Horizon Pharma plc
Form 10-K
February 29, 2016

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2015

or

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

Commission File Number 001-35238

HORIZON PHARMA PUBLIC LIMITED COMPANY

(Exact name of Registrant as specified in its charter)

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

011 353 1 772 2100

(Registrant's telephone number, including area code)

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

Title of Each Class	Name of Each Exchange on Which Registered
Ordinary shares, nominal value $0.0001 per share	The NASDAQ Global 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 x No o.

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 o No x.

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 x No o

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 x No o

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. x

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

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

The aggregate market value of the registrant's voting ordinary shares held by non-affiliates of the registrant, based upon the $34.74 per share closing sale price of the registrant's ordinary shares on June 30, 2015 (the last business day of the registrant's most recently completed second quarter), was approximately $4.7 billion. Solely for purposes of this calculation, the registrant's directors and executive officers and holders of 10% or more of the registrant's outstanding

ordinary shares have been assumed to be affiliates and an aggregate of 21,858,502 shares of the registrant's voting ordinary shares held by such persons on June 30, 2015 are not included in this calculation.

As of February 23, 2016, the registrant had outstanding 159,884,455 ordinary shares.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement for the registrant's 2016 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, 2015

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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 re differ materially from those indicated in the forward-looking statements are risks and uncertainties inherent in our business including, without limitation: our ability to successfully execute our sales and marketing strategy, including continuing to successfully recruit and retain sales and marketing personnel and to successfully build the market for our medicines; whether we will be able to realize the expected benefits of strategic transactions, such as our acquisitions of Hyperion Therapeutics Inc. and Crealta Holdings LLC, 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, any approved medicines from government and third-party payors 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 expenses, future revenues and profitability; our ability to successfully execute our strategy to develop or acquire additional medicines or companies, including disruption from any future acquisition, making it more difficult to conduct business as usual or maintain relationships with our customers, employees or suppliers, and the possibility that the potential benefits of any acquisition will not be achieved as rapidly or to the extent expected; 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 nine medicines through our orphan, primary care and rheumatology business units. Our marketed medicines are ACTIMMUNE® (interferon gamma-1b), BUPHENYL® (sodium phenylbutyrate) Tablets and Powder, DUEXIS® (ibuprofen/famotidine), KRYSTEXXA® (pegloticase), MIGERGOT® (ergotamine tartrate and caffeine suppositories), PENNSAID® (diclofenac sodium topical solution) 2% w/w, or PENNSAID 2%, RAVICTI® (glycerol phenylbutyrate) Oral Liquid, RAYOS® (prednisone) delayed-release tablets and VIMOVO® (naproxen/esomeprazole magnesium). We developed DUEXIS and RAYOS, known as LODOTRA® outside the United States, acquired the U.S. rights to VIMOVO from AstraZeneca AB, or AstraZeneca, in November 2013, acquired certain rights to ACTIMMUNE as a result of the Vidara Merger in September 2014, acquired the U.S. rights to PENNSAID 2% from Nuvo Research Inc., or Nuvo, in October 2014, acquired RAVICTI and BUPHENYL, known as AMMONAPS® in Europe, as a result of our acquisition of Hyperion Therapeutics Inc., or Hyperion, in May 2015, and acquired KRYSTEXXA and MIGERGOT as a result of our acquisition of Crealta Holdings LLC, or Crealta, in January 2016.

Our Strategy

Our strategy is to use the commercial strength and infrastructure we have established in creating a global biopharmaceutical company to continue the successful commercialization of our existing medicine portfolio while also expanding and leveraging these capabilities by identifying, developing, acquiring and commercializing additional differentiated and accessible medicines that address unmet medical needs.

We are building a sustainable biopharmaceutical company by helping patients access and afford their medicines and by investing in the further development of medicines to address the individual health challenges faced by patients with rare or underserved diseases. Our growing business is driven by a successful commercial model that focuses on differentiated, long-life medicines and patient access and is diversified across three business units: orphan, primary care and rheumatology 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 nine in January 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 program and generate data for possible new indications that may help more patients in need. We have a robust clinical development pipeline and nine separate clinical programs underway for ACTIMMUNE, RAVICTI, RAYOS and KRYSTEXXA.
- Business development – Our success and rapid transformation have led to an evolution in our business development strategy. While we remain focused on acquiring clinically differentiated assets and executing transactions that are accretive and net present value positive, we have expanded our criteria to potentially include late-stage development assets. We continue to prioritize orphan medicines.
- Global expansion – We continue to seek opportunities for our medicines outside of the United States, specifically in Europe, and are focused on capitalizing on current and future regulatory approvals.

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 hold intellectual property assets,

perform research and development or manufacturing operations, serve as distributors of our medicines, or provide us with services and financial support.

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

Vidara Merger and Hyperion Acquisition

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 comparative prior periods.

On May 7, 2015, we completed the acquisition of 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. Following the completion of the acquisition, Hyperion became our wholly-owned subsidiary and was renamed as Horizon Therapeutics, Inc. The consolidated financial statements presented herein include the results of operations of the acquired business from the date of acquisition.

Our Medicines

We believe our medicines address unmet therapeutic needs in orphan diseases, arthritis, pain and /or 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
RAVICTI	Urea cycle disorders	Worldwide (1)
BUPHENYL/AMMONAPS	Urea cycle disorders	Worldwide (2)
PRIMARY CARE BUSINESS UNIT MEDICINES:		
DUEXIS	Signs and symptoms of osteoarthritis and rheumatoid arthritis	Worldwide (3)
VIMOVO	Signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis	United States
PENNSAID 2%	Pain of osteoarthritis of the knee(s)	United States
MIGERGOT	Vascular headache	United States
RHEUMATOLOGY BUSINESS UNIT MEDICINES:		
RAYOS/LODOTRA	Rheumatoid arthritis, polymyalgia rheumatic, systemic lupus erythematosus and multiple other indications	Worldwide (4)
KRYSTEXXA	Chronic refractory gout	Worldwide

(1) RAVICTI distribution rights in the Middle East and North Africa have been licensed to Swedish Orphan Biovitrum AB, or SOBI.
(2) BUPHENYL/AMMONAPS distribution rights in Europe, certain Asian, Latin American, Middle Eastern, North African and other countries have been licensed to SOBI.
(3) DUEXIS rights in Latin America have been licensed to Grünenthal S.A., or Grünenthal.
(4) RAYOS/LODOTRA distribution rights in Europe, Australia, certain Asian, Latin American, Middle Eastern, African, and other countries have been licensed to Mundipharma International Corporation Limited, or Mundipharma.

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.

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 1 to 44 years old) at 13 medical centers across 4 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, 16 patients were randomized to receive either ACTIMMUNE with calcitriol or calcitriol alone. The age of patients ranged from 1 month to 8 years; with a mean age of 1.5 years. The median time to

progression in the ACTIMMUNE plus calcitriol arm was 165 days versus a median of 65 days in the calcitriol only arm. In a separate analysis that combined data from a second trial, 19 of 24 patients on ACTIMMUNE therapy (with or without calcitriol) for at least 6 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 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 otherwise registered or sold ACTIMMUNE in any other territories for which we currently hold commercial rights.

Potential for ACTIMMUNE in Friedreich's ataxia

Friedreich's ataxia, or FA, is a debilitating, life-shortening and degenerative neuro-muscular disorder that affects approximately 3,700 people in the United States. Onset of symptoms can vary from five years old to adulthood, with the childhood onset tending to be associated with a more rapid progression. A progressive loss of coordination and muscle strength leads to motor incapacitation and often the full-time use of a wheelchair. Most young people diagnosed with FA require mobility aids such as a cane, walker or wheelchair by their teens or early twenties. There are currently no approved treatments for FA.

In October 2014, we announced and presented data from the Phase 2 open-label study of ACTIMMUNE treatment in children with FA. The results showed ACTIMMUNE was well tolerated with no serious adverse events, and two subjects reporting severe events and subsequent dose reductions. The safety findings generally reflected the label safety profile for ACTIMMUNE. Changes in frataxin protein levels, the primary study endpoint, were statistically significant in red blood cells, white blood cells and platelets. Mean improvement in the modified Friedreich's Ataxia Rating Scale, or mFARS, was statistically significant. The mFARS score is used to measure neurological signs associated with FA, with higher scores reflecting a greater level of disability.

In June 2015, we initiated the Phase 3 Safety, Tolerability and Efficacy of ACTIMMUNE Dose Escalation in Friedreich's Ataxia Study, or STEADFAST, of ACTIMMUNE for the treatment of people with FA. This Phase 3 trial (NCT02415127) is a randomized, multi-center, double-blind, placebo-controlled study with patients randomized 1:1 to receive subcutaneous doses of either ACTIMMUNE or placebo three times a week for a total of 26 weeks. Approximately 90 patients will be enrolled at four sites in the United States. The primary endpoint will measure the change in neurological outcome and evaluate the effect of ACTIMMUNE versus placebo as measured by the mFARS score focused on objective neurologic measures such as upper and lower extremity coordination change from baseline. In addition to safety and efficacy, the STEADFAST trial will evaluate the pharmacokinetic characteristics of ACTIMMUNE in people with FA. We expect to complete enrollment in the second quarter of 2016, with top-line data anticipated to become available by the end of 2016. Assuming positive data from the trial, we would plan to submit a supplemental biologics license application in the first quarter of 2017, and given the fast-track designation of ACTIMMUNE for this potential indication, we would request priority review, which, if awarded, would allow us to potentially receive a decision from the FDA within six months of the submission, in the third quarter of 2017.

RAVICTI

RAVICTI is indicated for use as a nitrogen-binding agent for chronic management of adult and pediatric patients 2 years of age and older (2 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 (e.g., 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, noninferiority 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 24 hours of ammonia measurements.

Another study was conducted to assess monthly ammonia control and hyperammonemic crisis over a 12-month period. A total of 51 adults were in the study and all but six had been converted from sodium phenylbutyrate to RAVICTI. Venous ammonia levels were monitored monthly. Of 51 adult patients participating in the 12-month, open-label treatment with RAVICTI, seven patients (14 percent) reported a total of 10 hyperammonemic crises.

The efficacy of RAVICTI in pediatric patients two to 17 years of age was evaluated in two fixed-sequence, open-label, sodium phenylbutyrate to RAVICTI switchover studies, seven and 10 days in duration. These studies compared blood ammonia levels of patients on RAVICTI to venous ammonia levels of patients on sodium phenylbutyrate in 26 pediatric UCD patients. Twenty-four hour blood ammonia levels of UCD patients six to 17 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 (12-month), uncontrolled, open-label studies were conducted to assess monthly ammonia control and hyperammonemic crisis over a 12-month period. Of the 26 pediatric patients six to 17 years of age participating in these two trials, five patients (19 percent) reported a total of five hyperammonemic crises.

Commercial Status

RAVICTI was approved for marketing in the United States in 2013.

On November 30, 2015, we announced the European Commission, or EC, has 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 follows the Positive Opinion previously adopted on September 24, 2015 by the Committee for Medicinal Products for Human Use, or CHMP, of the European Medicines Agency, or EMA. The approval authorizes us to market RAVICTI in all 28 Member States of the European Union, or 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.

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 until 2018. We market and sell RAVICTI in the United States and plan to determine the marketing and sales distribution model for Europe in 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 (targeted supplemental new drug application, or sNDA, submission in the second quarter of 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.

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 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 EMA in Europe in 1999. We commercially market and distribute BUPHENYL in the United States. BUPHENYL is known as AMMONAPS in Europe, and the marketing and distribution rights are licensed to SOBI through the end of 2016. We provide BUPHENYL in certain other countries through various Special Access Programs and licensed distributors.

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.

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 osteoarthritis, or OA, rheumatoid arthritis, or 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 18 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 40 percent by 2030, impacting 67 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 nonsteroidal anti-inflammatory drugs, or NSAIDs, such as ibuprofen, naproxen and diclofenac, that have a rapid analgesic and anti-inflammatory response.

Rheumatoid Arthritis

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 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 NSAIDs.

Ankylosing Spondylitis

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

Market Opportunity and Limitations of Existing Treatments

GI-Associated Adverse Events

NSAIDs are very effective at providing pain relief, including pain associated with OA and RA; however, there are significant upper gastrointestinal, or 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 25 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 70 percent of patients with these serious GI complications, there are no prior symptoms.

Despite the fact that GI ulcers are one of the most prevalent adverse events resulting from the use of NSAIDs in the United States, according to a 2006 article published in BMC Muskoskeletal Disorders, 11 observational studies indicated that physicians do not commonly co-prescribe GI protective agents to high-risk patients. Physicians prescribe concomitant therapy to only 24 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, 37 percent of patients were non-compliant, a rate increasing to 61 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 5 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 is a proprietary single-tablet formulation 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 NSAID-induced upper GI ulcers.

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 12 months.

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

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 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

DUEXIS is indicated for the relief of signs and symptoms of RA and OA and to decrease the risk of developing GI ulcers in patients who are taking ibuprofen for these indications. We began marketing DUEXIS to 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.

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 17 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.

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 powerful 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.

Competition

Our industry is highly competitive and subject to rapid and significant technological change. Our potential 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. We believe that the key competitive factors that will affect the commercial success of our medicines, as well as future drug candidates that we may develop, are their efficacy, safety and tolerability profile, convenience in dosing, price and reimbursement.

DUEXIS and VIMOVO compete with other NSAIDs, including Celebrex® which is marketed by Pfizer Inc., and is also a generic medicine known as celecoxib and marketed 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.

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 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.

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%. In addition, PENNSAID 2% competes with two other branded topical NSAIDS, including Voltaren® Gel, marketed by Endo Pharmaceuticals, which is the 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.

RHEUMATOLOGY BUSINESS UNIT

Market

Rheumatoid Arthritis

The market for RA has been discussed above in the Primary Care Business Unit section (refer to page 8).

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 65 years of age. It rarely affects people younger than 50. 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 50. Prednisone is the standard of care for treating PMR and treatment is generally initiated at a relatively high dose (e.g., 10-20 mg per day) and reduced as clinical improvement is seen. Treatment usually lasts 18-24 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 62 patients across 25 sites will be enrolled in the United States. The primary endpoint will assess fatigue as measured by Functional Assessment of Chronic Illness Therapy-Fatigue, a 13-question survey to be completed by study participants that focuses on the daily fatigue experienced in patients with chronic illnesses.

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.

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 90 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. Patients with RA in general have substantially increased IL-6 levels, with peak IL-6 levels tending to occur in the early morning hours, and low levels typically occurring in the afternoon and evening. Therefore, 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, such as IL-6 and TNF-alpha. 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

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, 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 SkyePharma AG's, or SkyePharma, 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 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 and is currently approved for marketing in more than 30 countries outside the United States where Mundipharma holds the commercial rights. Reimbursement has been approved in Germany, Italy and a number of other European countries.

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 January 2011. KRYSTEXXA has biologic exclusivity until 2022 and a composition of matter patent until 2026. Orphan drug exclusivity was granted on February 21, 2011, which exclusivity lasts for 7 years and will expire in February 2018.

Competition

RAYOS/LODOTRA competes with a number of medicines on 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.

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 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. 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.

Distribution

Finished tablets of DUEXIS, VIMOVO, RAYOS, MIGERGOT and BUPHENYL, vials of ACTIMMUNE and KRYSTEXXA, bottles of RAVICTI and PENNSAID 2% 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, 2015, our sales force was composed of approximately 395 sales representatives consisting of approximately 15 orphan disease sales representatives, 340 primary care sales representatives and 40 rheumatology sales specialists. 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, hematology/oncology and metabolic disorders to help them understand the potential benefits of ACTIMMUNE for their patients with CGD and SMO, and the benefits of RAVICTI and BUPHENYL for patients with UCDs. Our primary care sales force is expected to total approximately 375 representatives in the first quarter of 2016 and markets DUEXIS, PENNSAID 2%, VIMOVO and MIGERGOT. Following the acquisition of Crealta our rheumatology sales force is expected to total approximately 80 representatives by mid-year 2016 and is now marketing RAYOS, KRYSTEXXA and PENNSAID 2%. We have entered into, and may continue to enter into, agreements with third parties for commercialization of our medicines outside the United States.

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Our medicines are distributed by retail and specialty pharmacies. Part of our commercial strategy for our primary care and rheumatology business units is to offer physicians the opportunity to have their patients fill prescriptions through pharmacies participating in our HorizonCares patient access program, previously known as Prescriptions Made Easy. This program does not involve us in the prescribing of medicines. The purpose of this program is solely to assist in ensuring that, when physicians determine one of our medicines offers a potential clinical benefit to their patients and prescribe the medicine for an eligible patient, financial assistance may be available to reduce the commercial patient's out-of-pocket costs. In 2015, this resulted in 96 percent of commercial patients having co-pay amounts of $10 or less when filling prescriptions for our medicines utilizing our patient access program. For commercial patients who were prescribed our primary care or rheumatology medicines, the HorizonCares program offers co-pay assistance when a third-party payor covers a prescription but requires an eligible patient to pay a co-pay or deductible, and offers full subsidization when a third-party payor rejects coverage for an eligible patient. For patients prescribed our orphan medicines, HorizonCares provides reimbursement support, a clinical nurse program, co-pay and other patient assistance. The aggregate commercial value of our patient access programs for the year ended December 31, 2015 was approximately $1,020 million. 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 our business. As of December 31, 2015, approximately 25 independent pharmacies participated in the HorizonCares program for our primary care and rheumatology medicines.

We have a 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 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 product manufacturing, 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. 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.

Under a development and marketing agreement with Boehringer Ingelheim, we are required to pay royalties on net sales in certain applicable markets in Latin America, Asia, Africa and Eastern Europe if we elect to commercialize ACTIMMUNE in those territories. To date, we have not pursued regulatory or other approvals or commercialized ACTIMMUNE in those territories.

Genentech License Agreement

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:

- Through November 25, 2014, a royalty of 45 percent of the first $3.7 million in net sales achieved in a calendar year, and 10 percent on all additional net sales in that year;
- For the period from November 26, 2014 through May 5, 2018, a royalty in the 20 percent to 30 percent range for the first tier in net sales and in the 1 percent to 9 percent range for the second tier; 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 30 days to cure the default before the license agreement may be terminated.

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 known as DPx Fine Chemicals GmbH & Co KG) on a purchase order basis. We have finished RAVICTI drug medicine manufactured by Lyne Laboratories, Inc. under a manufacturing agreement and we have an agreement in place for a fill/finish supplier, Halo Pharmaceuticals, Inc., for European supplies.

Ucyclyd Asset Purchase Agreement

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

Brusilow License Agreement

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

ASD Distribution Services Agreement

As a result of the Hyperion acquisition, we acquired a distribution services agreement, as amended, with ASD Healthcare, a division of ASD Specialty Healthcare, Inc., or ASD. Pursuant to the distribution services agreement, ASD is the exclusive reseller of RAVICTI and BUPHENYL in the United States. The distribution services agreement terminates on February 13, 2017, but may be renewed upon mutual written agreement with ASD. Either party may terminate the agreement without cause upon 120 days written notice to the other party, in the case of a material breach that is not cured by the other party, upon 30 days written notice, or in the case of bankruptcy or similar proceeding of the other party, immediately upon written notice.

BUPHENYL

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

DUEXIS

The DUEXIS manufacturing process is well-established and we validated the process in accordance with regulatory requirements prior to commercialization in the United States.

The first API in DUEXIS is ibuprofen in a direct compression blend called DC85 and is manufactured for us by BASF Corporation, or BASF, in Bishop, Texas. The second API in DUEXIS is famotidine, which is available from a number of international suppliers. We currently purchase famotidine manufactured by Dr. Reddy's in India. We currently receive both APIs in powder form and each is blended with a number of U.S. Pharmacopeia inactive ingredients. We purchase DUEXIS in final, packaged form exclusively from Sanofi-Aventis U.S. LLC, or Sanofi, for our commercial requirements in North America.

BASF Contract

In July 2010, we entered into a contract with BASF for the purchase of DC85. Pursuant to the agreement, we are obligated to purchase a significant majority of our commercial demand for DC85 from BASF. The contract expires in December 2017. Thereafter, the agreement automatically renews for successive renewal terms of three years each until terminated by either party giving specified prior written notice to the other party. Either party may also terminate the agreement in the event of uncured breach by the other party.

Manufacturing and Supply Agreement with Sanofi

In May 2011, we entered into a manufacturing and supply agreement with Sanofi, which was amended in September 2013. Pursuant to the agreement, Sanofi is obligated to manufacture and supply DUEXIS to us in final, packaged form, and we are obligated to purchase DUEXIS exclusively from Sanofi for our commercial requirements in North America and certain countries and territories in Europe, including the EU member states and Scandinavia, and South America. Sanofi must acquire the components necessary to manufacture DUEXIS, including the APIs, DC85 and famotidine, 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 30 days prior written notice to the other party in the event of breach by the other party that is not cured within 30 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 Pozen; Letter Agreement with AstraZeneca and Pozen

We entered into a license agreement with Pozen Inc., or Pozen, who subsequently entered into a business combination with Tribute Pharmaceuticals Canada Inc. to become known as Aralez Pharmaceuticals Inc. Under this agreement, we were granted an exclusive, royalty-bearing license under certain of Pozen’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 Pozen license agreement, we are required to pay Pozen a flat 10 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 Pozen’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 Pozen 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) 10 years after the first commercial sale of such medicines in the United States. In addition, we will be obligated to reimburse Pozen for costs, including attorneys' fees, incurred by Pozen 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. Pozen 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 Pozen 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 Pozen license agreement for cause upon certain defined medicine failures.

In November 2013, we, AstraZeneca and Pozen entered into a letter agreement in which Pozen consented to AstraZeneca's assignment of the Pozen license agreement to us and that addresses the rights and responsibilities of the parties in relation to the Pozen license agreement and the amended and restated collaboration and license agreement between Pozen and AstraZeneca for territories outside the United States, or the Pozen-AstraZeneca license agreement. Under the letter agreement, we and AstraZeneca agreed to pay Pozen 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 Pozen to us under the Pozen license agreement and to AstraZeneca under the Pozen-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 Pozen and us upon the termination of the Pozen 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 Pharmaceuticals Inc., or 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 24 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 product. 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.

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 90 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.

RAYOS/LODOTRA

We rely on well-established third-party manufacturers for the manufacture of RAYOS/LODOTRA. We purchase the primary active ingredients 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 SkyePharma, and we entered into an agreement with Patheon for the packaging and assembling of RAYOS/LODOTRA.

SkyePharma and Jagotec Agreements

Development and License Agreement

In August 2004, we entered into a development and license agreement with SkyePharma and Jagotec, a wholly-owned subsidiary of SkyePharma, regarding certain proprietary technology and know-how owned by SkyePharma 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 SkyePharma. 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, Jagotec or its affiliates manufacture and supply RAYOS/LODOTRA to us in bulk. Aenova France SAS, a large contract manufacturing organization, is now a subcontractor for Jagotec for the manufacture of RAYOS/LODOTRA, with our consent. As of December 31, 2015, our total remaining minimum purchase commitment was approximately $3.0 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.

The original agreement term has run such that the agreement now automatically extends on a yearly basis unless terminated by either party upon prior written notice. Either party may also terminate the agreement in the event of insolvency, liquidation or bankruptcy of the other party or upon an uncured breach by the other party. We have the right to receive a continuing supply of RAYOS/LODOTRA from Jagotec for a period of 24 months after termination by Jagotec, regardless of the reason for termination. In April 2015, the agreement automatically renewed for an additional one-year term. Therefore the earliest the right to receive a continuing supply from Jagotec would expire is April 15, 2018, absent any early termination of the agreement.

Pursuant to a letter agreement between Jagotec and us, Jagotec agreed to allow us to give Bayer Pharma AG, or Bayer, the right to manufacture, test and release quantities of RAYOS/LODOTRA in order to establish and maintain Bayer as a manufacturer of RAYOS/LODOTRA. Under certain circumstances, we may also purchase shortfall quantities of RAYOS/LODOTRA from Bayer to the extent Jagotec is unable to supply us. In March 2013, we entered into an agreement with Bayer to allow us to purchase quantities of RAYOS/LODOTRA for these purposes. We may also purchase quantities of RAYOS/LODOTRA from Bayer pursuant to our agreement with Bayer.

KRYSTEXXA

KRYSTEXXA is produced by fermentation and subsequent purification to produce the urate oxidase enzyme, uricase. Uricase is then PEGylated with a pegylation agent to produce the bulk medicine, pegloticase. Finally, pegloticase is filled and packaged to produce the final medicine.

NOF Supply Agreement

In August 2015, Crealta and NOF Corporation, or NOF, 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 in Crealta), or Savient, entered into a commercial supply agreement with Bio-Technology General (Israel) Ltd., or BTG Israel, for the production of the bulk KRYSTEXXA medicine, or bulk medicine. We assumed this agreement as part of the Crealta acquisition. Under this agreement, we are obligated to purchase at least 80 percent of our annual world-wide bulk medicine requirements from BTG Israel. In December 2015, Crealta received a notice of termination from BTG Israel and as a result the agreement will terminate on December 15, 2018. Either we or BTG Israel 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 or bankruptcy. We are seeking a new manufacturer and, under the terms of the agreement, BTG Israel has the obligation to convey all the know-how, licensed improvements, and other information related to the processing of the bulk

medicine sufficient to enable us to manufacture the medicine. BTG Israel also has an obligation not to compete against KRYSTEXXA for a period of 30 months subsequent to the termination of the agreement. If we determine to move the manufacture of the bulk medicine out of Israel, we may be required to obtain the approval of the Office of the Chief Scientist (Israel), or OCS, because certain KRYSTEXXA intellectual property was developed with a grant funded by OCS. Under the terms of our agreement, BTG Israel must help us obtain such consent. If we are unable to obtain such consent and we do not select a different supplier located in Israel, we may be required to pay additional amounts as a repayment for the OCS grant funding.

Sigma Tau PharmaSource Supply Agreement

In October 2008, Savient and Sigma Tau PharmaSource, Inc. (as successor in interest to Enzon Pharmaceuticals, Inc.), or Sigma Tau, 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 Sigma Tau may terminate the agreement with three years notice, given 30 days prior to the agreement anniversary date. Either we or Sigma Tau 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, 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.

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, 2015, 2014 and 2013, as well as the location of our long-lived assets, is included in Note 14, Segment and Other Information, 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, 2015, 2014 and 2013, we recorded $41.9 million, $17.5 million and $10.1 million, respectively, in research and development expenses.

The following chart depicts our current clinical development pipeline with respect to ACTIMMUNE, RAVICTI, RAYOS and KRYSTEXXA:

ACTIMMUNE

In February 2015, we submitted an IND application to the FDA for ACTIMMUNE in the treatment of FA, a degenerative neuro-muscular disorder. In June 2015, we commenced the Phase 3 STEADFAST study. This Phase 3 trial (NCT02415127) is a randomized, multi-center, double-blind, placebo-controlled study with patients randomized 1:1 to receive subcutaneous doses of either ACTIMMUNE or placebo three times a week for a total of 26 weeks. Approximately 90 patients will be enrolled at four sites in the United States. The primary endpoint will measure the change in neurological outcome and evaluate the effect of ACTIMMUNE versus placebo as measured by the mFARS score, focused on objective neurologic measures such as upper and lower extremity coordination improvement from baseline. The mFARS score is used to measure neurological signs associated with FA, with higher scores reflecting a greater level of disability. In addition to safety and efficacy, the STEADFAST trial will evaluate the pharmacokinetic characteristics of ACTIMMUNE in people with FA. The target date for the full enrollment of 90 patients is the second quarter of 2016, with data anticipated to become available in late 2016. Assuming positive data from the trial, we would plan to submit a supplemental biologics license application in the first quarter of 2017, and given the fast-track designation of ACTIMMUNE for this potential indication, we would request priority review, which, if awarded, would allow us to potentially receive a decision from the FDA within six months of the submission, in the third quarter of 2017.

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. 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), a registered trademark of Bristol-Meyers Squibb, in advanced solid tumors. The Phase 1 open label study will evaluate the combination of ACTIMMUNE and nivolumab in patients with advanced solid tumors who have progressed on at least one prior systemic therapy, which may include prior immunotherapy. Patients will be treated with a one week induction phase of ACTIMMUNE (starting dose 50 mcg/m^2 subcutaneously), 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 6+6 design, and if endpoints for safety (using dose-limiting toxicity criteria) are met, expansion cohorts in renal cell carcinoma (kidney cancer) and urothelial carcinoma (bladder cancer) are planned for up to 15 patients per cohort.

We are collaborating with 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 early 2016.

We are also collaborating with several partners to investigate opportunities for next generation formulations of ACTIMMUNE in current and new indications.

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 (targeted sNDA submission in the second quarter of 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