

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

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(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.

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

DOCUMENTS INCORPORATED BY REFERENCE

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

HORIZON PHARMA PLC

FORM 10-K — ANNUAL REPORT

For the Fiscal Year Ended December 31, 2016

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PART I

Special Note Regarding Forward-Looking Statements

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

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

Item 1. Business

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

Overview

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

Our Strategy

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

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

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

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

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

Our Company

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

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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.

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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.

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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.

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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 microspherized 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 fluoroquinolone 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.

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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 Musculoskeletal 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.

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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 Ucylyd Pharma, Inc., or Ucylyd, pursuant to which we are obligated to pay to Ucylyd 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 Ucylyd manufacturing technology, and Ucylyd 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 Ucyglyd'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 Pharmaceuticals International Inc.

Amended and Restated Collaboration Agreement

Under the terms of an amended and restated collaboration agreement with Ucyglyd, we are obligated to pay to Ucyglyd 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, Crelta 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 Sintetica (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.

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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/m² subcutaneously every other day), followed by a combination phase with ACTIMMUNE and nivolumab (3 mg/kg intravenously) for three cycles, followed by a single-agent phase of nivolumab alone for up to one year. The study will primarily assess the safety and tolerability of the combination of ACTIMMUNE and nivolumab. Secondary objectives, including overall response rate, progression free survival and overall survival, will also be assessed, as will various correlative analyses. Initial subject enrollment will occur using a modified 3+3 design, and if endpoints for safety (using dose-limiting toxicity criteria) are met, expansion cohorts in renal cell carcinoma and urothelial carcinoma are planned for up to fifteen patients per cohort. On February 23, 2017, at the American Society for Clinical Oncology - Society for Immunotherapy of Cancer meeting, investigators from Fox Chase Cancer Center presented safety data from the first two cohorts of the Phase 1 dose escalation trial evaluating ACTIMMUNE as part of a combination therapy in solid tumors for certain cancers. The preliminary data showed that combination therapy of ACTIMMUNE with nivolumab, a PD-1 inhibitor, was safe and well-tolerated in the first two cohorts. The third cohort of patients receiving ACTIMMUNE is still under study.

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

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

RAVICTI

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

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

RAYOS

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

KRYSTEXXA

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

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

Intellectual Property

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Third-Party Coverage and Reimbursement

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

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

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

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

Government Regulation

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

National MAs, which are issued by a single competent authority of the Member States of the EEA and only covers their respective territory, are also available for products not falling within the mandatory scope of the Centralized Procedure. Once a product has been authorized for marketing in a Member State of the EEA through the National Procedure, this National MA can also be recognized in other Member States through the MRP.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Irish Law Matters

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

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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 Depository 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

Edgar Filing: Horizon Pharma plc - Form 10-K

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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

qualify new contract manufacturers.

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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 United States, our opportunities to expand sales in other countries will be limited or we may experience greater costs with respect to our ex-U.S. commercial operations.

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

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

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

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

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 Ucylyd Pharma, Inc., or Ucylyd, and another external party, at the same royalty rates. While Ucylyd 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 hyperammonemic crises in N-acetylglutamate synthase deficiency, a rare UCD subtype, and is sold under the name Carbaglu. If the results of this trial are successful and 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.

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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;

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• compliance with German laws with respect to our Horizon Pharma GmbH subsidiary through which Horizon Pharma Switzerland GmbH conducts most of its European operations;

• foreign government taxes, regulations and permit requirements;

• U.S. and foreign government tariffs, trade restrictions, price and exchange controls and other regulatory requirements;

- anti-corruption laws, including the Foreign Corrupt Practices Act, or the FCPA;

• economic weakness, including inflation, natural disasters, war, events of terrorism or political instability in particular foreign countries;

• fluctuations in currency exchange rates, which could result in increased operating expenses and reduced revenues, and other obligations related to doing business in another country;

• compliance with tax, employment, immigration and labor laws, regulations and restrictions for employees living or traveling abroad;

• workforce uncertainty in countries where labor unrest is more common than in the United States;

• production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad;

• changes in diplomatic and trade relationships; and

• challenges in enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In January 2017, the United