115 %

Net sales. Net sales increased $460.1 million, or 155%, to $757.0 million during the year ended December 31, 2015, from $296.9 million during the year ended December 31, 2014.

The following table presents a summary of total net sales attributed to geographic sources for the years ended December 31, 2015 and 2014 (in thousands):

	Year Ended December 31, 2015		Year Ended December 31, 2014	
	Amount	% of Total Net Sales	Amount	% of Total Net Sales
United States	$ 744,036	98 %	$ 290,396	98 %
Rest of world	13,008	2 %	6,559	2 %
Total net sales	$ 757,044		$ 296,955	

The following table reflects the components of net sales for the years ended December 31, 2015 and 2014:

	Year Ended December 31,		Change	Change
	2015	2014	$	%
	(in thousands)			
DUEXIS	$190,357	$83,243	$107,114	129 %
VIMOVO	166,672	162,954	3,718	2 %
PENNSAID 2%	147,010	-	147,010	*
ACTIMMUNE	107,444	25,251	82,193	326 %
RAVICTI	86,875	-	86,875	*
RAYOS	40,329	19,020	21,309	112 %
BUPHENYL	13,458	-	13,458	*
LODOTRA	4,899	6,487	(1,588)	(25 %)
Total net sales	$757,044	$296,955	$460,089	155 %

*Percentage change is not meaningful.

The increase in net sales during the year ended December 31, 2015 was primarily due to the recognition of PENNSAID 2% sales beginning in January 2015 following our acquisition of the U.S. rights to PENNSAID 2% from Nuvo in October 2014, the growth in sales of DUEXIS, the recognition of RAVICTI and BUPHENYL sales following the acquisition of Hyperion in May 2015, full-period recognition of ACTIMMUNE sales during the year ended December 31, 2015 compared with partial-period recognition during the year ended December 31, 2014, following the Vidara Merger on September 19, 2014, and the growth of RAYOS sales.

DUEXIS. Net sales increased $107.1 million, or 129%, to $190.4 million during the year ended December 31, 2015, from $83.3 million during the year ended December 31, 2014. DUEXIS net sales increased $58.0 million as a result of prescription volume growth driven by the expansion of our field sales force and increased $49.1 million due to higher net pricing resulting from wholesale acquisition cost, or WAC, price increases partially offset by additional patient co-pay reimbursements.

VIMOVO. Net sales increased $3.7 million, or 2%, to $166.7 million during the year ended December 31, 2015, from $163.0 million during the year ended December 31, 2014. VIMOVO net sales increased by $23.5 million resulting from prescription volume growth, offset by a decrease of $19.8 million due to lower net pricing. While we have increased the WAC price for VIMOVO over the last 12 months, the increases were more than offset by additional patient co-pay reimbursements.

PENNSAID 2%. Net sales were $147.0 million during the year ended December 31, 2015. We began recognizing PENNSAID 2% sales in January 2015 following our acquisition of the U.S. rights to PENNSAID 2% from Nuvo in October 2014.

ACTIMMUNE. Net sales increased $82.2 million, or 326%, to $107.5 million during the year ended December 31, 2015, from $25.3 million during the year ended December 31, 2014. Net sales increased by approximately $47.1 million resulting from prescription volume growth and $35.1 million due to higher net pricing. We began recognizing ACTIMMUNE sales following the closing of the Vidara Merger on September 19, 2014, therefore only a partial period of ACTIMMUNE sales were recognized during the year ended December 31, 2014, compared with full-period recognition of sales during the year ended December 31, 2015.

RAVICTI. Net sales were $86.9 million during the year ended December 31, 2015. We began recognizing RAVICTI sales following the acquisition of Hyperion in May 2015.

RAYOS. Net sales increased $21.3 million, or 112%, to $40.3 million during the year ended December 31, 2015, from $19.0 million during the year ended December 31, 2014. The increase was primarily due to prescription growth and net price increases resulting in higher net sales of approximately $20.2 million and $1.1 million, respectively.

BUPHENYL. Net sales were $13.5 million during the year ended December 31, 2015. We began recognizing BUPHENYL sales following the acquisition of Hyperion in May 2015.

LODOTRA. Net sales decreased $1.6 million, or 25%, to $4.9 million during the year ended December 31, 2015, from $6.5 million during the year ended December 31, 2014. The decrease was due to fewer shipments to our European distribution partner, Mundipharma. LODOTRA sales to Mundipharma occur at the time we ship, based on Mundipharma’s estimated requirements. Accordingly, LODOTRA sales are not linear or directly tied to Mundipharma’s in-market sales and can therefore fluctuate significantly.

The table below reconciles our gross sales to net sales for the years ended December 31, 2015 and 2014 (in millions):

	Year Ended December 31, 2015		Year Ended December 31, 2014	
	Amount	% of Gross Sales	Amount	% of Gross Sales
Gross sales	$2,057.3	100.0%	$600.8	100.0%
Adjustments to gross sales:				
Prompt pay discounts	(41.3)	(2.0)%	(11.0)	(1.8)%
Medicine returns	(14.4)	(0.7)%	(7.2)	(1.2)%
Co-pay and other patient assistance	(1,020.2)	(49.6)%	(138.3)	(23.1)%
Wholesaler fees and commercial rebates	(66.1)	(3.2)%	(102.0)	(17.0)%
Government rebates and chargebacks	(158.3)	(7.7)%	(45.3)	(7.5)%
Total adjustments	(1,300.3)	(63.2)%	(303.8)	(50.6)%
Net sales	$757.0	36.8 %	$297.0	49.4 %

During the year ended December 31, 2015, co-pay and other patient assistance, as a percentage of gross sales, increased to 49.6% from 23.1% during the year ended December 31, 2014. The increase was primarily due to the rollout of our HorizonCares program to all sales territories during 2015 which helped ensure patient access to our medicines in the face of exclusionary actions by certain PBMs. During the year ended December 31, 2015, wholesaler fees and commercial rebates, as a percentage of gross sales, decreased to 3.2% from 17.0% during the year ended December 31, 2014, primarily due to a decrease in our managed care rebates following the termination of our agreements with CVS Caremark and Express Scripts in 2014.

Effective January 1, 2015, two significant PBMs placed DUEXIS and VIMOVO on their exclusion lists, which resulted in a loss of reimbursement for patients whose healthcare plans have adopted these PBM exclusion lists. However, this action did not negatively impact sales volume for either medicine. In fact, with successful adoption of our HorizonCares program by physicians, we saw increases in sales volume for both medicines. During the year ended December 31, 2015, DUEXIS sales volumes increased by 70% and VIMOVO sales volumes increased by 14%, each, when compared to the year ended December 31, 2014.

Cost of Goods Sold. Cost of goods sold increased $140.7 million to $219.5 million during the year ended December 31, 2015, from $78.8 million during the year ended December 31, 2014. As a percentage of net sales, cost of goods sold was 29.0% during the year ended December 31, 2015 compared to 26.5% during the year ended December 31, 2014. The increase in cost of goods sold was primarily attributable to an increase in intangible amortization expense of $100.0 million, a $19.1 million increase in medicine costs associated with higher sales, higher royalty accretion expense of $11.1 million and a $10.5 million increase in charges relating to the remeasurement of contingent royalty liabilities.

The increase in intangible amortization of $100.0 million during the year ended December 31, 2015 compared to the prior year was primarily due to increases in intangible amortization expense of $62.2 million in relation to RAVICTI and BUPHENYL (acquired on May 7, 2015), $31.1 million relating to ACTIMMUNE developed technology (acquired on September 19, 2014) and $7.3 million relating to PENNSAID 2% (U.S. rights acquired in October 2014).

Research and Development Expenses. Research and development expenses increased $24.4 million to $41.9 million during the year ended December 31, 2015, from $17.5 million during the year ended December 31, 2014. The increase in research and development expenses during the year ended December 31, 2015 was primarily associated with $17.1 million in research and development expenses for ACTIMMUNE, RAVICTI and BUPHENYL, which included $4.0 million related to the STEADFAST study. We also recorded an increase of $5.1 million in share-based compensation expense during the year ended December 31, 2015 compared to the year ended December 31, 2014 as a result of the increase in the number of employees involved in research and development activities following the Vidara Merger and Hyperion acquisition.

Sales and Marketing Expenses. Sales and marketing expenses increased $100.1 million to $220.4 million during the year ended December 31, 2015, from $120.3 million during the year ended December 31, 2014. The increase in sales and marketing expenses reflects the growth in revenue and increase in the number of sales representatives over the same period, and was primarily attributable to an increase of $58.5 million in employee costs, including $18.9 million related to share-based compensation, resulting from the increased staffing of our field sales force and the expansion of our HorizonCares support team. We also recorded an increase of $22.0 million in marketing and commercialization expenses and an increase of $6.8 million in medicine samples distributed.

General and Administrative Expenses. General and administrative expenses increased $130.9 million to $219.9 million during the year ended December 31, 2015, from $89.0 million during the year ended December 31, 2014. The increase in general and administrative expenses was primarily attributable to an increase of $48.6 million in share-based compensation expense, $18.4 million in acquisition-related general and administrative expenses, and $63.9 million related to our growth in headcount, facilities, finance fees, legal fees and information technology expenses following the Vidara Merger and Hyperion acquisition.

Interest Expense, Net. Interest expense, net, increased $46.1 million to $69.9 million during the year ended December 31, 2015, from $23.8 million during the year ended December 31, 2014. The increased interest expense, net, was due to a full year of interest expense in 2015 on borrowings to fund the Vidara Merger in September 2014 and interest on additional borrowings to partially fund the acquisition of Hyperion in May 2015, including the 2023 Senior Notes, the 2015 Term Loan Facility, and the Exchangeable Senior Notes, as compared to our prior year borrowings under the Convertible Senior Notes and 2014 Term Loan Facility.

Foreign Exchange Loss. During the year ended December 31, 2015, we reported a foreign exchange loss of $1.2 million.

Loss on Derivative Revaluation. During the year ended December 31, 2014, we recorded a $215.0 million non-cash charge related to the increase in the fair value of the embedded derivative associated with our Convertible Senior Notes. The loss on the derivative revaluation was primarily due to an increase in the market value of HPI’s common stock during the period from January 1, 2014 until June 27, 2014, the date HPI’s stockholders approved the issuance of in excess of 13,164,951 shares of HPI’s common stock upon conversion of the Convertible Senior Notes. The derivative liability was re-measured to a final fair value and the entire fair value of the derivative liability of $324.4 million was reclassified to additional paid-in capital. As such, there was no derivative revaluation subsequent to June 2014.

Loss on Induced Conversion of Debt and Debt Extinguishment. The loss on induced conversion of debt and debt extinguishment during the year ended December 31, 2015 of $77.6 million was composed of $20.7 million related to the induced conversions of Convertible Senior Notes, including $10.0 million for cash inducement payments, a $10.1 million charge for the extinguishment of debt and $0.6 million of expenses, and $56.9 million related to the extinguishment of the 2014 Term Loan Facility, consisting of a $45.4 million early redemption premium and a $11.5 million charge for the extinguishment of debt. The loss on induced conversion and debt extinguishment during the year ended December 31, 2014 of $29.4 million was a result of the Convertible Senior Notes induced conversions in the fourth quarter of 2014, which consisted of $16.7 million of loss on induced conversion for cash inducement payments, a $11.7 million charge for the extinguishment of debt and $1.0 million of expenses related to the induced debt conversions. The number of shares issued equaled the number of shares based on the underlying conversion option. The aggregate cash payments to the holders for additional exchange consideration were recorded as part of the extinguishment loss.

Loss on Sale of Long-Term Investments. The loss on sale of long-term investments during the year ended December 31, 2015 was $29.0 million. During the third quarter of 2015, we purchased 2,250,000 shares of common stock of Depomed, representing 3.75% of Depomed’s then outstanding common stock. The shares were acquired at a cost of $71.8 million. During the fourth quarter of 2015, following our decision to withdraw our offer to acquire Depomed, we sold all of our shares in Depomed, receiving sales proceeds of $42.8 million and recognized a realized loss of $29.0 million in the consolidated statement of comprehensive income.

Bargain Purchase Gain. During the year ended December 31, 2014, we recorded a bargain purchase gain of $22.2 million in connection with the Vidara Merger, representing the excess of the estimated fair values of net assets acquired over the acquisition consideration paid.

Other Expense, net. Other expense, net, during the year ended December 31, 2015 totaled $10.3 million, which primarily included the fees related to the Hyperion acquisition financing commitment. Other expense during the year ended December 31, 2014 totaled $11.3 million, representing $5.0 million of commitment fees incurred on the bridge financing in place prior to executing the 2014 Term Loan Facility in June 2014, $3.2 million of commitment fees incurred on the 2014 Term Loan Facility prior to its funding on September 19, 2014 and $2.9 million secondary offering expense fees incurred in the November 2014 underwritten public offering.

Benefit for Income Taxes. During the year ended December 31, 2015, we recorded an income tax benefit of $172.2 million compared to $6.1 million during the year ended December 31, 2014. The recognition of income tax benefit during the year ended December 31, 2015 was primarily attributable to the release of $103.1 million in valuation allowances in the U.S. tax consolidation group due to the recognition of significant deferred tax liabilities as a result of the Hyperion acquisition as well as the ability to recognize a tax benefit on losses incurred in the United States.

Non-GAAP Financial Measures

EBITDA, or earnings before interest, taxes, depreciation and amortization, and adjusted EBITDA are used and provided by us as non-GAAP financial measures. We provide certain other financial measures such as non-GAAP adjusted net sales, non-GAAP net income and non-GAAP earnings per share which include adjustments to GAAP figures. The exclusion of the $65.0 million litigation settlement from GAAP net sales is the only adjustment reflected in non-GAAP adjusted net sales for the year ended December 31, 2016. Adjusted EBITDA and non-GAAP net income are intended to provide additional information on our performance, operations and profitability. Adjustments to our GAAP figures as well as EBITDA exclude acquisition-related expenses, charges related to the discontinuation of ACTIMMUNE development for FA, an upfront fee for a license of a patent, the Express Scripts litigation settlement amount, loss on debt extinguishment and loss on sale of long-term investments, as well as non-cash items such as share-based compensation, inventory step-up expense, depreciation and amortization, remeasurement of royalties for medicines acquired through business combinations, royalty accretion, non-cash interest expense, the reversal of a pre-acquisition reserve upon the signing of a contract, intangible and other non-current asset impairment charges and other non-cash adjustments. Certain other special items or substantive events may also be included in the non-GAAP adjustments periodically when their magnitude is significant within the periods incurred. We maintain an established non-GAAP cost policy that guides the determination of what costs will be excluded in non-GAAP measures. We believe that these non-GAAP financial measures, when considered together with the GAAP figures, can enhance an overall understanding of our financial and operating performance. The non-GAAP financial measures are included with the intent of providing investors with a more complete understanding of our historical financial results and trends and to facilitate comparisons between periods and with respect to projected information. In addition, these non-GAAP financial measures are among the indicators our management uses for planning and forecasting purposes and measuring our performance. For example, adjusted EBITDA is used by us as one measure of management performance under certain incentive compensation arrangements. These non-GAAP financial measures should be considered in addition to, and not as a substitute for, or superior to, financial measures calculated in accordance with GAAP. The non-GAAP financial measures used by us may be calculated differently from, and therefore may not be comparable to, non-GAAP financial measures used by other companies.

Beginning in the second quarter of 2016, we modified the method of calculating non-GAAP income tax expense to align with guidance issued by the Securities and Exchange Commission on May 17, 2016. The new methodology calculates the income tax component of non-GAAP net income for each period by adjusting the GAAP tax expense (benefit) for the estimated tax impact of each non-GAAP adjustment based on the statutory income tax rate of the applicable jurisdictions for each non-GAAP adjustment. This new methodology does not reflect any use of net operating loss carryforwards that we potentially may have been able to use if our actual earnings for these periods had been the non-GAAP net income. Previously, we had calculated the income tax component of non-GAAP net income by using the estimated cash taxes that we expected to pay for the period. The non-GAAP net income and diluted net income per share amounts shown in the GAAP to non-GAAP reconciliation tables below are based on the new methodology.

Reconciliations of reported GAAP net sales to non-GAAP adjusted net sales, reported GAAP net (loss) income to EBITDA, adjusted EBITDA and non-GAAP net income, and the related per share amounts, are as follows (in thousands, except share and per share amounts):

	For the Years Ended December 31,		
	2016	2015	2014
GAAP Net Sales	$981,120	$757,044	$296,955
Litigation settlement	65,000	-	-
Non-GAAP Adjusted Net Sales	$1,046,120	$757,044	$296,955

	For the Years Ended December 31,		
	2016	2015	2014
GAAP Net (Loss) Income	$(166,834)	$39,532	$(263,603)
Non-GAAP adjustments:			
Remeasurement of royalties for medicines acquired through business combinations (1)	386	21,151	10,660
Acquisition-related costs	52,874	72,221	48,835
Upfront fee for license of global patent	2,000	—	—
Loss on sale of long-term investments	—	29,032	—
Loss on derivative revaluation	—	—	214,995
Loss on induced conversion of debt and debt extinguishment	—	77,624	29,390
Bargain purchase gain	—	—	(22,171)
Secondary offering costs	—	—	2,857
Amortization, accretion and step-up:			
Intangible amortization expense	216,875	132,923	32,306
Amortization of debt discount and deferred financing costs	18,546	18,810	9,273
Accretion of royalty liabilities	40,616	20,088	9,020
Inventory step-up expense	71,137	11,495	11,065
Share-based compensation	114,144	85,786	13,198
Depreciation expense	4,962	5,420	1,702
Litigation settlement	65,000	—	—
Reversal of pre-acquisition reserve upon signing of contract	(6,900)	—	—
Impairment of in-process research and development	66,000	—	—
Charges relating to discontinuation of Friedreich's ataxia program (2)	23,513	—	—
Royalties for medicines acquired through business combinations (1)	(37,593)	(29,834)	(18,264)
Total of pre-tax non-GAAP adjustments	631,560	444,716	342,866
Income tax effect of pre-tax non-GAAP adjustments (3)	(110,290)	(122,214)	(76)
Other non-GAAP income tax adjustments (4)	—	(105,133)	—
Total of non-GAAP adjustments	521,270	217,369	342,790
Non-GAAP Net Income	354,436	256,901	79,187
Non-GAAP Earnings Per Share:			
Weighted average ordinary shares – Basic	160,699,543	148,788,020	83,751,129
Non-GAAP Earnings Per Share – Basic			
GAAP (loss) earnings per share - Basic	$(1.04)	$0.27	$(3.15)
Non-GAAP adjustments	3.25	1.46	4.10
Non-GAAP earnings per share – Basic	$2.21	$1.73	$0.95
Weighted average ordinary shares – Diluted			
Weighted average ordinary shares – Basic	160,699,543	148,788,020	83,751,129
Ordinary share equivalents	3,626,570	7,135,231	20,737,726
Weighted average ordinary shares – Diluted	164,326,113	155,923,251	104,488,855
Non-GAAP Earnings Per Share – Diluted			
GAAP (loss) earnings per share – Diluted	$(1.04)	$0.25	(3.15)

Non-GAAP adjustments	3.25	1.40	4.10
Diluted earnings per share effect of ordinary share equivalents	(0.05)	—	(0.19)
Non-GAAP earnings per share – Diluted	$2.16	$1.65	$0.76

108

	For the Years Ended December 31,		
	2016	2015	2014
GAAP Net (Loss) Income	$(166,834)	$39,532	$(263,603)
Depreciation			