BIOMARIN PHARMACEUTICAL INC
Form 10-K
February 27, 2017
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

(Mark One)

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

Or

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

Commission file number: 000-26727

BioMarin Pharmaceutical Inc.

(Exact name of registrant as specified in its charter)

Delaware	68-0397820
(State of other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
770 Lindaro Street San Rafael, California	94901
(Address of principal executive offices)	(Zip Code)

Registrant’s telephone number, including area code: (415) 506-6700

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

Title of Each Class	Name of Each Exchange on Which Registered
Common Stock, $.001 par value	The NASDAQ Global Select Market

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

None

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

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

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

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

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

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

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

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

The aggregate market value of the voting and non-voting common stock held by non-affiliates of the registrant as of June 30, 2016 was $7.6 billion, based on the closing price reported for such date on the NASDAQ Global Select Market.

As of February 13, 2017, the registrant had 172,866,495 shares of common stock, par value $0.001, outstanding.

The documents incorporated by reference are as follows: Portions of the Registrant's Proxy Statement for our annual meeting of stockholders to be held June 6, 2017, are incorporated by reference into Part III.

BIOMARIN PHARMACEUTICAL INC.

2016 FORM 10-K ANNUAL REPORT

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Part I

FORWARD LOOKING STATEMENTS

This Annual Report on Form 10-K contains "forward-looking statements" as defined under federal securities laws. Many of these statements can be identified by the use of terminology such as "believes," "expects," "intends," "anticipates," "plans," "may," "will," "projects," "continues," "estimates," "potential," "opportunity" or the negative versions of these terms similar expressions. These forward-looking statements may be found in "Risk Factors," "Business," "Management's Discussion and Analysis of Financial Condition and Results of Operations" and other sections of this Annual Report on Form 10-K. Our actual results or experience could differ significantly from the forward-looking statements. Factors that could cause or contribute to these differences include those discussed in "Risk Factors," as well as those discussed in "Management's Discussion and Analysis of Financial Condition and Results of Operations" and elsewhere in this Annual Report on Form 10-K. You should carefully consider that information before you make an investment decision.

You should not place undue reliance on these statements, which speak only as of the date that they were made. These cautionary statements should be considered in connection with any written or oral forward-looking statements that we may make in the future. We do not undertake any obligation to release publicly any revisions to these forward-looking statements after completion of the filing of this Annual Report on Form 10-K to reflect later events or circumstances or to reflect the occurrence of unanticipated events.

The following discussion of our financial condition and results of operations should be read in conjunction with our Consolidated Financial Statements and the notes thereto appearing elsewhere in this Annual Report on Form 10-K. In addition to the other information in this Annual Report on Form 10-K, investors should carefully consider the following discussion and the information under "Risk Factors" when evaluating us and our business.

Item 1. Business

Overview

BioMarin Pharmaceutical Inc. (BioMarin, we, us or our) is a global biotechnology company that develops and commercializes innovative therapies for people with serious and life-threatening rare diseases and medical conditions. We select product candidates for diseases and conditions that represent a significant unmet medical need, have well-understood biology and provide an opportunity to be first-to-market or offer a significant benefit over existing products. Our therapy portfolio consists of five products and multiple clinical and pre-clinical product candidates.

Our commercial products are Aldurazyme (laronidase) for Mucopolysaccharidosis I (MPS I), Firdapse (amifampridine phosphate) for Lambert Eaton Myasthenic Syndrome (LEMS), Kuvan (sapropterin dihydrochloride) for phenylketonuria (PKU), Naglazyme (galsulfase) for Mucopolysaccharidosis VI (MPS VI) and Vimizim (elosulfase alpha) for Mucopolysaccharidosis IV Type A (MPS IV A).

We continue to invest in our clinical and pre-clinical product pipeline by committing significant resources to research and development programs and business development opportunities within our areas of scientific, manufacturing and technical expertise. We are conducting clinical trials on several product candidates for the treatment of various diseases. Our clinical product candidates include Brineura (formerly referred to as cerliponase alfa or BMN 190) for the treatment of late infantile neuronal ceroid lipofuscinosis (CLN2), a form of Batten disease; pegvaliase (formerly referred to as PEG PAL), an enzyme substitution therapy for the treatment of phenylketonuria (PKU); vosoritide (formerly referred to as BMN 111), a peptide therapeutic for the treatment of achondroplasia, the leading cause of dwarfism; BMN 270, an AAV VIII vector and Factor VIII gene therapy drug development candidate, for the treatment of hemophilia A; and BMN 250, a novel fusion of alpha-N-acetyglucosaminidase (NAGLU) with a peptide derived from insulin-like growth factor 2 (IGF2), for the treatment of Sanfilippo B syndrome, or mucopolysaccharidosis type

IIIB (MPS IIIB). We are conducting or planning to conduct preclinical development of several other product candidates for genetic and other metabolic diseases.

Recent Developments

Gene Therapy Product Candidate BMN 270 for the Treatment of Hemophilia A

In January 2017, we announced an update to our positive interim results of an open-label Phase 1/2 study of BMN 270 in patients with severe hemophilia A, which were announced at the XXXII International Congress of the World Federation of Hemophilia in July 2016. A total of nine patients with severe hemophilia A received a single dose of BMN 270, seven of whom have been treated at the highest dose of 6 x 10^{13} vg/kg. According to the World Federation of Hemophilia rankings of severity of hemophilia A, the normal range of Factor VIII activity levels is between 50% and 150%, expressed as a percentage of normal factor activity in blood, and the mild hemophilia A range of Factor VIII activity levels is between 5% and 40%. As of the December 9, 2016 data cutoff, of those seven patients treated at the highest dose, six continued to have Factor VIII levels above 50%, and the seventh continued to have levels above 15%. For the six patients at the high dose and previously on a Factor VIII prophylactic regimen, the mean annualized bleeding rate dropped 91% from 16.3 before the BMN 270 infusion to 1.5 two weeks after being dosed (median annualized bleeding rate dropped from 16.5 to 0). For those same six patients, the mean annualized Factor VIII infusions fell 98% from 136.7 to 2.9 (median annualized Factor VIII infusions fell from 138.5 to 0).

In February 2017, we announced that the European Medicines Agency (EMA) granted access to its Priority Medicines (PRIME) regulatory initiative for BMN 270. To be accepted for PRIME, an investigational therapy has to show its potential to benefit patients with unmet medical needs based on early clinical data.

Product Candidate BMN 250 for the Treatment of Sanfilippo B syndrome or MPS IIIB

In January 2017, we announced preliminary results from a Phase 1/2 trial, which began enrolling patients in April 2016, demonstrating that BMN 250, an investigational enzyme replacement therapy using a novel fusion of recombinant human NAGLU with a peptide derived from IGF2, for the treatment of Sanfilippo B syndrome or MPS IIIB, reduced heparan sulfate levels to normal range in cerebral spinal fluid of MPS IIIB patients. Additionally, patients have safely escalated to 100mg dosage.

Product Candidate Vosoritide for the Treatment of Achondroplasia

In December 2016, we initiated the pivotal Phase 3 study of vosoritide, an analog of C-type Natriuretic peptide, in children with achondroplasia, the most common form of dwarfism. The Phase 3 study is a randomized, placebo-controlled 12-month treatment study in approximately 110 children with achondroplasia, ages 5-14. In October 2016, we provided an update on our Phase 2 study of vosoritide. Results from eight children in cohort 4, who completed six months of daily dosing at 30 µg/kg/daily, experienced a 46% or 2.1 cm/year increase in mean annualized growth velocity from baseline. These data are comparable to those observed at the lower dose of 15 µg/kg/day in cohort 3. Results from 10 children in cohort 3, who completed six months of daily dosing at 15 µg/kg/day, experienced a 50% or 2.0 cm/year increase in mean annualized growth velocity from baseline.

Regulatory Review of Brineura

In September 2016, we announced that the EMA validated the Marketing Authorization Application (MAA) for Brineura, an investigational therapy to treat children with CLN2 disease, a form of Batten disease. Validation of the MAA confirmed that the submission was accepted and starts the formal review process by the EMA's Committee for

Human Medicinal Products (CHMP). The EMA previously granted our request for accelerated assessment for the MAA. The CHMP opinion and decision from the European Commission (EC) is expected in the third quarter of 2017. Accelerated assessments are granted on the grounds that a product may satisfy an unmet medical need and is of major interest from the point of view of therapeutic innovation and public health.

In July 2016, we announced that the Food and Drug Administration (FDA) accepted for review the submission of a Biologics License Application (BLA) for Brineura. During their initial review of the BLA, the FDA requested, and we provided, updated efficacy data from the ongoing extension study. In September 2016, the FDA designated this submission as a major amendment to the application, thus extending the Prescription Drug User Fee Act (PDUFA) action date by three months to April 27, 2017. The FDA granted Brineura Priority Review status,

which is designated to drugs that, if approved, would be a significant improvement in treatment or provide a treatment where no adequate therapy exists. Brineura was previously granted orphan drug designation by the FDA and EMA and breakthrough therapy designation by the FDA.

Summary of Commercial Products and Development Programs

A summary of our commercial products and major development programs, including key metrics as of December 31, 2016, is provided below:

Commercial Products	Indication	U.S. Orphan Drug Exclusivity Expiration [1]	U.S. Biologic Exclusivity Expiration [2]	EU Orphan Drug Exclusivity Expiration [1]	2016 Total Net Product Revenues (in millions)	2016 Research & Development Expense (in millions)
Aldurazyme [3]	MPS I [4]	Expired	Expired	Expired	$ 93.8	$ 1.5
Firdapse	LEMS[5]	NA [6]	NA	2019	18.0	4.4
Kuvan	PKU [7]	Expired	NA	2020 [8]	348.0	24.7
Naglazyme	MPS VI [9]	Expired	2017	Expired	296.5	10.0
Vimizim	MPS IVA [10]	2021	2026	2024	354.1	24.4

Major Products in Development	Target Indication	U.S. Orphan Designation	EU Orphan Designation	Stage	2016 Research & Development Expense (in millions)
BMN 270 [11]	Hemophilia A	Yes	Yes	Clinical Phase 1/2	$ 58.9
Brineura	CLN2 [12]	Yes	Yes	Marketing authorization regulatory review	77.2
BMN 250	MPS IIIB [13]	Yes	Yes	Clinical Phase 1/2	46.1
Pegvaliase	PKU	Yes	Yes	Clinical Phase 3	88.6
Vosoritide	Achondroplasia	Yes	Yes	Clinical Phase 3	55.8

(1) See “Government Regulation—Orphan Drug Designation” below for further discussion.
(2) See “Government Regulation— Health Reform” below for further discussion.
(3) The Aldurazyme total net product revenues noted above are the total net product revenues recognized by us in accordance with the terms of our agreement with Genzyme Corporation (Genzyme). See “Major Commercial Products—Aldurazyme” below for further discussion.
(4) Mucopolysaccharidosis I, or MPS I
(5) Lambert Eaton Myasthenic Syndrome, or LEMS
(6) Firdapse has not received marketing approval in the U.S. We have licensed the North American rights to develop and market Firdapse to a third-party.
(7) Phenylketonuria, or PKU
(8) Kuvan has been granted orphan drug status in the EU, which together with pediatric exclusivity, confers 12 years of market exclusivity in the EU that expires in 2020. Furthermore, Merck Serono marketed Kuvan in the EU until

January 1, 2016 and continues to provide critical transition services for the sale and distribution of Kuvan in four countries where the regulatory approvals have not yet been transferred to us. See “Major Commercial Products—Kuvan” below for further discussion.

(9) Mucopolysaccharidosis VI, or MPS VI

(10) Mucopolysaccharidosis IV Type A, or MPS IVA

(11) BMN 270 is an investigational gene therapy for Hemophilia A, also called factor VIII deficiency or classic hemophilia.
(12) CLN2, or late infantile neuronal ceroid lipofuscinosis, is a lysosomal storage disorder primarily affecting the brain.
(13) Sanfilippo B syndrome, or mucopolysaccharidosis type IIIB (MPS IIIB).

See “Patents and Proprietary Rights” below for additional information on our market protection.

Major Commercial Products

Aldurazyme

Aldurazyme is approved for marketing in the U.S., the EU and other international markets for patients with mucopolysaccharidosis I (MPS I). MPS I is a progressive and debilitating life-threatening genetic disease, for which no other drug treatment currently exists, that is caused by the deficiency of alpha-L-iduronidase, a lysosomal enzyme normally required for the breakdown of GAGs. Patients with MPS I typically become progressively worse and experience multiple severe and debilitating symptoms resulting from the build-up of carbohydrate residues in all tissues in the body. These symptoms include: inhibited growth, delayed and regressed mental development (in the severe form of the disease), enlarged liver and spleen, joint deformities and reduced range of motion, impaired cardiovascular function, upper airway obstruction, reduced pulmonary function, frequent ear and lung infections, impaired hearing and vision, sleep apnea, malaise and reduced endurance.

We developed Aldurazyme through collaboration with Genzyme, now a wholly-owned subsidiary of Sanofi. Under our collaboration agreement with Genzyme, we are responsible for manufacturing Aldurazyme and supplying it to Genzyme. We receive a payment ranging from 39.5% to 50% on worldwide net Aldurazyme sales by Genzyme depending on sales volume. We recognize a portion of this amount as product transfer revenue when the product is released to Genzyme because all of our performance obligations are fulfilled at that point and title to, and risk of loss for, the product has transferred to Genzyme. The product transfer revenue represents the fixed amount per unit of Aldurazyme that Genzyme is required to pay us if the product is unsold by Genzyme. The amount of product transfer revenue will eventually be deducted from the calculated royalty rate when the product is sold by Genzyme. Additionally, Genzyme and we are members of BioMarin/Genzyme LLC, a 50/50 limited liability company (the BioMarin/Genzyme LLC) that: (1) holds the intellectual property relating to Aldurazyme and other collaboration products and licenses all such intellectual property on a royalty-free basis to us and Genzyme to allow us to exercise our rights and perform our obligations under the agreements related to the BioMarin/Genzyme LLC, and (2) engages in research and development activities that are mutually selected and funded by Genzyme and us.

Aldurazyme net product revenues for the years ended December 31, 2016, 2015 and 2014 totaled $93.8 million, $98.0 million and $105.6 million, respectively. In the future, to the extent that Genzyme net sales of Aldurazyme remain consistent, we expect that our total Aldurazyme revenues will continue to approximate 39.5% to 50% of net product sales by Genzyme as described above.

Kuvan

Kuvan is a proprietary synthetic oral form of 6R-BH4, a naturally occurring enzyme co-factor for phenylalanine hydroxylase (PAH), indicated for patients with phenylketonuria (PKU). Kuvan is the first drug for the treatment of PKU, which is an inherited metabolic disease that affects at least 50,000 diagnosed patients under the age of 40 in the developed world. We believe that approximately 30% to 50% of those with PKU could benefit from treatment with Kuvan. PKU is caused by a deficiency of activity of an enzyme, PAH, which is required for the metabolism of phenylalanine (Phe). Phe is an essential amino acid found in all protein-containing foods. Without sufficient quantity or activity of PAH, Phe accumulates to abnormally high levels in the blood, resulting in a variety of serious

neurological complications, including severe mental retardation and brain damage, mental illness, seizures and other cognitive problems. As a result of newborn screening efforts implemented in the 1960s and early 1970s, virtually all PKU patients under the age of 40 in developed countries have been diagnosed at birth. Currently, PKU can be managed by a Phe-restricted diet, which is supplemented by nutritional replacement products, like formulas and specially manufactured foods; however, it is difficult for most patients to adhere to the strict diet to the extent needed for achieving adequate control of blood Phe levels.

Kuvan tablets were granted marketing approval for the treatment of PKU in the U.S. in December 2007 and in the EU in December 2008. In December 2013, the FDA approved the use of Kuvan powder for oral solution that is provided in a dose sachet packet allowing faster dissolution of powder in solution compared to the current tablet form. This new dosage form is expected to have increasing appeal for young patients in the one to seven year age range. We commenced the commercial launch of this new form of Kuvan in February 2014. We market Kuvan in the U.S. and Canada (and effective as of January 1, 2016, in the rest of the world, except for Japan and four other countries in which we have not yet completed the transfer of certain regulatory approvals from Merck Serono to us. In certain international markets, Kuvan is also approved for, or is only approved for, the treatment of primary BH4 deficiency, a different disorder than PKU. Kuvan net product revenues for the years ended December 31, 2016, 2015 and 2014 totaled $348.0 million, $239.3 million and $203.0 million, respectively.

In the fourth quarter of 2015, we entered into the Termination and Transition Agreement with Ares Trading S.A. (Merck Serono), as amended and restated on December 23, 2015 (the A&R Kuvan Agreement) to terminate the Development, License and Commercialization Agreement, dated May 13, 2005, as amended (the License Agreement), including the license to Kuvan granted in the License Agreement from us to Merck Serono. Also in the fourth quarter of 2015, we and Merck Serono entered into a Termination Agreement (the Pegvaliase Agreement) to terminate the license to pegvaliase granted in the License Agreement from us to Merck Serono.

On January 1, 2016, pursuant to the A&R Kuvan Agreement and the Pegvaliase Agreement, we completed the acquisition from Merck Serono and its affiliates of certain rights and other assets, and the assumption from Merck Serono and its affiliates of certain liabilities, in each case with respect to Kuvan and pegvaliase. As a result, we acquired all global rights to Kuvan and pegvaliase from Merck Serono, with the exception of Kuvan in Japan. Previously, we had exclusive rights to Kuvan in the U.S. and Canada and pegvaliase in the U.S. and Japan.

Pursuant to the A&R Kuvan Agreement, the Company paid Merck Serono $374.5 million, in cash, and is obligated to pay Merck Serono up to a maximum of €60.0 million, in cash, if future sales milestones are met. Pursuant to the Pegvaliase Agreement, the Company is obligated to pay Merck Serono up to a maximum of €125.0 million, in cash, if future development milestones are met.

Two companies have filed paragraph IV certifications and submitted abbreviated new drug applications (ANDAs) to produce sapropterin dihydrochloride tablets and powder. In September 2015, we entered into a settlement agreement regarding Kuvan tablets with one of these companies. Please see “Government Regulation – Hatch-Waxman Act” below and “Legal Proceedings” in Part I, Item 3 of this Annual Report on Form 10-K for additional information.

Naglazyme

Naglazyme is a recombinant form of N-acetylgalactosamine 4-sulfatase (arylsulfatase B) indicated for patients with mucopolysaccharidosis VI (MPS VI). MPS VI is a debilitating life-threatening genetic disease for which no other drug treatment currently exists and is caused by the deficiency of arylsulfatase B, an enzyme normally required for the breakdown of certain complex carbohydrates known as glycosaminoglycans (GAGs). Patients with MPS VI typically become progressively worse and experience multiple severe and debilitating symptoms resulting from the build-up of carbohydrate residues in tissues in the body. These symptoms include: inhibited growth, spinal cord compression, enlarged liver and spleen, joint deformities and reduced range of motion, skeletal deformities, impaired cardiovascular function, upper airway obstruction, reduced pulmonary function, frequent ear and lung infections, impaired hearing and vision, sleep apnea, malaise and reduced endurance.

Naglazyme is approved for marketing in the U.S., the EU and other international markets. Naglazyme net product revenues for the years ended December 31, 2016, 2015 and 2014 totaled $296.5 million, $303.1 million and $334.4 million, respectively.

Vimizim

Vimizim is an enzyme replacement therapy for the treatment of MPS IV A, a lysosomal storage disorder. MPS IV A is a disease characterized by deficient activity of Nacetylgalactosamine- 6-sulfatase (GALNS) causing excessive lysosomal storage of glycosaminoglycans such as keratan sulfate and chondroitin sulfate. This excessive storage causes a systemic skeletal dysplasia, short stature, and joint abnormalities, which limit mobility and endurance. Malformation of the chest impairs respiratory function, and looseness of joints in the neck cause spinal instability and potentially spinal cord compression. Other symptoms may include hearing loss, corneal clouding, and heart disease. Initial symptoms often become evident in the first five years of life. The disease substantially limits both the quality and length of life of those affected. We have identified over 2,000 patients worldwide suffering from MPS IV A and estimate that the total number of patients suffering from MPS IV A worldwide could be as many as 3,000.

Vimizim was granted marketing approval in the U.S. and the EU in February 2014 and April 2014, respectively, and subsequently in several other international markets. Vimizim net product revenues for the years ended December 31, 2016, 2015 and 2014 totaled $354.1 million, $228.1 million and $77.3 million, respectively.

Product Candidates in Clinical Development

Brineura

Brineura is a recombinant human tripeptidyl peptidase 1 in development for the treatment of patients with CLN2, a form of Batten disease. CLN2 is an incurable, rapidly progressive disease that ends in patient death by 10-12 years of age. Patients are initially healthy but begin to decline at approximately the age of three. We estimate that 1,200-1,600 cases exist worldwide. In January 2015, we announced interim data from an open-label, dose-escalation Phase 1/2 study for Brineura in 24 patients with CLN2 , which indicates that in all nine of the patients in the trial who were followed for at least six months and up to 15 months, the treatment appeared to show stabilization of the disease compared to the natural history based on a standardized measure of motor and language function. The primary objectives of the Phase 1/2 study are to evaluate the safety and tolerability of Brineura and to evaluate effectiveness using a CLN2-specific rating scale score in comparison with natural history data, and the second objectives are to evaluate the impact of treatment on brain atropy in comparison with CLN2 natural history and to characterize pharmacokinetics and immunogenicity. In July 2016, the FDA accepted for priority review our submission of a BLA for Brineura. The EMA validated our MAA in September 2016. We reported data on an additional eight months of treatment in September 2016, which showed a durable and consistent treatment response with all patients continuing to tolerate the therapeutic dose. Although the primary endpoint of our Phase 1/2 study for Brineura was met, our BLA and MAA rely on results from a single Phase 1/2 uncontrolled study in a small patient population of patients. Additionally, Brineura is intended to be used in combination with a delivery device, such as an injector or other delivery system, so Brineura may not be approved or may be substantially delayed in receiving approval if the devices do not gain and/or maintain their own regulatory approvals or clearances. Please see “Risk Factors” included in Part I, Item 1A of this Annual Report on Form 10-K for further discussion of the risk of not obtaining regulatory approval for Brineura and “Government Regulation – Combination Products” below for additional information on combination products. The FDA’s PDUFA action date for Brineura was extended to April 27, 2017, while we anticipate the EMA’s decision in third quarter 2017.

Pegvaliase

Pegvaliase is an investigational enzyme substitution therapy that we are developing as a subcutaneous injection for the treatment of PKU. In August 2010, we announced preliminary results from a Phase 2, open-label dose finding clinical trial of pegvaliase that showed of the seven patients who received at least one mg/kg per week of pegvaliase for at least four weeks, six patients had achieved Phe levels below 600 micromoles per liter. Mild to moderate self-limiting injection site reactions were the most commonly reported toxicity. In April 2011, we initiated an extension of the Phase 2 study to find a shorter induction and titration dosing regimen to an efficacious maintenance dose. In March

2016, we announced that our pivotal Phase 3 PRISM-2 study for pegvaliase met the primary endpoint of change in blood Phe compared with placebo ($p<0.0001$). This ongoing Phase 3 clinical trial includes an open-label study to evaluate safety and blood Phe levels in naïve patients and a randomized controlled study of the Phase 2 extension study patients and patients from the open-label trial to evaluate blood Phe levels and neurocognitive endpoints. Although we met the primary endpoint of the Phase 3 PRISM-2 study, we did not

demonstrate a statistically significant improvement in inattention or mood scores, a key secondary clinical neurocognitive endpoint. The FDA has indicated that lowering Phe blood levels in adults could form the basis for an accelerated approval; however, a favorable outcome on prospectively-specified analyses of inattention in patients with baseline problems with attention would likely be required for full approval. Although we intend to file a BLA for pegvaliase with the FDA in the second quarter of 2017, there is no assurance that a reduction in blood Phe alone will be sufficient to support the FDA's full regulatory approval of pegvaliase.

Vosoritide

Vosoritide (formerly referred to as BMN 111) is a peptide therapeutic in development for the treatment of achondroplasia, the most common form of dwarfism. In September 2012, we announced the results of a Phase 1 clinical trial for vosoritide, which showed vosoritide was generally well-tolerated over the range of single and repeat doses studied. Pharmacokinetic data indicated that the dose levels studied resulted in exposure levels that are expected to stimulate growth based on non-clinical findings. In April 2016, we reported 12-month data for the patients in the 15 µg/kg/day cohort of the Phase 2 open-label, sequential cohort, dose-escalation study of vosoritide in children who are 5-14 years old, which showed a durable and consistent increase in mean annualized growth velocity of 46%-65% from baseline in the group. Vosoritide continued to be well tolerated with no treatment-related serious adverse events or adverse events leading to discontinuation. As further described above under "Recent Developments", in October 2016 we provided a positive update on our Phase 2 study of vosoritide. In December 2016, we initiated the pivotal Phase 3 study of vosoritide, which is a randomized, placebo-controlled 12-month treatment study in approximately 110 children with achondroplasia, ages 5-14.

BMN 270

BMN 270 is an AAV-factor VIII vector, designed to restore factor VIII plasma concentrations, essential for blood clotting in patients with hemophilia A. Hemophilia A, also called factor VIII (FVIII) deficiency or classic hemophilia, is a genetic disorder caused by missing or defective factor VIII, a clotting protein. People living with the disease are not able to form blood clots efficiently and are at risk for excessive bleeding from modest injuries, potentially endangering their lives. People with severe hemophilia often bleed spontaneously into their muscles or joints. The gene therapy program for hemophilia A was originally licensed from University College London and St. Jude Children's Research Hospital in February 2013 and has since been developed at our facilities. According to the World Federation of Hemophilia rankings of severity of hemophilia A, the normal range of Factor VIII activity levels is between 50% and 150%, expressed as a percentage of normal factor activity in blood, and the mild hemophilia A range of Factor VIII activity levels is between 5% and 40%. In July 2016, we announced positive proof-of-concept data from a Phase 1/2 dose-escalation study for BMN 270 in patients with severe hemophilia A, where six of the seven patients treated with the highest dose achieved Factor VIII levels above 50%, and the seventh was above 10%. Post-treatment follow-up ranges were from 12 to 28 weeks. Data from high-dose patients since July 2016 reveals stabilized Factor VIII levels, with a mean annualized bleed rate decline of 91% for patients previously on prophylactic Factor VIII. ALT levels (liver function) for these patients remain in or around normal range. As further described above under "Recent Developments", in January 2017 we announced a positive update to our interim results from the Phase 1/2 study. Patients in the Phase 1/2 study will be monitored for safety for five years. A potentially registration-enabling Phase 2b study is scheduled to begin in the third quarter of 2017.

BMN 250

BMN 250 is an enzyme replacement therapy using a novel fusion NAGLU with a peptide derived from IGF2 for the treatment of MPS IIIB (also known as Sanfilippo Syndrome, Type B). MPS IIIB is a rapidly progressive pediatric brain disease caused by NAGLU enzyme deficiency resulting in accumulation of heparan sulfate (HS) in the brain. The accumulation of HS leads to progressive cognitive decline, loss of developmental milestones, severe hyperactivity, sleep disorders, loss of mobility, and early death. BMN 250 is delivered directly into the central nervous system via an intracerebroventricular access device into the cerebrospinal fluid, which allows for the drug to bypass

the blood brain barrier and distribute directly within the brain. As further described above under “Recent Developments”, in January 2017 we announced positive, preliminary results from a multicenter, international Phase 1/2 clinical trial for BMN 250, which began enrolling patients in April 2016. A complimentary observational study has also been initiated to study the progression of MPS IIIB over time.

Product Candidate Programs Terminated in 2016

Kyndrisa

In January 2015, we completed the acquisition of Prosensa Holding N.V. (Prosensa), a public limited liability company organized under the laws of the Netherlands, for a total purchase price of $751.5 million. Prosensa's lead product candidate was Kyndrisa, an exon-51 skipping compound for the potential treatment of Duchenne muscular dystrophy amenable to exon 51 skipping. As previously reported, in January 2016, the FDA issued a complete response letter to our New Drug Application for Kyndrisa (drisapersen), concluding that the standard of substantial evidence of Kyndrisa's effectiveness had not been met. In May 2016, we withdrew our MAA from the EMA for Kyndrisa. We subsequently discontinued clinical and regulatory development of Kyndrisa as well as the programs for the three other first generation follow-on product candidates, BMN 044, BMN 045 and BMN 053 (other exons).

Reveglucosidase Alfa

As previously reported, in June 2016, we discontinued the clinical and regulatory development program for reveglucosidase alfa. We continue to explore out-licensing opportunities for this program.

Manufacturing

We manufacture Aldurazyme, Naglazyme, Vimizim, Brineura, pegvaliase, and vosoritide in our production facilities located in Novato, California. These facilities have demonstrated compliance with current Good Manufacturing Practices (cGMPs) to the satisfaction of the FDA, the EC and health agencies in other countries for the commercial production of Aldurazyme, Naglazyme and Vimizim. Vialing and packaging are performed by contract manufacturers. We believe that we have ample manufacturing capacity to support commercial demand for both Aldurazyme and Naglazyme for at least the next five years.

We currently manufacture Vimizim and Brineura in our manufacturing facility in Shanbally, Cork, Ireland. This facility has been approved by the FDA, Health Product Regulatory Authorities, EMA, EC, and health agencies in other countries for the testing and release of Vimizim. The Shanbally facility, once approved for bulk substance production, will enhance our business continuity and increase our operating capacity to support the anticipated commercial demand of Vimizim for the next five years. We believe that with this facility and our Novato, California facility, we have ample manufacturing capacity to support commercial demand for Vimizim for at least the next five years. Additionally, we intend to manufacture BMN 250 in this facility.

Firdapse, Kuvan tablet and powder sachet, and BMN 270 are currently manufactured on a contract basis by third-parties. In general, we expect to continue to contract with outside service providers for certain manufacturing services, including drug substance, active pharmaceutical ingredient (API), final product vialing, tableting and sachet production and packaging operations for our products. All of our facilities and those of any third-party manufacturers will be subject to periodic inspections confirming compliance with applicable law and must pass inspection before we can manufacture our drugs for commercial sales. Third-party manufacturers' facilities are subject to periodic inspections to confirm compliance with applicable law and must be cGMPs certified. We believe that our current agreements with third-party manufacturers and suppliers provide for ample operating capacity to support the anticipated clinical and commercial demand for these products. In certain instances, there is only one approved contract manufacturer for certain aspects of the manufacturing process. In such cases, we attempt to prevent disruption of supplies through supply agreements, maintaining safety stock and other appropriate strategies. Although we have never experienced a disruption in supply from our contract manufacturers, we cannot provide assurance that we will not experience a disruption in the future.

In 2016 we began converting an existing facility in Novato, California into a new gene therapy manufacturing facility. We expect to commission this new facility by mid-2017, at which time we plan to manufacture clinical lots of BMN

270 in-house at this new facility. We designed the facility to support the commercial launch of BMN 270, if approved.

Raw Materials

Raw materials and supplies required for the production of our products and product candidates are available in some instances from one supplier and in other instances from multiple suppliers. In those cases where raw materials are only available through one supplier, such supplier may be either a sole source (the only recognized supply source available to us) or a single source (the only approved supply source for us among other sources). We have adopted policies to attempt, to the extent feasible, to minimize our raw material supply risks, including maintenance of greater levels of raw materials inventory and implementation of multiple raw materials sourcing strategies, especially for critical raw materials. Although to date we have not experienced any significant delays in obtaining any raw materials from our suppliers, we cannot provide assurance that we will not face shortages from one or more of them in the future.

Sales and Marketing

We have established a commercial organization, including a sales force, to support our product lines directly in the U.S., Europe, South America and certain other significant markets. For other selected markets, we have signed agreements with other companies to act as distributors of Kuvan, Naglazyme, and Vimizim. Most of these agreements generally grant the distributor the right to market the product in the territory and the obligation to secure all necessary regulatory approvals for commercial or named patient sales. Additional markets are being assessed at this time and additional agreements may be signed in the future.

Genzyme has the exclusive right to distribute, market and sell Aldurazyme globally and is required to purchase its requirements exclusively from us.

In the U.S., our products (other than Aldurazyme) are marketed through our commercial teams, including sales representatives and supporting staff members, who promote our products, directly to physicians in specialties appropriate for each product. Outside of the U.S., our sales representatives and supporting staff members market our products (other than Aldurazyme). We believe that with moderate changes in 2017, the size of our sales force will be appropriate to effectively reach our target audience in markets where our products are directly marketed. The launch of any future products will likely require expansion of our commercial organization, including our sales force, in the U.S. and abroad, and we would need to commit significant additional funds, management’s attention and other resources to such expansion.

We utilize third-party logistics companies to store and distribute our products. Moreover, we use third-party vendors, such as advertising agencies, market research firms and suppliers of marketing and other sales support-related services, to assist with our commercial activities.

Customers

Our Firdapse, Kuvan, Naglazyme, and Vimizim customers include a limited number of specialty pharmacies and end-users, such as hospitals and foreign government agencies. We also sell Naglazyme and Vimizim to our authorized distributors and to certain larger pharmaceutical wholesalers globally, which act as intermediaries between us and end-users and generally do not stock significant quantities of our products. However, in certain countries, particularly in Latin America, governments place large periodic orders for Naglazyme and Vimizim. The timing of these orders can be inconsistent and can create significant quarter to quarter variation in our revenue. During 2016, 42% of our net Firdapse, Kuvan, Naglazyme, and Vimizim product revenues were generated by three customers. Genzyme is our sole customer for Aldurazyme and is responsible for marketing and selling Aldurazyme to third-parties.

Competition

The biopharmaceutical industry is rapidly evolving and highly competitive. Within the industry, there are many public and private companies, including pharmaceutical companies and biotechnology companies that have or may

soon initiate programs for the same indications that our candidate drugs and commercial drugs are intended to treat. Furthermore, universities and non-profit research organizations may have research programs, both early-stage and clinical, in the same disease areas. Our competitors may have advantages over us due to greater financial or

scientific resources, lower labor and other costs, or due to higher headcount and more robust organizational structures. Our competitors have considerable experience in drug manufacturing, preclinical and clinical research, regulatory affairs, marketing, sales, and distribution. They pursue broad patent portfolios and other intellectual property to protect the products they are developing. Their products may outcompete ours due to one or more factors, including faster progress through preclinical and clinical development, lower manufacturing costs, superior safety and efficacy, lower pricing, stronger patent protection, and better marketing, sales, and distribution capabilities. In this event, our products, even if approved, could fail to gain significant market share, and as a result, our business, financial condition and results of operations could be adversely affected.

Our products have no direct approved competition currently on the market, however, other companies are in the development phase with new and generic products. The following is a summary of some of the primary possible future competitors for our products.

Naglazyme, Aldurazyme and Vimizim

In the mucopolysaccharidosis field, several companies are researching treatments using small molecules, gene therapy, and other novel technologies. These companies, however, are likely a year or more away from commercial therapies.

Kuvan and Pegvaliase

There are currently no other approved drugs for the treatment of PKU. However, two companies have filed paragraph IV certifications and submitted ANDAs to produce sapropterin dihydrochloride tablets and powder. In September 2015, we entered into a settlement agreement regarding Kuvan tablets with one of these companies. Please see “Government Regulation – Hatch-Waxman Act” below and “Legal Proceedings” in Part I, Item 3 of this Annual Report on Form 10-K for additional information.

Product Candidates

Brineura, for the treatment of CLN2, has potential competition from earlier stage products, including a preclinical gene therapy product candidate under development by Spark Therapeutics, Inc. Vosoritide, for the treatment of achondroplasia, could have competition from earlier stage products, including preclinical product candidates from Therachon AG and Ascendis Pharma A/S. BMN 250, for the treatment of MPS IIIB, has potential competition from earlier stage product candidates, including a recombinant protein product candidate under development by Alexion Pharmaceuticals Inc. and a preclinical gene therapy program from Abeona Therapeutics Inc. BMN 270, for the treatment of hemophilia A, could have competition from marketed Factor VIII replacement therapies and earlier stage gene therapy programs, including a product candidate under development by Spark Therapeutics, Inc. and preclinical product candidates from other companies. In addition, Hoffmann-La Roche AG and Alnylam Pharmaceuticals, Inc. are developing novel, long-acting product candidates in the clinic for the treatment of hemophilia A. Our other

product candidates have potential competition from earlier stage product candidates, either using similar technology to our programs or different treatment strategies.

Patents and Proprietary Rights

Our success depends on an intellectual property portfolio that supports our future revenue streams and also erects barriers to our competitors. We are maintaining and building our patent portfolio through: filing new patent applications; prosecuting existing applications; and licensing and acquiring new patents and patent applications. Furthermore we seek to protect our ownership of know-how, trade secrets and trademarks through an active program of legal mechanisms including registrations, assignments, confidentiality agreements, material transfer agreements, research collaborations and licenses.

As of January 25, 2017, the number of our worldwide issued patents now stands at 1,170, including 96 patents issued by the U.S. Patent and Trademark Office (the USPTO). Furthermore, our portfolio of pending patent applications totals 426 applications, including 85 pending U.S. applications.

With respect to Naglazyme, we have 53 issued patents, including three U.S. patents. Claims cover our ultrapure N -acetylgalactosamine-4-sulfatase compositions of Naglazyme, methods of treating deficiencies of N -acetylgalactosamine-4-sulfatase, including MPS VI, methods of producing and purifying such ultrapure N -acetylgalactosamine-4-sulfatase compositions and methods of detecting. These patents will expire between 2021 and 2028.

With respect to Kuvan, we own, co-own or have licensed a number of patents and pending patent applications that relate generally to formulations and forms of our drug substance, methods of use for various indications under development and dosing regimens. We have rights to 141 issued patents including 15 issued U.S. patents with claims to a stable tablet and oral solution formulation of 6R-BH4, methods of treating PKU using a once daily dosing regimen, methods of administration of Kuvan with food, crystalline forms of 6R-BH4, and methods of producing 6R-BH4. These patents will expire between 2024 and 2032.

We have rights to 33 issued patents, including six U.S. patents, related to Aldurazyme. These patents cover our ultra-pure alpha-L-iduronidase composition of Aldurazyme, methods of treating deficiencies of alpha-L-iduronidase by administering pharmaceutical compositions comprising such ultra-pure alpha-L-iduronidase, a method of purifying such ultra-pure alpha-L-iduronidase and the use of compositions of ultra-pure biologically active fragments of alpha-L-iduronidase. These patents will expire in 2019 and 2020. There are U.S. patents on alpha-L-iduronidase owned and controlled by a third-party. We have examined such issued U.S. patents, the related U.S. and foreign applications and their file histories, the prior art and other information. Corresponding foreign applications were filed in Canada, Europe and Japan. The European application was rejected and abandoned and cannot be re-filed. The Japanese application has also lapsed and cannot be re-filed. Claims in the related Canadian application issued in 2007. We believe that such patents may not survive a challenge to patent validity but that it is unlikely that a court in any country would order us to stop marketing the only life-saving drug that is currently approved for this disease. However, the processes of patent law are uncertain and any patent proceeding is subject to multiple unanticipated outcomes. We believe that it is in the best interest of our joint venture with Genzyme to market Aldurazyme with commercial diligence, in order to provide MPS I patients with the benefits of Aldurazyme. We believe that these patents and patent applications do not affect our ability to market Aldurazyme in Europe.

We have patent protection in the European Patent Organization countries for Firdapse for the treatment of LEMS. We have no issued patents in the U.S. for Firdapse for the treatment of LEMS. These patents will expire in 2022.

With respect to Vimizim, we own or have licensed a number of patents and pending patent applications that relate generally to compositions of matter, methods of use and methods of production. We have rights to 173 issued patents including 15 issued U.S. patents with claims to compositions of purified recombinant N-acetylgalactosamine-6-sulfate sulfatase (Vimizim) methods of treating Morquio Syndrome and sulfatase-modifying factor I (SUMF1) polypeptides and nucleic acids used in the manufacture of Vimizim. Issued U.S. patents cover SUMF1 compositions (set to expire in 2019), purified recombinant Vimizim compositions (set to expire in 2029) and methods of treating Morquio Syndrome (set to expire in 2029). We also have issued U.S. and European patents that cover methods of production (set to expire in 2024) and formulations (set to expire in 2031).

With respect to our clinical product candidates, we believe we have the necessary intellectual property rights to allowing us to undertake the development of these candidates. Certain of our product candidates are in therapeutic areas that have been the subject of many years of extensive research and development by academic organizations and third-parties who may control patents or other intellectual property that they might assert against us, should one or more of our product candidates in these therapeutic areas succeed in obtaining regulatory approval and thereafter be commercialized. We continually evaluate the intellectual property rights of others in these areas in order to determine whether a claim of infringement may be made by others against us. Should we determine that a third-party has intellectual property rights that could impact our ability to freely market a compound we consider a number of factors in determining how best to prepare for the commercialization of any such product candidate. In making this determination we consider, among other things, the stage of development of our product candidate and whether we

and our outside counsel believe the intellectual property rights of others are valid, whether we infringe the intellectual property rights of others, whether a license is available upon commercially reasonable terms, whether we will seek to challenge the intellectual property rights of others, and the likelihood of and liability resulting from an adverse outcome should we be found to infringe the intellectual property rights of others.

Government Regulation

Regulation by governmental authorities in the U.S. and other countries is a significant factor in the development, manufacture, commercialization, pricing and reimbursement of our products. Our industry is subject to significant federal, state, local and foreign regulation. Our present and future business has been, and will continue to be, subject to a variety of laws in the U.S. and other jurisdictions. In the U.S., failure to comply with applicable U.S. requirements may subject a company to a variety of administrative or judicial sanctions, such as FDA refusal to approve pending new drug applications, or NDAs, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties, and criminal prosecution.

Our products require approval from the FDA, the EMA and corresponding agencies in other countries before they can be marketed.

Approval Process in the U.S. and EU

Pharmaceutical product development in the U.S. and the EU typically involves preclinical laboratory and animal tests, the submission to the applicable regulatory agency of an application (e.g., an investigational new drug application (IND) or a clinical trial application (CTA)), which must become effective before clinical testing may commence, and adequate and well-controlled human clinical trials to establish the safety and effectiveness of the drug for each indication for which marketing approval is sought. Satisfaction of FDA and EMA pre-market approval requirements typically takes many years and the actual time required may vary substantially based upon the type, complexity and novelty of the product or disease.

Preclinical tests include laboratory evaluation, as well as animal studies, to assess the characteristics and potential pharmacology, pharmacokinetics and toxicity of the product. The conduct of the preclinical tests must comply with FDA and/or EMA regulations and requirements, including good laboratory practices. The results of preclinical testing, along with other information, including information about product chemistry, manufacturing and controls and a proposed clinical trial protocol are submitted to the applicable regulatory agency as part of an IND or CTA. Long term preclinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue after the IND or CTA is submitted. Until the CTA or IND is approved, or deemed approved following a waiting period, we may not start the clinical trial in the relevant jurisdiction.

Clinical trials involve the administration of the investigational new drug to healthy volunteers or patients under the supervision of a qualified investigator. Clinical trials must be conducted in compliance with applicable regulations, good clinical practices (GCP), as well as under protocols detailing the objectives of the trial and the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. Each protocol involving testing on patients and subsequent protocol amendments must be submitted to the FDA as part of the IND and to the relevant regulatory agency in the EU as part of a new CTA.

The regulatory agencies may order the temporary halt or permanent discontinuation of a clinical trial at any time or impose other sanctions if they believe that the clinical trial is not being conducted in accordance with applicable requirements or presents an unacceptable risk to the clinical trial patients. The study protocol and informed consent information for patients in clinical trials must also be submitted to an institutional review board (IRB) or ethics committee, for approval. An IRB/ethics committee may also require the clinical trial at the site to be halted, either temporarily or permanently, for failure to comply with the IRB/ethics committee’s requirements, or may impose other conditions.

Clinical trials to support NDAs, biologics license applications BLAs, or MAAs for marketing approval are typically conducted in three sequential phases, but the phases may overlap or be combined. In Phase 1, the initial introduction of the drug into healthy human subjects or patients, the drug is tested to assess metabolism, pharmacokinetics, pharmacological actions, side effects associated with increasing doses and, if possible, early evidence on

effectiveness. Phase 2 usually involves trials in a limited patient population, to determine the effectiveness of the drug for a particular indication or indications, dosage tolerance and optimum dosage, and to identify common adverse effects and safety risks. If a compound demonstrates evidence of effectiveness and an acceptable safety profile in Phase 2 evaluations, Phase 3 trials are undertaken to obtain the additional information about clinical efficacy and safety in a larger number of patients, typically at geographically dispersed clinical trial

sites. After completion of the required clinical testing, an NDA or BLA is prepared and submitted to the FDA and an MAA is prepared and submitted to the EMA. FDA approval of the NDA or BLA is required before marketing of the product may begin in the U.S. and approval of the MAA by the EC is required before marketing of the product may begin in the EU. The NDA, BLA or MAA must include the results of all preclinical, clinical and other testing, a compilation of data relating to the product's pharmacology, chemistry, manufacture and controls and proposed labeling, among other things. In the U.S., each NDA or BLA is subject to a significant user fee at the time of submission, unless a waiver is granted by the FDA.

The FDA and the EMA initially review the applications for a threshold determination that it is sufficiently complete to permit substantive review, typically within 30-60 days. The FDA or the EMA may request additional information rather than accepting an NDA/BLA or MAA, respectively, for filing or validation. Once the submission is accepted, the applicable agency begins an in-depth review. For the FDA, the review period for standard review applications is typically an additional ten months and, for priority review of drugs, that is, drugs that the FDA determines address a significant unmet need and represent a significant improvement over existing therapy, the review period is typically an additional six months in duration. The review process may be extended by the FDA for three additional months to consider new information submitted during the review or clarification regarding information already provided in the submission. The FDA may also refer applications for novel products or products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations. After the FDA evaluates the information provided in the NDA/BLA, it issues an approval letter, or a complete response letter. A complete response letter outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed, the FDA will re-initiate review. If it is satisfied that the deficiencies have been addressed, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. It is not unusual, however, for the FDA to issue a complete response letter because it believes that the drug is not safe enough or effective enough or because it does not believe that the data submitted are reliable or conclusive.

For the EMA, an application designated as standard review typically lasts approximately eleven months depending on the length of time sponsors take to address EMA questions. The accelerated assessment procedure is applicable to marketing authorization applications for medicinal products that are expected to be of major public health interest. For applications that receive accelerated assessment designation and are able to remain on this timeline the review typically lasts approximately seven months depending on the length of time sponsors take to address EMA questions. It is not unusual, however, for applications that receive accelerated assessment designation to revert to standard review, typically because the EMA has determined that the significance of the questions that the company needs to address would be more appropriate under the standard review timelines. At the end of the review period, EMA will issue an opinion either in support of marketing authorization (positive opinion) or recommending refusal of a marketing authorization (negative opinion). In the event of a negative opinion, the company may request a re-examination of the application. Within 60 days the company must provide the EMA detailed grounds for requesting re-examination. Within 60 days of providing this information, the EMA will issue an opinion either in support of marketing authorization (positive opinion) or recommending refusal of a marketing authorization (negative opinion). In the event of a positive opinion, the EC will then grant marketing authorization in approximately 67 days. The EC follows the recommendation of the EMA in almost all cases.

During the review period, the FDA and/or the EMA will typically inspect one or more clinical sites and/or the sponsor to assure compliance with GCP regulations and will inspect the facility or the facilities at which the drug is manufactured to ensure compliance with cGMPs regulations. Neither the FDA nor the EMA will approve the product unless compliance is satisfactory and the application contains data that provide substantial evidence that the drug is safe and effective in the indication studied.

A marketing approval authorizes commercial marketing of the drug with specific prescribing information for specific indications. As a condition of NDA or BLA approval, the FDA may require a risk evaluation and mitigation strategy (REMS), to help ensure that the benefits of the drug outweigh the potential risks. REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use (ETASU). ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing

only under certain circumstances, special monitoring and the use of patient registries. The requirement for REMS can materially affect the potential market and profitability of the drug. Moreover, product approval may require substantial post-approval testing and surveillance to monitor the drug's safety or efficacy. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

Combination Products

A combination product is a product comprised of (i) two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; (ii) two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products; (iii) a drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or (iv) any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

The FDA is divided into various branches, or Centers, by product type. Different Centers typically review drug, biologic, or device applications. In order to review an application for a combination product, the FDA must decide which Center should be responsible for the review. FDA regulations require that the FDA determine the combination product's primary mode of action, or PMOA, which is the single mode of a combination product that provides the most important therapeutic action of the combination product. The Center that regulates that portion of the product that generates the PMOA becomes the lead evaluator. If there are two independent modes of action, neither of which is subordinate to the other, the FDA makes a determination as to which Center to assign the product based on consistency with other combination products raising similar types of safety and effectiveness questions or to the Center with the most expertise in evaluating the most significant safety and effectiveness questions raised by the combination product. When evaluating an application, a lead Center may consult other Centers but still retain complete reviewing authority, or it may collaborate with another Center, by which the Center assigns review of a specific section of the application to another Center, delegating its review authority for that section. Typically, the FDA requires a single marketing application submitted to the Center selected to be the lead evaluator, although the agency has the discretion to require separate applications to more than one Center. One reason to submit multiple evaluations is if the applicant wishes to receive some benefit that accrues only from approval under a particular type of application, like new drug product exclusivity. If multiple applications are submitted, each may be evaluated by a different lead Center.

The 21st Century Cures Act was signed into law on December 13, 2016. In Section 3038, the FDA is instructed that if a combination product has an approved constituent (e.g., an investigational drug delivered with devices already 510(k) cleared by the FDA), the FDA may only require the sponsor to submit data or information necessary to meet the standard for clearance or approval, taking into consideration incremental risks and benefits posed by the combination product, using a risk-based approach and taking into account any prior finding of safety and effectiveness or substantial equivalence for the approved constituent. It appears that the primary purpose of this provision is to reduce the burden of proving the safety and effectiveness of the approved constituent by leveraging the FDA's prior clearance or approval. The FDA is instructed to focus on the new constituent plus the incremental risk created by a new use of the approved constituent. It is too soon to understand how the FDA will implement this provision.

Disclosure of Clinical Trial Information

Sponsors of clinical trials of FDA-regulated products, including drugs and biologics, are required to register and disclose certain clinical trial information. Information related to the product, patient population, phase of investigation, study sites and investigators, and other aspects of the clinical trial are then made public as part of the registration. Sponsors are also obligated to discuss the results of their clinical trials after completion. In certain

circumstances, disclosure of the results of these trials can be delayed for up to two years after the date of completion of the trial. Competitors may use this publicly-available information to gain knowledge regarding the progress of development programs. Moreover, there is an increasing trend in the EU requiring public disclosure of development data, in particular clinical trial data. These data were traditionally regarded as confidential commercial information; however, under policies recently adopted in the EU, clinical study data submitted to the EMA in MAAs, including pre-clinical data, and patient level data, may be subject to public disclosure.

The Hatch-Waxman Act

Upon approval of a drug through an NDA, applicants are required to submit to the FDA each patent that covers the applicant's product or FDA approved method of using this product. Those patents are then published in the FDA's Orange Book. Drugs listed in the Orange Book can, in turn, be cited by potential competitors in support of approval of an ANDA. Generally, an ANDA provides for marketing of a drug product that has the same active ingredients in the same strength(s), route of administration, and dosage form as the listed drug and has been shown through bioequivalence testing to be therapeutically equivalent to the listed drug. ANDA applicants are not required to conduct or submit results of pre-clinical or clinical tests to prove the safety or effectiveness of their drug product, other than the requirement for bioequivalence testing. Drugs approved in this way are commonly referred to as "generic equivalents" to the listed drug, and can often be substituted by pharmacists under prescriptions written for the original listed drug.

The ANDA applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book. Specifically, the applicant must certify that: (i) the required patent information has not been filed; (ii) the listed patent has expired; (iii) the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or (iv) the listed patent is invalid or will not be infringed by the new product. A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid is called a paragraph IV certification. If the applicant does not challenge the listed patents, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired. Alternatively, for a patent covering an approved method of use, an ANDA applicant may submit a statement to the FDA that the company is not seeking approval for the covered use.

If the ANDA applicant has submitted a paragraph IV certification to the FDA, the applicant must also send notice of the paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the paragraph IV certification. The filing of a patent infringement lawsuit within 45 days of the receipt of a paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months, expiration of the patent, settlement of the lawsuit or a decision in the infringement case that is favorable to the ANDA applicant.

The ANDA application also will not be approved until any non-patent exclusivity, such as exclusivity for obtaining approval of a new chemical entity, listed in the Orange Book for the referenced product has expired. Federal law provides a period of five years following approval of a drug containing no previously approved active moiety, during which ANDAs for generic versions of those drugs cannot be submitted unless the submission contains a paragraph IV challenge to a listed patent, in which case the submission may be made four years following the original product approval. Federal law provides for a period of three years of exclusivity following approval of a listed drug that contains previously approved active ingredients but is approved in a new dosage form, route of administration or combination, or for a new condition of use, the approval of which was required to be supported by new clinical trials conducted by or for the sponsor, during which the FDA cannot grant effective approval of an ANDA based on that listed drug. Both of the five-year and three-year exclusivity periods, as well as any unexpired patents listed in the Orange Book for the listed drug, can be extended by six months if the FDA grants the NDA sponsor a period of pediatric exclusivity based on studies submitted by the sponsor in response to a written request.

Orphan Drug Designation

Orphan drug designation is granted by the FDA and EMA to drugs intended to treat a rare disease or condition, which in the U.S. is defined as having a prevalence of less than 200,000 individuals in the U.S. and in the

EU is defined as no more than five in 10,000 people in the EU, which is equivalent to around 250,000 people or less. Orphan drug designation must be requested before submitting a marketing application.

Orphan drug designation does not shorten the regulatory review and approval process, nor does it provide any advantage in the regulatory review and approval process. However, if an orphan drug later receives approval for the indication for which it has designation, the relevant regulatory authority may not approve any other applications to market the same drug for the same indication, except in very limited circumstances, for seven years in the U.S. and ten years in the EU. Among the other benefits of orphan drug designation are tax credits for certain research and a waiver of the NDA/BLA application user fee. Although obtaining approval to market a product with orphan drug exclusivity may be advantageous, we cannot be certain:

- that we will be the first to obtain approval for any drug for which we obtain orphan drug designation;
- that orphan drug designation will result in any commercial advantage or reduce competition; or
- that the limited exceptions to this exclusivity will not be invoked by the relevant regulatory authority.

Orphan drug exclusive marketing rights may be lost under certain conditions, such as if the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug.

Breakthrough Therapy Designation

The FDA is also required to expedite the development and review of the application for approval of drugs that are intended to treat a serious or life-threatening disease or condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Under the breakthrough therapy program, the sponsor of a new drug candidate may request that the FDA designate the drug candidate for a specific indication as a breakthrough therapy concurrent with, or after, the filing of the IND for the drug candidate. The FDA must determine if the drug candidate qualifies for breakthrough therapy designation within 60 days of receipt of the sponsor's request.

PRIME Designation

The EMA launched its Priority Medicines (PRIME) regulatory initiative to enhance support for the development of therapies that target an unmet medical need. The initiative focuses on drugs that may offer a major therapeutic advantage over existing treatments, or benefit patients with no treatment options. These therapies are considered priority medicines within the EU. Through PRIME, the EMA offers early, proactive and enhanced support to drug developers to optimize the generation of robust data on a therapy's benefits and risks and enable accelerated assessment of drug applications.

Pediatric Information

Under the Pediatric Research Equity Act of 2007 (PREA), NDAs or BLAs or supplements to NDAs or BLAs must contain data to assess the safety and effectiveness of the drug for the claimed indication(s) in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any drug for an indication for which orphan drug designation has been granted. The Best Pharmaceuticals for Children Act (BPCA) provides sponsors of NDAs with an additional six-month period of market exclusivity for all unexpired patent or non-patent exclusivity on all forms of the drug containing the active moiety if the sponsor submits results of pediatric studies specifically requested by the FDA under BPCA within required timeframes. The Biologics Price Competition and Innovation Act of 2009 (BPCIA) provides sponsors of BLAs an additional six-month extension for all unexpired non-patent market exclusivity on all forms of the biological containing the active moiety pursuant to the BPCA if the conditions under the BPCA are met.

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Fast Track Designation

The FDA is required to facilitate the development and expedite the review of drugs that are intended for the treatment of a serious or life-threatening condition for which there is no effective treatment and that demonstrate the potential to address unmet medical needs for the condition. Under the FDA's fast track program, the sponsor of a new drug candidate may request that the FDA designate the drug candidate for a specific indication as a fast track drug concurrent with or after the filing of the IND for the drug candidate. The FDA must determine if the drug candidate qualifies for fast track designation within 60 days of receipt of the sponsor's request.

In addition to other benefits, such as the ability to use surrogate endpoints and have greater interactions with the FDA, the FDA may initiate review of sections of a fast track drug's NDA or BLA before the application is complete. This rolling review is available if the applicant provides and the FDA approves a schedule for the submission of the remaining information and the applicant pays applicable user fees. However, the FDA's time period goal for reviewing an application does not begin until the last section of the NDA or BLA is submitted. Additionally, the fast track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Post-Approval Regulatory Requirements

Following approval, the FDA and the EMA will impose certain post-approval requirements related to a product. For instance, the FDA closely regulates the post-approval marketing and promotion of approved products, including standards and regulations for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities and promotional activities involving the Internet.

Approved products may be marketed only for the approved indications and in accordance with the provisions of the approved labeling. Changes to some of the conditions established in an approved application, including changes in indications, labeling, or manufacturing processes or facilities, may require a submission to and approval by the FDA or the EMA, as applicable, before the change can be implemented. An NDA/BLA or MAA supplement for a new indication typically requires clinical data similar to that in the original application, and similar procedures and actions in reviewing NDA/ BLA or MAA supplements as in reviewing NDAs/BLAs and MAAs.

Adverse event reporting and submission of periodic reports is required following marketing approval. Either the FDA or EMA may also require post-marketing testing, known as Phase 4 testing, REMS, and surveillance to monitor the effects of an approved product or place conditions on an approval that could restrict the distribution or use of the product. In addition, quality control as well as the manufacture, packaging, and labeling procedures must continue to conform to cGMPs after approval. Drug and biological product manufacturers and certain of their subcontractors are subject to periodic unannounced inspections by the FDA or the EMA during which the agency inspects manufacturing facilities to access compliance with cGMPs. Accordingly, manufacturers must continue to expend time, money and effort in the areas of production and quality control to maintain compliance with cGMPs. Regulatory authorities may withdraw product approvals or request product recalls if a company fails to comply with regulatory standards, if it encounters problems following initial marketing, or if previously unrecognized problems are subsequently discovered. In addition, prescription drug manufactures in the U.S. must comply with applicable provisions of the Drug Supply Chain Security Act and provide and receive product tracing information, maintain appropriate licenses, ensure they only work with other properly licensed entities and have procedures in place to identify and properly handle suspect and illegitimate products.

Good Manufacturing Practices

The FDA, the EMA and other regulatory agencies regulate and inspect equipment, facilities and processes used in the manufacture of pharmaceutical and biologic products prior to approving a product. If, after receiving approval from regulatory agencies, a company makes a material change in manufacturing equipment, location or process, additional regulatory review and approval may be required. All facilities and manufacturing techniques used for the manufacture of our products must comply with applicable regulations governing the production of pharmaceutical products known as “Good Manufacturing Practices,” or GMPs.

The FDA, the EMA and other regulatory agencies also conduct regular, periodic visits to re-inspect equipment, facilities and processes following initial approval of a product. If, as a result of these inspections, it is determined that our equipment, facilities or processes do not comply with applicable regulations and conditions of product approval, regulatory agencies may require product recall, issue warning or similar letters or may seek civil, criminal, or administrative sanctions against us.

Health Reform

The U.S. and some foreign jurisdictions are considering or have enacted a number of legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our products profitably. For example, in the U.S. the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010 (as amended, the PPACA), is a sweeping measure intended to improve quality of care, constrain healthcare spending, and expand healthcare coverage within the U.S., primarily through the imposition of health insurance mandates on employers and individuals and expansion of the Medicaid program.

The BPCIA, which was enacted as part of the PPACA, created an abbreviated approval pathway for biological products that are demonstrated to be “biosimilar” or “interchangeable” with an FDA-licensed reference biological product. Biosimilarity sufficient to reference a prior FDA-licensed product requires that there be no differences in conditions of use, route of administration, dosage form, and strength, and no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency. Biosimilarity must be shown through analytical studies, animal studies, and at least one clinical study, absent a waiver from the Secretary of the U.S. Department of Health and Human Services. In order to meet the higher hurdle of interchangeability, a sponsor must demonstrate that the biosimilar product can be expected to produce the same clinical result as the reference product, and for a product that is administered more than once, that the risk of switching between the reference product and biosimilar product is not greater than the risk of maintaining the patient on the reference product. The first biosimilar product was approved under the BPCIA in 2015, though no interchangeable products have been approved to date. Complexities associated with the larger, and often more complex, structures of biological products, as well as the process by which such products are manufactured, pose significant hurdles to implementation that are still being evaluated by the FDA. A reference biologic is granted 12 years of exclusivity from the time of first licensure of the reference product and no application for a biosimilar can be submitted for four years from the date of licensure of the reference product. The first biologic product submitted under the abbreviated approval pathway that is determined to be interchangeable with the reference product has exclusivity against a finding of interchangeability for other biologics for the same condition of use for the lesser of (i) one year after first commercial marketing of the first interchangeable biosimilar, (ii) eighteen months after the first interchangeable biosimilar is approved if there is not patent challenge, (iii) eighteen months after resolution of a lawsuit over the patents of the reference biologic in favor of the first interchangeable biosimilar applicant, or (iv) 42 months after the first interchangeable biosimilar’s application has been approved if a patent lawsuit is ongoing within the 42-month period.

The PPACA also imposed a new fee on certain manufacturers and importers of branded prescription drugs (excluding orphan drugs under certain conditions). The annual fee is apportioned among the participating companies based on each company’s sales of qualifying products to, or use by, certain U.S. government programs during the preceding year. Other provisions of the law, which have varying effective dates, may also affect us and will likely increase

certain of our costs. For example, the Medicaid rebate rate was increased and the volume of rebated drugs has been expanded to include beneficiaries in Medicaid managed care organizations. Among other things, the PPACA also expanded the 340B drug discount program (excluding orphan drugs), including the creation of new

penalties for non-compliance, and included a 50% discount on brand name drugs for Medicare Part D participants in the coverage gap, or "donut hole." The law also revised the definition of "average manufacturer price" for reporting purposes, which could increase the amount of the Medicaid drug rebates paid to states. Substantial new provisions affecting compliance also have been added, which may require us to modify our business practices with health care practitioners.

In addition, drug manufacturers are required to collect and report annually information on payments or transfers of value to physicians and teaching hospitals, as well as investment interests held by physicians and their immediate family members during the preceding calendar year. The reported data are posted in searchable form on a public web site. Failure to submit required information may result in civil monetary penalties. It is still unclear the full impact that the PPACA will have on our business. There have been judicial and Congressional challenges to certain aspects of the PPACA, and we expect that there will be additional challenges and amendments in the future, especially with the recent change in administration.

In January 2017, Congress voted to adopt a budget resolution for fiscal year 2017, or the Budget Resolution, that authorizes the implementation of legislation that would repeal portions of the PPACA. Although the Budget Resolution is not a law, it is widely viewed as the first step toward the passage of legislation that would repeal certain aspects of the PPACA. Further, on January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the PPACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the PPACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. Congress also could consider subsequent legislation to replace elements of the PPACA that are repealed.

Other legislative changes have been proposed and adopted since the PPACA was enacted. These changes included the Budget Control Act of 2011, which caused aggregate reductions to Medicare payments to providers of up to 2% per fiscal year effective April 1, 2013 which, following passage of the Bipartisan Budget Act of 2015, will stay in effect through 2025 unless additional Congressional action is taken. Further, the American Taxpayer Relief Act of 2012, among other things, further reduced Medicare payments to several types of providers. Additionally, there has been increasing legislative and enforcement interest in the U.S. with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed bills designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs.

Other U.S. Regulatory Requirements

In addition to FDA restrictions on marketing of pharmaceutical products, several other types of state and federal laws have been applied to restrict certain business and marketing practices in the pharmaceutical industry in recent years. These laws include anti-kickback, false claims, patient data privacy and security, and transparency statutes and regulations.

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce or in return for purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item or service reimbursable under Medicare, Medicaid or other federally financed healthcare programs. The PPACA amended the intent requirement of the federal Anti-Kickback and criminal healthcare fraud statutes such that a person or entity no longer needs to have actual knowledge of these statutes or specific intent to violate them in order to commit a violation. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers on the other. Although there are a number of statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution or other regulatory sanctions, the exemptions and safe harbors are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor.

Federal false claims laws prohibit any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government, or knowingly making, or causing to be made, a false statement to have a false claim paid. The PPACA amended the statute so that the government may assert that a claim including items or services resulting from a violation of the federal anti-kickback statute constitutes a false or fraudulent claim for

purposes of the false claims laws. Recently, several pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly inflating drug prices they report to pricing services, which in turn are used by the government to set Medicare and Medicaid reimbursement rates, and for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. In addition, certain marketing practices, including off-label promotion, may also violate false claims laws.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for, among other things, executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters.

HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, on certain types of individuals and entities, with respect to safeguarding the privacy, security and transmission of individually identifiable health information.

The federal Physician Payments Sunshine Act requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to the Centers for Medicare & Medicaid Services, or CMS, information related to payments or other transfers of value made to physicians and teaching hospitals, and applicable manufacturers and applicable group purchasing organizations to report annually to CMS ownership and investment interests held by the physicians and their immediate family members.

The majority of states also have statutes or regulations similar to the federal Anti-Kickback Statute and false claims laws, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payer. Sanctions under these federal and state laws may include civil monetary penalties, damages, monetary fines, disgorgement, exclusion of a company's products from reimbursement under federal healthcare programs, criminal fines, contractual damages, reputational harm, diminished profits and future earnings, curtailment of operations and imprisonment. Several states now require pharmaceutical companies to report expenses relating to the marketing and promotion of pharmaceutical products and to report gifts and payments to individual physicians in these states. Other states prohibit providing various other marketing-related activities. Still other states require the posting of information relating to clinical studies and their outcomes. In addition, states including California, Connecticut, Nevada and Massachusetts require pharmaceutical companies to implement compliance programs or marketing codes. Currently, several additional states are considering similar proposals. Compliance with these laws is difficult and time consuming, and companies that do not comply with these state laws face civil penalties.

Approval Outside of the U.S./EU

For marketing outside the U.S. and the EU, we are subject to foreign regulatory requirements governing human clinical testing and marketing approval for our products. These requirements vary by jurisdiction, can differ from those in the U.S. and the EU and may require us to perform additional pre-clinical or clinical testing. The amount of time required to obtain necessary approvals may be longer or shorter than that required for FDA or EMA approval. In many countries outside of the U.S., approvals for pricing, coverage and reimbursement offered by third-party payers, including government payers and private insurance plans, are also required.

Anti-Corruption Legislation

The U.S. Foreign Corrupt Practices Act (FCPA), to which we are subject, prohibits corporations and individuals from engaging in certain activities to obtain or retain business or to influence a person working in an official capacity. It is

illegal to pay, offer to pay or authorize the payment of anything of value to any foreign government official, government staff member, political party or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in an official capacity. Similar laws exist in other countries, such as the United Kingdom, that restrict improper payments to public and private parties. Many countries have laws prohibiting these types of payments within the respective country. Historically, pharmaceutical companies have been the target of FCPA and other anti-corruption investigations and penalties.

Pricing and Reimbursement

Because the course of treatment for patients using our products is expensive, sales of our products depend, in significant part, on the availability and extent of coverage and reimbursement offered by third-party payers, including government payers and private insurance plans. Governments may regulate access to, prices of or reimbursement levels for our products to control costs or to affect levels of use of our products, and private insurers may be influenced by government reimbursement methodologies.

Third-party payers, such as government or private health care insurers, carefully review and increasingly challenge the prices charged for drugs, examine their medical necessity, and review their cost effectiveness. Reimbursement rates from private companies vary depending on the third-party payer, the insurance plan and other factors. One payer's determination to provide coverage for a product does not assure that other payers will also provide coverage for the product. Moreover, the process for determining whether a third-party payer will provide coverage for a product may be separate from the process for setting the price of a product or for establishing the reimbursement rate that such a payer will pay for the product. A payer's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development. In addition, emphasis on managed care in the U.S. has increased and we expect will continue to increase the pressure on pharmaceutical pricing. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we or our collaborators receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Outside of the U.S. our products are paid for by a variety of payers, with governments being the primary source of payment. Reimbursement in the EU and many other territories must be negotiated on a country-by-country basis and in many countries the product cannot be commercially launched until reimbursement is approved. In many countries the government closely regulates drug pricing and reimbursement and often has a significant discretion in determining whether a product will be reimbursed at all and, if it is, how much will be paid. Negotiating prices with governmental authorities can delay patient access to and commercialization of our products. Payers in many countries use a variety of cost-containment measures that can include referencing prices in other countries and using those reference prices to set their own price, mandatory price cuts and rebates. This international patchwork of price regulation has led to different prices across countries and some cross-border trade in our products from markets with lower prices. Even after a price is negotiated, countries frequently request or require adjustments to the price and other concessions over time.

Government Programs for Marketed Drugs in the U.S.

Medicaid, the 340B Drug Pricing Program, and Medicare

Federal law requires that a pharmaceutical manufacturer, as a condition of having its products receive federal reimbursement under Medicaid and Medicare Part B, must pay rebates to state Medicaid programs for all units of its covered outpatient drugs dispensed to Medicaid beneficiaries and paid for by a state Medicaid program under either a fee-for-service arrangement or through a managed care organization. This federal requirement is effectuated through a Medicaid drug rebate agreement between the manufacturer and the Secretary of Health and Human Services. CMS administers the Medicaid drug rebate agreements, which provide, among other things, that the drug manufacturer will pay rebates to each state Medicaid agency on a quarterly basis and report certain price information on a monthly and quarterly basis. The rebates are based on prices reported to CMS by manufacturers for their covered outpatient drugs. For non-innovator products, generally generic drugs marketed under ANDAs, the rebate amount is 13% of the average manufacturer price (AMP) for the quarter. The AMP is the weighted average of prices paid to the manufacturer (1) directly by retail community pharmacies and (2) by wholesalers for drugs distributed to retail community pharmacies. For innovator products (i.e., drugs that are marketed under NDAs or BLAs), the rebate amount is the

greater of 23.1% of the AMP for the quarter or the difference between such AMP and the best price for that same quarter. The best price is essentially the lowest price available to non-governmental entities. Innovator products may also be subject to an additional rebate that is based on the amount, if any, by which the product's AMP for a given quarter exceeds the inflation-adjusted baseline AMP, which for most drugs is the AMP for the first full quarter after launch. Beginning in 2017, non-innovator products are also subject to an additional rebate.

The statutory definition of AMP was amended in 2010. CMS has released the final rule pertaining to AMP and other aspects of the Medicaid drug rebate program, which was effective as of April 1, 2016.

The terms of participation in the Medicaid drug rebate program impose an obligation to correct the prices reported in previous quarters, as may be necessary. Any such corrections could result in additional or lesser rebate liability, depending on the direction of the correction. In addition to retroactive rebates, if a manufacturer were found to have knowingly submitted false information to the government, federal law provides for civil monetary penalties for failing to provide required information, late submission of required information, and false information.

A manufacturer must also participate in a federal program known as the 340B drug pricing program in order for federal funds to be available to pay for the manufacturer's drugs under Medicaid and Medicare Part B. Under this program, the participating manufacturer agrees to charge certain safety net healthcare providers no more than an established discounted price for its covered outpatient drugs. The formula for determining the discounted price is defined by statute and is based on the AMP and the unit rebate amount as calculated under the Medicaid drug rebate program, discussed above.

Federal law also requires that manufacturers report data on a quarterly basis to CMS regarding the pricing of drugs that are separately reimbursable under Medicare Part B. These are generally drugs, such as injectable products, that are administered "incident to" a physician service and are not generally self-administered. The pricing information submitted by manufacturers is the basis for reimbursement to physicians and suppliers for drugs covered under Medicare Part B. As with the Medicaid drug rebate program, federal law provides for civil monetary penalties for failing to provide required information, late submission of required information, and false information.

Medicare Part D provides prescription drug benefits for seniors and people with disabilities. Medicare Part D beneficiaries have a gap in their coverage (between the initial coverage limit and the point at which catastrophic coverage begins) where Medicare does not cover their prescription drug costs, known as the coverage gap. However, by 2020 Medicare Part D beneficiaries will pay 25% of drug costs after they reach the initial coverage limit – the same percentage they were responsible for before they reached that limit – thereby closing the coverage gap. The cost of closing the coverage gap is being borne by innovator companies and the government through subsidies. Beginning in 2011, each manufacturer of drugs approved under NDAs or BLAs was required to enter into a Medicare Part D coverage gap discount agreement and provide a 50% discount on those drugs dispensed to Medicare beneficiaries in the coverage gap, in order for its drugs to be reimbursed by Medicare Part D.

Federal Contracting/Pricing Requirements

Manufacturers are also required to make their covered drugs, which are generally drugs approved under NDAs or BLAs, available to authorized users of the Federal Supply Schedule (FSS) of the General Services Administration. The law also requires manufacturers to offer deeply discounted FSS contract pricing for purchases of their covered drugs by the Department of Veterans Affairs, the Department of Defense, the Coast Guard, and the Public Health Service (including the Indian Health Service) in order for federal funding to be available for reimbursement or purchase of the manufacturer's drugs under certain federal programs. FSS pricing to those four federal agencies for covered drugs must be no more than the Federal Ceiling Price (FCP), which is at least 24% below the Non-Federal Average Manufacturer Price (Non-FAMP) for the prior year. The Non-FAMP is the average price for covered drugs sold to wholesalers or other middlemen, net of any price reductions.

The accuracy of a manufacturer's reported Non-FAMPs, FCPs, or FSS contract prices may be audited by the government. Among the remedies available to the government for inaccuracies is recoupment of any overcharges to the four specified federal agencies based on those inaccuracies. If a manufacturer were found to have knowingly reported false prices, in addition to other penalties available to the government, the law provides for civil monetary penalties of $100,000 per incorrect item. Finally, manufacturers are required to disclose in FSS contract proposals all commercial pricing that is equal to or less than the proposed FSS pricing, and subsequent to award of an FSS contract,

manufacturers are required to monitor certain commercial price reductions and extend commensurate price reductions to the government, under the terms of the FSS contract Price Reductions Clause. Among the remedies available to the government for any failure to properly disclose commercial pricing and/or to extend FSS contract price reductions is recoupment of any FSS overcharges that may result from such omissions.

Employees

As of January 23, 2017, we had 2,293 full-time employees, 998 of whom were in operations, 632 of whom were in research and development, 313 of whom were in sales and marketing and 350 of whom were in administration.

We consider our employee relations to be good. Our employees are not covered by a collective bargaining agreement. We have not experienced employment related work stoppages.

Research and Development

For information regarding research and development expenses incurred during 2016, 2015 and 2014, see Item 7, Management's Discussion and Analysis of Financial Condition and Results of Operations—Research and Development.

Geographic Area Financial Information

Our chief operating decision maker (i.e., our chief executive officer) reviews financial information on a consolidated basis, for the purposes of allocating resources and evaluating financial performance. Accordingly, we consider ourselves to have a single reporting segment and operating unit structure.

Net product revenues by geography are based on patients' locations for our commercial products, which are sold directly by us, and global sales of Aldurazyme, which is marketed by Genzyme. Genzyme is our sole customer for Aldurazyme and is responsible for marketing and selling Aldurazyme to third-parties. Although Genzyme sells Aldurazyme worldwide, the revenues earned by us on Genzyme's net sales are not broken out by geographic region as the underlying revenue transactions are with Genzyme, whose headquarters are located in the U.S.

The following table outlines net product revenues by geographic area (in millions):

	Years Ended December 31,		
	2016	2015	2014
Net product revenues:			
Net product revenues marketed by BioMarin:			
United States	$505.6	$441.4	$375.7
Europe	252.6	171.2	$130.7
Latin America	147.5	142.3	$118.6
Rest of the world	204.7	129.6	$113.4
Total net product revenues	$1,110.4	884.5	$738.4

Total revenues generated outside the U.S. was $609.3 million, $445.8 million and $365.5 million, in the years ended December 31, 2016, 2015 and 2014, respectively.

The following table outlines non-monetary long-lived assets by geographic area (in millions):

	December 31,		
	2016	2015	2014
Non-monetary long-lived assets:			

United States	$1,183.9	$940.5	$827.9
Europe	812.8	865.2	102.5
Rest of World	2.6	2.3	1.6
Total long-lived assets	$1,999.3	$1,808.0	$932.0

The increase in non-monetary long-lived assets in 2016 compared to 2015 was primarily attributable to increased costs related to our in-process projects at our manufacturing facilities, partially offset by a net decrease in intangible assets. The increase in non-monetary long-lived assets in 2015 compared to 2014 was primarily

attributable to increased in-process R&D (IPR&D). The increase in intangible assets was primarily attributable to Kyndrisa and other exon-skipping in-process research and development assets we acquired in connection with our acquisition of Prosensa Holding N.V. in January 2015. These IPR&D assets were impaired during 2016 due to the termination of the related programs.

See “Risk Factors” included in Part I, Item 1A of this Annual Report on Form 10-K for additional information regarding the risks we face related to our foreign operations.

Other Information

We were incorporated in Delaware in October 1996. Our principal executive offices are located at 770 Lindaro Street, San Rafael, California 94901 and our telephone number is (415) 506-6700. Our annual reports on Form 10-K, quarterly reports on Form 10-Q, proxy statements, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended (the Exchange Act) are available free of charge at www.bmrn.com as soon as reasonably practicable after electronically filing such reports with the SEC. Such reports and other information may be obtained by visiting the SEC’s Public Reference Room at 100 F Street, NE, Washington, D.C. 20549 or by calling the SEC at 1-800-SEC-0330. Additionally, these reports are available at the SEC’s website at http://www.sec.gov. Information contained in our website is not part of this or any other report that we file with or furnish to the SEC.

Item 1A. Risk Factors

An investment in our securities involves a high degree of risk. We operate in a dynamic and rapidly changing industry that involves numerous risks and uncertainties. The risks and uncertainties described below are not the only ones we face. Other risks and uncertainties, including those that we do not currently consider material, may impair our business. If any of the risks discussed below actually occur, our business, financial condition, operating results or cash flows could be materially adversely affected. This could cause the value of our securities to decline, and you may lose all or part of your investment.

Risks Related to Our Business

If we fail to obtain regulatory approval to commercially market and sell our product candidates, or if approval of our product candidates is delayed, we will be unable to generate revenue from the sale of these product candidates, our potential for generating positive cash flow will be diminished, and the capital necessary to fund our operations will increase.

We must obtain and maintain regulatory approval to market and sell our product candidates. For example, in the U.S., we must obtain Food and Drug Administration (FDA) approval for each product candidate that we intend to commercialize, and in Europe we must obtain approval from the European Medicines Agency (EMA). The FDA and EMA approval processes are typically lengthy and expensive, and approval is never certain. Accordingly, there are no assurances that we will obtain regulatory approval for any of our product candidates, including Brineura and pegvaliase, in any jurisdiction. For example, although the FDA has accepted for review the submission of our BLA for Brineura, and we have also received validation of the MAA from the EMA for Brineura, there are no assurances that we will obtain regulatory approval of Brineura from the FDA or EMA. Even though the primary endpoint of our Phase 1/2 study for Brineura was met, our BLA and MAA rely on results from a single Phase 1/2 uncontrolled study in a small patient population of 24 patients and we used natural history data as a control arm of the trial. In addition, effectiveness of Brineura was evaluated using a CLN2-specific rating scale score based on individual physicians’

assessments. Furthermore, even though the pivotal Phase 3 PRISM-2 study of pegvaliase met the primary endpoint of change in blood Phe compared with placebo ($p<0.0001$), we did not demonstrate a statistically significant improvement in inattention or mood scores, a key secondary clinical neurocognitive endpoint. Although we intend to file a BLA for pegvaliase with the FDA in the second quarter of 2017, there is no assurance that a reduction in blood Phe alone will be sufficient to support the FDA's full regulatory approval of pegvaliase.

Although the FDA and the EMA have programs to facilitate accelerated approval processes, the timelines agreed under legislative goals or mandated by regulations are subject to the possibility of substantial delays. In

addition, the FDA, the EMA and other international regulatory authorities have substantial discretion over the approval process for pharmaceutical products. These regulatory agencies may not agree that we have demonstrated the requisite level of product safety and efficacy to grant approval and may require additional data. If we fail to obtain regulatory approval for our product candidates, we will be unable to market and sell those product candidates. Because of the risks and uncertainties in pharmaceutical development, our product candidates could take a significantly longer time to gain regulatory approval than we expect or may never gain approval. We also rely on independent third-party contract research organizations (CROs) to file some of our foreign marketing applications and important aspects of the services performed for us by the CROs are out of our direct control. If we fail to adequately manage our CROs, if the CRO elects to prioritize work on our projects below other projects or if there is any dispute or disruption in our relationship with our CROs, the filing of our applications may be delayed.

In addition, some of our product candidates, including Brineura, are intended to be used in combination with a delivery device, such as an injector or other delivery system. Medical products containing a combination of new drugs, biological products or medical devices may be regulated as “combination products” in the U.S. A combination product generally is defined as a product consisting of components from two or more regulatory categories (e.g., drug/device, device/biologic, drug/biologic). Each component of a combination product is subject to the requirements established by the FDA for that type of component, whether a new drug, biologic or device. In order to facilitate pre-market review of combination products, the FDA designates one of its centers to have primary jurisdiction for the pre-market review and regulation of the overall product based upon a determination by the FDA of the primary mode of action of the combination product. The determination whether a product is a combination product or two separately regulated products is made by the FDA on a case-by-case basis. Our product candidates intended for use with such devices, or expanded indications that we may seek for our products used with such devices, may not be approved or may be substantially delayed in receiving approval if the devices do not gain and/or maintain their own regulatory approvals or clearances. Where approval of the drug or biologic product and device is sought under a single application, the increased complexity of the review process may delay approval. The FDA review process and criteria is not a well-established area, which could also lead to delays in the approval process. In addition, because these delivery devices are provided by unaffiliated third-party companies, we are dependent on the sustained cooperation and effort of those third-party companies both to obtain regulatory approval and to maintain their own regulatory compliance. Failure of third-party companies to assist in the approval process or to maintain their own regulatory compliance could delay or prevent approval of our product candidates, or limit our ability to sell a product once it is approved.

From time to time during the regulatory approval process for our products and our product candidates, we engage in discussions with the FDA and comparable international regulatory authorities regarding the regulatory requirements for our development programs. To the extent appropriate, we accommodate the requests of the regulatory authorities. However, we are often unable to determine the outcome of such deliberations until they are final. If we are unable to effectively and efficiently resolve and comply with the inquiries and requests of the FDA and other non-U.S. regulatory authorities, the approval of our product candidates may be delayed and their value may be reduced.

Any product for which we have obtained regulatory approval, or for which we obtain approval in the future, is subject to, or will be subject to, extensive ongoing regulatory requirements by the FDA, the EMA and other comparable international regulatory authorities, and if we fail to comply with regulatory requirements or if we experience unanticipated problems with our products, we may be subject to penalties, we will be unable to generate revenue from the sale of such products, our potential for generating positive cash flow will be diminished, and the capital necessary to fund our operations will be increased.

All of our products have received regulatory approval to be commercially marketed and sold in the U.S., the EU and certain other countries, with the exception of Firdapse, which has received regulatory approval to be commercially marketed only in the EU. Any product for which we have obtained regulatory approval, or for which we obtain regulatory approval in the future, along with the manufacturing processes and practices, post-approval clinical research, product labeling, advertising and promotional activities for such product, are subject to continual

requirements of, and review by, the FDA, the EMA and other comparable international regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, current good manufacturing practices (cGMP) requirements relating to manufacturing, quality control,

quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians, import and export requirements and recordkeeping.

Promotional communications with respect to prescription drugs, including biologics, are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved labeling. Thus, we will not be able to promote any products we develop for indications or uses for which they are not approved.

In addition, the FDA often requires post-marketing testing and surveillance to monitor the effects of products. The FDA, the EMA and other comparable international regulatory agencies may condition approval of our product candidates on the completion of such post-marketing clinical studies. These post-marketing studies may suggest that a product causes undesirable side effects or may present a risk to the patient.

Discovery after approval of previously unknown problems with any of our products, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in actions such as:

- restrictions on our ability to conduct clinical trials, including full or partial clinical holds on ongoing or planned trials;
- restrictions on product manufacturing processes;
- restrictions on the marketing of a product;
- restrictions on product distribution;
- requirements to conduct post-marketing clinical trials;
- untitled or warning letters or other adverse publicity;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- refusal to permit the import or export of our products;
- product seizure;
- fines, restitution or disgorgement of profits or revenue;
- injunctions; or
- imposition of civil or criminal penalties.

If such regulatory actions are taken, the value of our company and our operating results will be adversely affected. Additionally, if the FDA, the EMA or any other comparable international regulatory agency withdraws its approval of a product, we will be unable to generate revenue from the sale of that product in the relevant jurisdiction, our potential for generating positive cash flow will be diminished and the capital necessary to fund our operations will be increased. Accordingly, we continue to expend significant time, money and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance, post-marketing studies and quality control.

If we fail to obtain or maintain orphan drug exclusivity for some of our products, our competitors may obtain approval to sell the same drugs to treat the same conditions and our revenues will be reduced.

As part of our business strategy, we have developed and may in the future develop some drugs that may be eligible for FDA and EU orphan drug designation. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is intended to treat a rare disease or condition, defined as a patient population of fewer than 200,000 in the U.S. In the EU, orphan drug designation is granted to drugs intended to treat a rare disease or condition, defined as having a prevalence of no more than five in 10,000 people in the EU, which is equivalent to

around 250,000 people or fewer. The company that first obtains FDA approval for a designated orphan drug for a given rare disease receives marketing exclusivity for use of that drug for the stated condition for a period of seven years. Orphan drug exclusive marketing rights may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug. Similar regulations are available in the EU with a ten-year period of market exclusivity.

Because the extent and scope of patent protection for some of our products is limited, orphan drug designation is especially important for our products that are eligible for orphan drug designation. For eligible products, we plan to rely on the exclusivity period under the Orphan Drug Act to maintain a competitive position. If we do not obtain orphan drug exclusivity for our products that do not have broad patent protection, our competitors may then sell the same drug to treat the same condition and our revenues will be reduced.

Even though we have obtained orphan drug designation for certain of our product candidates and even if we obtain orphan drug designation for our future product candidates, due to the uncertainties associated with developing biopharmaceutical products, we may not be the first to obtain marketing approval for any particular orphan indication, which means that we may not obtain orphan drug exclusivity and could also potentially be blocked from approval of certain product candidates until the competitor product's orphan drug exclusivity period expires. Further, even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs can be approved for the same condition and the same drug can be approved for different conditions and potentially used off-label in the orphan indication. Even after an orphan drug is approved and granted orphan drug exclusivity, the FDA can subsequently approve the same drug for the same condition if the FDA concludes that the later drug is safer or more effective or makes a major contribution to patient care. Orphan drug designation neither shortens the development time or regulatory review time of a drug, nor gives the drug any advantage in the regulatory review or approval process.

We may face competition from biosimilars approved through an abbreviated regulatory pathway.

Our Aldurazyme, Naglazyme and Vimizim products are regulated by the FDA as biologics under the Federal Food, Drug, and Cosmetic Act (the FDC Act) and the Public Health Service Act (the PHS Act). Biologics require the submission of a BLA and approval by the FDA prior to being marketed in the U.S. Historically, a biologic product approved under a BLA was not subject to the generic drug review and approval provisions of the FDC Act. However, the Biologics Price Competition and Innovation Act of 2009 (BPCIA) created a regulatory pathway under the PHS Act for the abbreviated approval of biological products that are demonstrated to be "biosimilar" or "interchangeable" with an FDA-approved biological product. In order to meet the standard of interchangeability, a sponsor must demonstrate that the biosimilar product can be expected to produce the same clinical result as the reference product, and for a product that is administered more than once, that the risk of switching between the reference product and biosimilar product is not greater than the risk of maintaining the patient on the reference product. Such biosimilars would reference biological products approved in the U.S. The BPCIA establishes a period of 12 years of data exclusivity for reference products, which protects the data in the original BLA by prohibiting sponsors of biosimilars from gaining FDA approval based in part on reference to data in the original BLA. Aldurazyme's data exclusivity under the BPCIA expired in 2015, Naglazyme's data exclusivity under the BPCIA expires in 2017, and Vimizim's data exclusivity under the BPCIA expires in 2026. Our products approved under BLAs, as well as products in development that may be approved under BLAs in the future, could be reference products for biosimilar marketing applications.

To obtain regulatory approval to market our products, preclinical studies and costly and lengthy clinical trials are required and the results of the studies and trials are highly uncertain.

As part of the drug development process we must conduct, at our own expense, preclinical studies in the laboratory, including studies in animals, and clinical trials on humans for each product candidate. We expect the number of preclinical studies and clinical trials that the regulatory authorities will require will vary depending on the product candidate, the disease or condition the drug is being developed to address and regulations applicable to the particular

drug. Generally, new drugs for diseases or conditions that affect larger patient populations, are less severe, or are treatable by alternative strategies must be validated through additional preclinical and clinical trials and/or clinical trials with higher enrollments. With respect to our early stage product candidates, we may need to perform multiple preclinical studies using various doses and formulations before we can begin clinical trials, which could

result in delays to our development timeline. Furthermore, even if we obtain favorable results in preclinical studies, the results in humans may be significantly different. After we have conducted preclinical studies, we must demonstrate that our product candidates are safe and efficacious for use in the targeted human patients in order to receive regulatory approval for commercial sale. Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. The results of preclinical studies and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials, and favorable data from interim analyses do not ensure the final results of a trial will be favorable. Product candidates may fail to show the desired safety and efficacy traits despite having progressed through preclinical studies and initial clinical trials, or despite having favorable data in connection with an interim analysis. A number of companies in the biopharmaceutical industry, including us with respect to Kyndrisa, have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials.

Adverse or inconclusive clinical results could stop us from obtaining regulatory approval of our product candidates. Additional factors that can cause delay or termination of our clinical trials include:

- slow or insufficient patient enrollment;
- slow recruitment of, and completion of necessary institutional approvals at, clinical sites;
- budgetary constraints or prohibitively high clinical trial costs;
- longer treatment time required to demonstrate efficacy;
- lack of sufficient supplies of the product candidate;
- adverse medical events or side effects in treated patients, including immune reactions;
- lack of effectiveness of the product candidate being tested;
    - availability of competitive therapies to treat the same indication as our product candidates;
- regulatory requests for additional clinical trials or pre-clinical studies;
- deviations in standards for Good Clinical Practice (GCP); and
- disputes with or disruptions in our relationships with clinical trial partners, including CROs, clinical laboratories, clinical sites, and principal investigators

Moreover, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and receive compensation in connection with such services reportable to the FDA or other regulatory authority. If the FDA or other regulatory authority concludes that a financial relationship between us and a principal investigator has created a conflict of interest, the FDA or other regulatory authority may question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized.

Our BMN 270 program is based on a gene therapy approach, which, as a novel technology, presents additional treatment, regulatory, manufacturing, and commercial risks in relation to our other, more traditional drug development programs.

In addition to the risks set forth in this Risk Factors section associated with developing and commercializing more traditional pharmaceutical drugs, there are additional, unique risks associated with gene therapy products like our product candidate BMN 270. The goal of gene therapy is to be able to correct an inborn genetic defect through one-time administration of therapeutic genetic material containing non-defective gene copies. The gene copies are designed to reside permanently in a patient, allowing the patient to produce an essential protein or ribonucleic acid (RNA) molecule that a healthy person would normally produce. There is a risk, however, that the new gene copies will produce too much or too little of the desired protein or RNA. There is also a risk that production of the desired protein or RNA will increase or decrease over time. Because the treatment is irreversible, there may be challenges in managing side effects, particularly those caused by overproduction. Adverse effects would not be able to be reversed or relieved by stopping dosing, and we may have to develop additional clinical safety procedures. Furthermore,

because the new gene copies are designed to reside permanently in a patient, there is a risk that they will disrupt other normal biological molecules and processes, including other healthy genes, and we may not learn the nature and magnitude of these side effects until long after clinical trials have been completed.

We may experience development problems related to our gene therapy program that cause significant delays or unanticipated costs, or that cannot be solved. Given that there are currently no approved gene therapy products in the U.S. and very few precedents outside the U.S., it is difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our product candidate in any jurisdiction. Regulatory requirements governing gene and cell therapy products are still evolving and may continue to change in the future. Regulatory review agencies and the new requirements and guidelines they promulgate may lengthen the regulatory review process, require us to perform additional or larger studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of our treatment candidate or lead to significant post-approval studies, limitations or restrictions. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring BMN 270 to market could have a negative effect on our business and financial condition. Even if we do obtain regulatory approval, ethical, social and legal concerns about gene therapy arising in the future could result in additional regulations restricting or prohibiting sale of our product.

Even if we obtain regulatory approval for BMN 270, we may experience delays, and increased costs, in developing a sustainable, reproducible and large-scale manufacturing process. Gene therapy products are novel, complex and difficult to manufacture, and have, only in limited cases, been manufactured at scales sufficient for pivotal trials and commercialization. Few pharmaceutical contract manufacturers specialize in gene therapy products and those that do are still developing appropriate processes and facilities for large-scale production. Whether we produce BMN 270 at a contract manufacturer or at our own gene therapy manufacturing facility, we will likely face technical and scientific challenges, considerable capital costs, and potential difficulty in recruiting and hiring experienced, qualified personnel. As a result, we could experience manufacturing delays that prevent us from completing our clinical studies or commercializing BMN 270 in a timely, or on a profitable, basis, if at all.

Due to the relative novelty of gene therapy and the potential to provide extended duration therapeutic treatment with a one-time administration, we also face uncertainty with respect to the pricing, coverage and reimbursement of BMN 270, if approved. In order to recover our research and development costs and commercialize this one-time treatment on a profitable basis, we expect the cost of a single administration of BMN 270 to be substantial. Therefore, we expect that coverage and reimbursement by governments and other third-party payors will be essential for the vast majority of patients to be able to afford BMN 270. Accordingly, sales of BMN 270, if approved, will depend substantially, both domestically and internationally, on the extent to which its cost will be paid by third-party payors. Even if coverage is provided, the reimbursement amounts approved by third-party payors may not be high enough to allow us to realize a sufficient return on our investment.

We also face uncertainty as to whether gene therapy will gain the acceptance of the public or the medical community. Even if we obtain regulatory approval for BMN 270, the commercial success of BMN 270 will depend, in part, on the acceptance of physicians, patients and health care payors of gene therapy products in general, and our product candidate in particular, as medically necessary, cost-effective and safe. In particular, our success will depend upon physicians prescribing our product candidate in lieu of existing treatments they are already familiar with and for which greater clinical data may be available. Even if BMN 270 displays a favorable efficacy and safety profile in clinical trials and is ultimately approved, market acceptance of BMN 270 will not be fully known until after it is launched. Negative public opinion or more restrictive government regulations or could have a negative effect on our business and financial condition and may delay or impair the development and commercialization of, and demand for, BMN 270.

If we continue to incur operating losses and experience net cash outflows for a period longer than anticipated, we may be unable to continue our operations at planned levels and be forced to reduce our operations.

Since we began operations in March 1997, we have been engaged in substantial research and development and capital investments, and we have operated at a net loss for each year since our inception, with the exception of 2008 and 2010. Based upon our current plan for investments in research and development for existing and new programs, as well as capital investments in our facilities and working capital needs, such as for inventory, we expect to operate

at a net loss and experience net cash outflows for at least the next 12 months. Our future profitability and cash flows depend on our marketing and selling of our products, the receipt of regulatory approval of our product candidates, our ability to successfully manufacture and market any products, either by ourselves or jointly with others, our spending on our development programs, the impact of any possible future business development transactions and other risks set forth in this Risk Factors section. The extent of our future losses and the timing of profitability and positive cash flows are highly uncertain. If we fail to become profitable and cash flow positive or are unable to sustain profitability and positive cash flows on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce our operations.

If we fail to obtain the capital necessary to fund our operations, our financial results and financial condition will be adversely affected and we will have to delay or terminate some or all of our product development programs.

As of December 31, 2016, we had cash, cash equivalents and short and long-term investments totaling $1.4 billion and long-term debt obligations of $772.5 million (undiscounted). In January 2016 we terminated our License and Commercialization Agreement with Ares Trading, S.A. (Merck Serono). Pursuant to the Termination and Transition Agreement related to Kuvan and the Termination Agreement related to pegvaliase, we made cash payments on this transaction totaling $374.5 million, and may pay Merck Serono up to a maximum of €60 million, in cash, if future sales milestones are met with respect to Kuvan and up to a maximum of €125 million, in cash, if future development milestones are met with respect to pegvaliase. In October 2013, we completed an offering of senior subordinated convertible notes and received net proceeds of approximately $696.4 million, after deducting commissions, offering expenses payable by us and the purchase of the related capped calls. We will need cash to not only repay the principal amount of our 1.875% senior subordinated convertible notes due 2017 (the 2017 Notes), 0.75% senior subordinated convertible notes due 2018 (the 2018 Notes) and 1.50% senior subordinated convertible notes due in 2020 (the 2020 Notes and, together with the 2017 Notes and 2018 Notes, the Notes) but also the ongoing interest due on the Notes during their term.

We may require additional financing to fund the repayment of our Notes, future milestone payments and our future operations, including the commercialization of our products and product candidates currently under development, preclinical studies and clinical trials, and potential licenses and acquisitions. We may be unable to raise additional financing due to a variety of factors, including our financial condition, the status of our product programs, and the general condition of the financial markets. If we fail to raise any necessary additional financing we may have to delay or terminate some or all of our product development programs and our financial condition and operating results will be adversely affected.

We expect to continue to spend substantial amounts of capital for our operations for the foreseeable future. The amount of capital we will need depends on many factors, including:

- our ability to successfully market and sell our products;
    - Genzyme’s ability to continue to successfully commercialize Aldurazyme;
- the progress and success of our preclinical studies and clinical trials (including studies and the manufacture of materials);
- the timing, number, size and scope of our preclinical studies and clinical trials;
- the time and cost necessary to obtain regulatory approvals and the costs of post-marketing studies which may be required by regulatory authorities;
- the time and cost necessary to develop commercial manufacturing processes, including quality systems, and to build or acquire manufacturing capabilities;
- the progress of research programs carried out by us;
- our possible achievement of milestones identified in our purchase agreements with the former stockholders of LEAD Therapeutics, Inc., ZyStor Therapeutics, Inc., Huxley Pharmaceuticals, Inc., and Zacharon Pharmaceuticals Inc., and under the termination agreements with Merck Serono related to Kuvan and pegvaliase milestones;

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- any changes made to, or new developments in, our existing collaborative, licensing and other commercial relationships or any new collaborative, licensing and other commercial relationships that we may establish; and
- whether our convertible debt is converted to common stock in the future.

Moreover, our fixed expenses such as rent, license payments, interest expense and other contractual commitments are substantial and may increase in the future. These fixed expenses may increase because we may enter into:

- additional licenses and collaborative agreements;
- additional contracts for product manufacturing; and
- additional financing facilities or arrangements.

We will need to raise additional funds from equity or debt securities, loans or collaborative agreements if we are unable to satisfy our liquidity requirements. The sale of additional securities will result in additional dilution to our stockholders. Furthermore, additional financing may not be available in amounts or on terms satisfactory to us or at all. This could result in the delay, reduction or termination of our research, which could harm our business.

We have incurred substantial indebtedness that may decrease our business flexibility, access to capital, and/or increase our borrowing costs, which may adversely affect our operations and financial results.

As of December 31, 2016, we had $772.5 million (undiscounted) principal amount of indebtedness, including $375.0 million (undiscounted) of indebtedness under the 2018 Notes and $375.0 million (undiscounted) principal amount of indebtedness under the 2020 Notes. In November 2016, we also entered into a credit agreement (Credit Agreement) with Bank of America, N.A., as the administrative agent, swing line lender and letter of credit issuer, providing for up to $100.0 million in revolving loans. Our indebtedness may:

- limit our ability to incur liens on our assets or use our cash flow, borrow additional funds or obtain additional financing for future working capital, capital expenditures, acquisitions or other general business purposes;
- require us to use a substantial portion of our cash flow from operations to make debt service payments;
- limit our flexibility to plan for, or react to, changes in our business and industry, including taking advantage of certain business opportunities that may be presented to us;
- place us at a competitive disadvantage compared to our less leveraged competitors;
- increase our vulnerability to the impact of adverse economic and industry conditions; and
- result in dilution to our existing stockholders in the event exchanges of our 2018 Notes or 2020 Notes are converted into shares of our common stock.

In addition, if we default under the Credit Agreement, the outstanding borrowings thereunder could become immediately due and payable, the Credit Agreement lenders could refuse to permit additional borrowings under the facility, or it could lead to defaults under agreements governing our current or future indebtedness, including the indentures governing our 2018 Notes and 2020 Notes.

In addition, our ability to refinance our indebtedness will depend on the capital markets and our financial condition at such time.

Our indebtedness consists primarily of the 2018 and 2020 Notes, which, if not converted, will be required to be repaid in cash at maturity in 2018 and 2020. In addition, in the event the conditional conversion feature of the Notes is triggered, holders of Notes will be entitled to convert the Notes at any time during specified periods at their option. Our liquidity could be adversely affected if we settle the principal amount of our conversion obligation in cash. Even if holders do not elect to convert their Notes, we could be required under applicable accounting rules to reclassify all or a portion of the outstanding principal of the Notes as a current rather than long-term liability, which

would result in a material reduction of our net working capital. Moreover, if we are unable to refinance the Notes, we must repay the Notes. While we could seek to obtain third-party financing to pay for any amounts due in cash upon such events, we cannot be sure that such third-party financing will be available on commercially reasonable terms, if at all. Furthermore, if we are required to share settle any conversions of Notes, due to lack of requisite liquidity or otherwise, we may cease to be eligible to account for the Notes using the treasury stock method, which may adversely impact our diluted earnings per share.

If we fail to comply with manufacturing regulations, our financial results and financial condition will be adversely affected.

Before we can begin commercial manufacture of our products, regulatory authorities must approve marketing applications that identify manufacturing facilities operated by us or our contract manufacturers that have passed regulatory inspection and manufacturing processes that are acceptable to the regulatory authorities. In addition, our pharmaceutical manufacturing facilities are continuously subject to scheduled and unannounced inspection by the FDA and international regulatory authorities, before and after product approval, to monitor and ensure compliance with cGMP and other regulations. Our manufacturing facility in the U.S. has been approved by the FDA, the EC, and health agencies in other countries for the manufacture of Aldurazyme, Naglazyme and Vimizim. Our manufacturing facility in Shanbally, Cork, Ireland has been approved by the FDA, the EC, and health agencies in other countries for the manufacture of Vimizim. In addition, our third-party manufacturers' facilities involved with the manufacture of our products have also been inspected and approved by various regulatory authorities. Although we are not involved in the day-to-day operations of our contract manufacturers, we are ultimately responsible for ensuring that our products are manufactured in accordance with cGMP regulations.

Due to the complexity of the processes used to manufacture our products and product candidates, we may be unable to continue to pass or initially pass federal or international regulatory inspections in a cost-effective manner. For the same reason, any potential third-party manufacturer of our products or our product candidates may be unable to comply with cGMP regulations in a cost-effective manner and may be unable to initially or continue to pass a federal or international regulatory inspection.

If we, or third-party manufacturers with whom we contract, are unable to comply with manufacturing regulations, we may be subject to delay of approval of our product candidates, warning or untitled letters, fines, unanticipated compliance expenses, recall or seizure of our products, total or partial suspension of production and/or enforcement actions, including injunctions, and criminal or civil prosecution. These possible sanctions would adversely affect our financial results and financial condition.

If we are unable to successfully develop and maintain manufacturing processes for our products to produce sufficient quantities at acceptable costs, we may be unable to meet demand for our products and lose potential revenue, have reduced margins or be forced to terminate a program.

Due to the complexity of manufacturing our products, we may not be able to manufacture products successfully with a commercially viable process or at a scale large enough to support their respective commercial markets or at acceptable margins.

The development of commercially viable manufacturing processes typically is very difficult to achieve and is often very expensive and may require extended periods of time. Changes in manufacturing processes (including manufacturing cell lines), equipment or facilities (including moving manufacturing from one of our facilities to another one of our facilities or a third-party facility, or from a third-party facility to one of our facilities) may require us to complete clinical trials to receive regulatory approval of any manufacturing modifications.

Also, we may be required to demonstrate product comparability between a biological product made after a manufacturing change and the product made before implementation of the change through additional types of

analytical and functional testing or may have to complete additional clinical studies. If we contract for manufacturing services with an unproven process, our contractor is subject to the same uncertainties, high standards and regulatory controls, and may therefore experience difficulty if further process development is necessary.

Even a developed manufacturing process can encounter difficulties. Problems may arise during manufacturing for a variety of reasons, including human error, mechanical breakdowns, problems with raw materials and cell banks, malfunctions of internal information technology systems, and other events that cannot always be prevented or anticipated. Many of the processes include biological systems, which add significant complexity, as compared to chemical synthesis. We expect that, from time to time, consistent with biotechnology industry expectations, certain production lots will fail to produce product that meets our quality control release acceptance criteria. To date, our historical failure rates for all of our product programs, including Aldurazyme, Naglazyme and Vimizim, have been within our expectations, which are based on industry norms. If the failure rate increased substantially, we could experience increased costs, lost revenue, damage to customer relations, time and expense investigating the cause and, depending upon the cause, similar losses with respect to other lots or products. If problems are not discovered before the product is released to the market, recall and product liability costs may also be incurred.

In order to produce product within our time and cost parameters, we must continue to produce product within our expected success rate and yield expectations. Because of the complexity of our manufacturing processes, it may be difficult or impossible for us to determine the cause of any particular lot failure and we must effectively take corrective action in response to any failure in a timely manner.

Although we have entered into contractual relationships with third-party manufacturers to produce the active ingredient in Firdapse and Kuvan, if those manufacturers are unwilling or unable to fulfill their contractual obligations, we may be unable to meet demand for Firdapse and Kuvan or sell these products at all, we may lose potential revenue, and we may be forced to terminate a program. We have contracts for the production of final product for Firdapse and Kuvan. We also rely on third-parties for portions of the manufacture of Aldurazyme, Naglazyme and Vimizim. If those manufacturers are unwilling or unable to fulfill their contractual obligations or satisfy demand outside of or in excess of the contractual obligations, we may be unable to meet demand for these products or sell these products at all and we may lose potential revenue. Further, the availability of suitable contract manufacturing capacity at scheduled or optimum times is not certain.

In addition, our manufacturing processes subject us to a variety of federal, state and local laws and regulations governing the use, generation, manufacture, storage, handling and disposal of hazardous materials and wastes resulting from their use. We incur significant costs in complying with these laws and regulations.

Supply interruptions may disrupt our inventory levels and the availability of our products and product candidates and cause delays in obtaining regulatory approval for our product candidates, or harm our business by reducing our revenues.

We depend on single-source suppliers for critical raw materials and a limited number of manufacturing facilities to manufacture our finished products and product candidates. Numerous factors could cause interruptions in the supply or manufacture of our products and product candidates, including:

- timing, scheduling and prioritization of production by our contract manufacturers or a breach of our agreements by our contract manufacturers;
- labor interruptions;
- changes in our sources for manufacturing;
- the timing and delivery of shipments;
- our failure to locate and obtain replacement suppliers and manufacturers as needed on a timely basis; and
- conditions affecting the cost and availability of raw materials.

If one of our suppliers or manufacturers fails or refuses to supply us with necessary raw materials or finished products or product candidates on a timely basis or at all, it would take a significant amount of time and expense to qualify a new supplier or manufacturer. We may not be able to obtain active ingredients or finished products from new suppliers or manufacturers on acceptable terms and at reasonable prices, or at all.

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Any interruption in the supply of finished products could hinder our ability to distribute finished products to meet commercial demand.

With respect to our product candidates, production of product is necessary to perform clinical trials and successful registration batches are necessary to file for approval to commercially market and sell product candidates. Delays in obtaining clinical material or registration batches could adversely impact our clinical trials and delay regulatory approval for our product candidates.

Because the target patient populations for our products are small, we must achieve significant market share and maintain high per-patient prices for our products to achieve profitability.

All of our products target diseases with small patient populations. As a result, our per-patient prices must be relatively high in order to recover our development and manufacturing costs and achieve profitability. For Naglazyme and Vimizim in particular, we must market worldwide to achieve significant market penetration of the product. In addition, because the number of potential patients in each disease population is small, it is not only important to find patients who begin therapy to achieve significant market penetration of the product, but we also need to be able to maintain these patients on therapy for an extended period of time. Due to the expected costs of treatment for our products, we may be unable to maintain or obtain sufficient market share at a price high enough to justify our product development efforts and manufacturing expenses.

If we fail to obtain an adequate level of coverage and reimbursement for our products by third-party payors, the sales of our products would be adversely affected or there may be no commercially viable markets for our products.

The course of treatment for patients using our products is expensive. We expect patients to need treatment for extended periods, and for some products throughout the lifetimes of the patients. We expect that most families of patients will not be capable of paying for this treatment themselves. There will be no commercially viable market for our products without coverage and reimbursement from third-party payors. Additionally, even if there is a commercially viable market, if the level of reimbursement is below our expectations, our revenue and gross margins will be adversely affected.

Third-party payors, such as government or private health care insurers, carefully review and increasingly challenge the prices charged for drugs. Reimbursement rates from private companies vary depending on the third-party payor, the insurance plan and other factors. Reimbursement systems in international markets vary significantly by country and by region, and reimbursement approvals must be obtained on a country-by-country basis.

Government authorities and other third-party payors are developing increasingly sophisticated methods of controlling healthcare costs, such as by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices as a condition of coverage, are using restrictive formularies and preferred drug lists to leverage greater discounts in competitive classes, and are challenging the prices charged for medical products. Further, no uniform policy requirement for coverage and reimbursement for drug products exists among third-party payors in the U.S. Therefore, coverage and reimbursement for drug products can differ significantly from payor to payor. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance.

We cannot be sure that coverage and reimbursement will be available for any product that we commercialize or will continue to be available for any product that we have commercialized and, if reimbursement is available, what the level of reimbursement will be. Coverage and reimbursement may impact the demand for, or the price of, any product candidate for which we obtain marketing approval. If coverage and reimbursement are not available or reimbursement is available only to limited levels, we may not successfully commercialize any product candidate for which we obtain

marketing approval or continue to market any product that has already been commercialized.

Reimbursement in the EU and many other territories must be negotiated on a country-by-country basis and in many countries the product cannot be commercially launched until reimbursement is approved. The timing to complete the negotiation process in each country is highly uncertain, and in some countries we expect that it will exceed 12 months. Even after a price is negotiated, countries frequently request or require reductions to the price and other concessions over time.

For our future products, we will not know what the reimbursement rates will be until we are ready to market the product and we actually negotiate the rates. If we are unable to obtain sufficiently high reimbursement rates for our products, they may not be commercially viable or our future revenues and gross margins may be adversely affected.

A significant portion of our international sales are made based on special access programs, and changes to these programs could adversely affect our product sales and revenue in these countries.

We make a significant portion of our international sales of Naglazyme and Vimizim through special access or “named patient” programs, which do not require full product approval. The specifics of the programs vary from country to country. Generally, special approval must be obtained for each patient. The approval normally requires an application or a lawsuit accompanied by evidence of medical need. Generally, the approvals for each patient must be renewed from time to time.

These programs are not well defined in some countries and are subject to changes in requirements and funding levels. Any change to these programs could adversely affect our ability to sell our products in those countries and delay sales. If the programs are not funded by the respective government, there could be insufficient funds to pay for all patients. Further, governments have in the past undertaken and may in the future undertake unofficial measures to limit purchases of our products, including initially denying coverage for purchasers, delaying orders and denying or taking excessively long to approve customs clearance. Any such actions could materially delay or reduce our revenues from such countries.

Without the special access programs, we would need to seek full product approval to commercially market and sell our products in certain jurisdictions. This can be an expensive and time-consuming process and may subject our products to additional price controls. Because the number of patients is so small in some countries, it may not be economically feasible to seek and maintain a full product approval, and therefore the sales in such country would be permanently reduced or eliminated. For all of these reasons, if the special access programs that we are currently using are eliminated or restricted, our revenues could be adversely affected.

If we fail to compete successfully with respect to product sales, we may be unable to generate sufficient sales to recover our expenses related to the development of a product program or to justify continued marketing of a product and our revenue could be adversely affected.

Our competitors may develop, manufacture and market products that are more effective or less expensive than ours. They may also obtain regulatory approvals for their products faster than we can obtain them (including those products with orphan drug designation, which may prevent us from marketing our product entirely) or commercialize their products before we do. If we do not compete successfully, our revenue would be adversely affected, and we may be unable to generate sufficient sales to recover our expenses related to the development of a product program or to justify continued marketing of a product.

Government price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our current and future products, which would adversely affect our revenue and results of operations.

We expect that coverage and reimbursement may be increasingly restricted both in the U.S. and internationally. The escalating cost of health care has led to increased pressure on the health care industry to reduce costs. In particular, drug pricing by pharmaceutical companies has recently come under increased scrutiny and continues to be subject to

intense political and public debate in the U.S. and abroad. Governmental and private third-party payors have proposed health care reforms and cost reductions. A number of federal and state proposals to

control the cost of health care, including the cost of drug treatments, have been made in the U.S. Specifically, there have been several recent U.S. Congressional inquiries and proposed bills designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. In some international markets, the government controls the pricing, which can affect the profitability of drugs. Current government regulations and possible future legislation regarding health care may affect coverage and reimbursement for medical treatment by third-party payors, which may render our products not commercially viable or may adversely affect our future revenues and gross margins.

International operations are also generally subject to extensive price and market regulations, and there are many proposals for additional cost-containment measures, including proposals that would directly or indirectly impose additional price controls or mandatory price cuts or reduce the value of our intellectual property portfolio. As part of these cost containment measures, some countries have imposed or threatened to impose revenue caps limiting the annual volume of sales of our products. To the extent that these caps are significantly below actual demand, our future revenues and gross margins may be adversely affected.

We cannot predict the extent to which our business may be affected by these or other potential future legislative or regulatory developments. However, future price controls or other changes in pricing regulation or negative publicity related to our product pricing or the pricing of pharmaceutical drugs generally could restrict the amount that we are able to charge for our current and future products or our sales volume, which would adversely affect our revenue and results of operations.

Government health care reform could increase our costs and adversely affect our revenue and results of operations.

Our industry is highly regulated and changes in law may adversely impact our business, operations or financial results. The PPACA is a sweeping measure intended to, among other things, expand healthcare coverage within the U.S., primarily through the imposition of health insurance mandates on employers and individuals and expansion of the Medicaid program. Several provisions of the law have affected us and increased certain of our costs.

In January 2017, Congress voted to adopt a budget resolution for fiscal year 2017, or the Budget Resolution, that authorizes the implementation of legislation that would repeal portions of the PPACA. Although the Budget Resolution is not a law, it is widely viewed as the first step toward the passage of legislation that would repeal certain aspects of the PPACA. Further, on January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the PPACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the PPACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. Congress also could consider subsequent legislation to replace elements of the PPACA that are repealed. Thus, the full impact of the PPACA on our business remains unclear.

In addition, other legislative changes have been adopted since the PPACA was enacted. These new laws may result in additional reductions in Medicare and other healthcare funding, which could have a material adverse effect on our customers and, accordingly, our financial operations.

We anticipate that the PPACA, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and an additional downward pressure on the reimbursement our customers may receive for our products. Further, there have been judicial and Congressional challenges to certain aspects of the PPACA, and we expect there will be additional challenges and amendments to the PPACA in the future, especially with the recent change in administration. Any reduction in reimbursement from Medicare and other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our products. For more information regarding government health care reform, see “Government Regulation – Health Reform” in Part I, Item 1 of this Annual Report on Form 10-K.

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We face credit risks from government-owned or sponsored customers outside of the U.S. that may adversely affect our results of operations.

Our product sales to government-owned or supported customers in various countries outside of the U.S. are subject to significant payment delays due to government funding and reimbursement practices. This has resulted and may continue to result in an increase in days sales outstanding due to the average length of time that we have accounts receivable outstanding. If significant changes were to occur in the reimbursement practices of these governments or if government funding becomes unavailable, we may not be able to collect on amounts due to us from these customers and our results of operations would be adversely affected.

If we are found in violation of federal or state health care laws, we may be required to pay a penalty or be suspended from participation in federal or state health care programs, which may adversely affect our business, financial condition and results of operation.

We are subject to various federal and state health care laws and regulations, including anti-kickback laws, false claims laws, data privacy and security laws, and laws related to ensuring compliance. The federal Anti-Kickback Statute makes it illegal for any person or entity, including a pharmaceutical company, to knowingly and willfully offer, solicit, pay or receive any remuneration, directly or indirectly, in exchange for or to induce the referral of business, including the purchase, order or prescription of a particular drug, for which payment may be made under federal health care programs, such as Medicare and Medicaid. Under federal government regulations, certain arrangements, or safe harbors, are deemed not to violate the federal Anti-Kickback Statute. However, the exemptions and safe harbors are drawn narrowly, and practices that involve remuneration not intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor. Our practices may not in all cases meet all of the criteria for safe harbor protection from Anti-Kickback liability, although we seek to comply with these safe harbors. Many states have adopted laws similar to the federal Anti-Kickback Statute, some of which apply to referral of patients for health care services reimbursed by any source, not just governmental payors.

Federal and state false claims laws, including the civil False Claims Act, prohibit any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government, or knowingly making, or causing to be made, a false statement to have a false claim paid, or knowingly making, using, or causing to be made or used, a false record or statement to avoid, decrease or conceal an obligation to pay money to the federal government. In addition, certain marketing practices, including off-label promotion, may also violate false claims laws. Under the Health Insurance Portability and Accountability Act of 1996 (HIPAA), we also are prohibited from knowingly and willfully executing a scheme to defraud any health care benefit program, including private payors, or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for health care benefits, items or services.

HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, on certain types of individuals and entities, with respect to safeguarding the privacy, security and transmission of individually identifiable health information. Many state and foreign laws also govern the privacy and security of health information. They often differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Substantial new provisions affecting compliance have also been adopted, which may require us to modify our business practices with health care practitioners. The PPACA, through the Physician Payments Sunshine Act, requires drug manufacturers to collect and report to CMS information on payments or transfers of value to physicians and teaching hospitals, as well as investment and ownership interests held by physicians and their immediate family members during the preceding calendar year. Failure to submit required information may result in civil monetary penalties.

In addition, there has been a recent trend of increased state regulation of payments made to physicians. Certain states mandate implementation of compliance programs, compliance with the Office of Inspector General Compliance Program Guidance for Pharmaceutical Manufacturers and the Pharmaceutical Research and

Manufacturers of America (PhRMA) Code on Interactions with Healthcare Professionals, and/or the tracking and reporting of gifts, compensation and other remuneration to physicians. The shifting compliance environment and the need to implement systems to comply with multiple jurisdictions with different compliance and/or reporting requirements increases the possibility that a pharmaceutical manufacturer may violate one or more of the requirements.

Due to the breadth of these laws, the narrowness of available statutory and regulatory exceptions and the increased focus by law enforcement agencies in enforcing such laws, our business activities could be subject to challenge under one or more of such laws. For example, in August 2016, we received a subpoena from the staff of the SEC requesting that we produce documents in connection with a non-public, fact-finding inquiry related to our former drisapersen program. The letter enclosing the subpoena states that the investigation and the subpoena do not mean that the Company or anyone else has broken the law, or that the SEC has a negative opinion of any person, entity or security. We intend to cooperate fully with the SEC in this matter. We are not able to predict whether any proceeding may be instituted in connection with the subpoena, or the outcome of any proceeding that may be instituted.

In addition, recent health care reform legislation has strengthened these laws. For example, the PPACA, among other things, amends the intent requirement of the federal Anti-Kickback Statute and criminal healthcare fraud statutes. A person or entity no longer needs to have actual knowledge of these statutes or specific intent to violate them in order to commit a violation. Moreover, the PPACA provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act. If we are found in violation of one of these laws, we may be subject to criminal, civil or administrative sanctions, including damages, fines, disgorgement, imprisonment, contractual damages, reputational harm, diminished profits and future earnings, curtailment of our operations, debarment, suspension or exclusion from participation in federal or state health care programs, any of which could adversely affect our business, financial condition and results of operation.

We conduct a significant amount of our sales and operations outside of the U.S., which subjects us to additional business risks that could adversely affect our revenue and results of operations.

A significant portion of the sales of Aldurazyme, Kuvan, Naglazyme and Vimizim, and all of the sales of Firdapse are generated from countries other than the U.S. We have operations in Canada and in several European, Middle Eastern, Asian, and Latin American countries. We expect that we will continue to expand our international operations in the future. International operations inherently subject us to a number of risks and uncertainties, including:

- the increased complexity and costs inherent in managing international operations;
- diverse regulatory and compliance requirements, and changes in those requirements that could restrict our ability to manufacture, market and sell our products;
- political and economic instability;
- diminished protection of intellectual property in some countries outside of the U.S.;
- trade protection measures and import or export licensing requirements;
- difficulty in staffing and managing international operations;
- differing labor regulations and business practices;
- potentially negative consequences from changes in or interpretations of tax laws;
- changes in international medical reimbursement policies and programs;
- financial risks such as longer payment cycles, difficulty collecting accounts receivable, exposure to fluctuations in foreign currency exchange rates and potential currency controls imposed by foreign governments;

- regulatory and compliance risks that relate to maintaining accurate information and control over sales and distributors' and service providers' activities that may fall within the purview of the Foreign Corrupt Practices Act (the FCPA); and
- regulations relating to data security and the unauthorized use of, or access to, commercial and personal information.

Any of these factors may, individually or as a group, have a material adverse effect on our business and results of operations.

As we continue to expand our existing international operations, we may encounter new risks. For example, as we focus on building our international sales and distribution networks in new geographic regions, we must continue to develop relationships with qualified local distributors and trading companies. If we are not successful in developing and maintaining these relationships, we may not be able to grow sales in these geographic regions. These or other similar risks could adversely affect our revenue and profitability.

Our international operations pose currency risks, which may adversely affect our operating results and net income.

A significant and growing portion of our revenues and earnings, as well as our substantial international net assets, are exposed to changes in foreign exchange rates. As we operate in multiple foreign currencies, including the euro, the Brazilian real, the U.K. pound, the Canadian dollar, the Swiss franc, the Japanese yen and several other currencies, changes in those currencies relative to the U.S. dollar will impact our revenues and expenses. If the U.S. dollar were to weaken against another currency, assuming all other variables remained constant, our revenues would increase, having a positive impact on earnings, and our overall expenses would increase, having a negative impact on earnings. Conversely, if the U.S. dollar were to strengthen against another currency, assuming all other variables remained constant, our revenues would decrease, having a negative impact on earnings, and our overall expenses would decrease, having a positive impact on earnings. In addition, because our financial statements are reported in U.S. dollars, changes in currency exchange rates between the U.S. dollar and other currencies have had, and will continue to have, an impact on our results of operations. Therefore, significant changes in foreign exchange rates can impact our results and our financial guidance.

We implement currency hedges intended to reduce our exposure to changes in foreign currency exchange rates. However, our hedging strategies may not be successful, and any of our unhedged foreign exchange exposures will continue to be subject to market fluctuations. These risks could cause a material adverse effect on our business, financial position and results of operations and could cause the market value of our common stock to decline.

If we are unable to protect our intellectual property, we may not be able to compete effectively.

Where appropriate, we seek patent protection for certain aspects of our technology. Patent protection may not be available for some of the products we are developing. If we must spend significant time and money protecting or enforcing our patents, designing around patents held by others or licensing, potentially for large fees, patents or other proprietary rights held by others, our business and financial prospects may be harmed.

The patent positions of biopharmaceutical products are complex and uncertain. The scope and extent of patent protection for some of our products and product candidates are particularly uncertain because key information on some of our product candidates has existed in the public domain for many years. The composition and genetic sequences of animal and/or human versions of Aldurazyme, Naglazyme and many of our product candidates have been published and are believed to be in the public domain. The chemical structure of 6R-BH4 (the active ingredient in Kuvan) and 3,4-DAP (the active ingredient in Firdapse) have also been published. Publication of this information may prevent us from obtaining or enforcing patents relating to our products and product candidates, including without limitation composition-of-matter patents, which are generally believed to offer the strongest patent protection.

We own or have licensed patents and patent applications related to our products. However, these patents and patent applications do not ensure the protection of our intellectual property for a number of reasons, including without limitation the following:

- With respect to pending patent applications, unless and until actually issued, the protective value of these applications is impossible to determine. We do not know whether our patent applications will result in issued patents.
- Competitors may interfere with our patent process in a variety of ways. Competitors may claim that they invented the claimed invention prior to us or that they filed their application for a patent on a claimed invention before we did. Competitors may also claim that we are infringing on their patents and therefore we cannot practice our technology. Competitors may also contest our patents by showing the patent examiner or a court that the invention was not original, was not novel or was obvious, for example. In litigation, a competitor could claim that our issued patents are not valid or are unenforceable for a number of reasons. If a court agrees, we would not be able to enforce that patent. We have no meaningful experience with competitors interfering with or challenging the validity or enforceability of our patents or patent applications.
- Generic manufacturers may use litigation and regulatory means to obtain approval for generic versions of our products notwithstanding our filed patents or patent applications.
- Enforcing patents is expensive and may absorb significant time of our management. Management would spend less time and resources on developing products, which could increase our operating expenses and delay product programs.
- Receipt of a patent may not provide much, if any, practical protection. For example, if we receive a patent with a narrow scope, then it will be easier for competitors to design products that do not infringe on our patent.
- The Leahy-Smith America Invents Act of 2011, which reformed certain patent laws in the U.S., may create additional uncertainty. Among the significant changes are switching from a “first-to-invent” system to a “first-to-file” system, and the implementation of new procedures that permit competitors to challenge our patents in the U.S. Patent and Trademark Office after grant.

It is also unclear whether our trade secrets are adequately protected. Our current and former employees, consultants or contractors may unintentionally or willfully disclose trade secrets to competitors. Enforcing a claim that someone else illegally obtained and is using our trade secrets, as with patent litigation, is expensive and time consuming, requires significant resources and has an unpredictable outcome. In addition, courts outside of the U.S. are sometimes less willing to protect trade secrets. Furthermore, our competitors may independently develop equivalent knowledge, methods and know-how, in which case we would not be able to enforce our trade secret rights against such competitors.

Moreover, there is an increasing trend in the EU requiring public disclosure of development data, in particular clinical trial data. These data were traditionally regarded as confidential commercial information; however, under policies recently adopted in the EU, data submitted to the EMA in MAAs may be subject to public disclosure. Exactly how the new disclosure policy will be implemented is unclear; however, it could result in the EMA’s public disclosure of certain of our clinical study reports, including pre-clinical data, and patient level data. The move toward public disclosure of development data could adversely affect our business in many ways, including, for example, resulting in the disclosure of our confidential methodologies for pre-clinical and clinical development of our products, preventing us from obtaining intellectual property right protection for innovations, requiring us to allocate significant resources to prevent other companies from violating our intellectual property rights, adding even more complexity to processing health data from clinical trials consistent with applicable data privacy regulations, and enabling competitors to use our data to gain approvals for their own products.

If we are unable to protect our intellectual property, third-parties could develop competing products, which could adversely affect our revenue and financial results generally.

Competitors and other third-parties may have developed intellectual property that could limit our ability to market and commercialize our products and product candidates, if approved.

Similar to us, competitors continually seek intellectual property protection for their technology. Several of our development programs, such as BMN 270, focus on therapeutic areas that have been the subject of extensive research and development by third-parties for many years. Due to the amount of intellectual property in our field of technology, we cannot be certain that we do not infringe intellectual property rights of competitors or that we will not infringe intellectual property rights of competitors granted or created in the future. For example, if a patent holder believes our product infringes its patent, the patent holder may sue us even if we have received patent protection for our technology. If someone else claims we infringe its intellectual property, we would face a number of issues, including the following:

- Defending a lawsuit takes significant executive resources and can be very expensive.
- If a court decides that our product infringes a competitor's intellectual property, we may have to pay substantial damages.
- With respect to patents, in addition to requiring us to pay substantial damages, a court may prohibit us from making, selling, offering to sell, importing or using our product unless the patent holder licenses the patent to us. The patent holder is not required to grant us a license. If a license is available, it may not be available on commercially reasonable terms. For example, we may have to pay substantial royalties or grant cross licenses to our patents and patent applications.
- We may need to redesign our product so it does not infringe the intellectual property rights of others.
- Redesigning our product so it does not infringe the intellectual property rights of competitors may not be possible or could require substantial funds and time.

We may also support and collaborate in research conducted by government organizations, hospitals, universities or other educational institutions. These research partners may be unwilling to grant us any exclusive rights to technology or products derived from these collaborations.

If we do not obtain required licenses or rights, we could encounter delays in our product development efforts while we attempt to design around other patents or may be prohibited from making, using, importing, offering to sell or selling products requiring these licenses or rights. There is also a risk that disputes may arise as to the rights to technology or products developed in collaboration with other parties. If we are not able to resolve such disputes and obtain the licenses or rights we need, we may not be able to develop or market our products.

If our Manufacturing, Marketing and Sales Agreement with Genzyme were terminated, we could be prevented from continuing to commercialize Aldurazyme or our ability to successfully commercialize Aldurazyme would be delayed or diminished.

Either party may terminate the Manufacturing, Marketing and Sales Agreement (the MMS Agreement) between Genzyme and us related to Aldurazyme for specified reasons, including if the other party is in material breach of the MMS Agreement, has experienced a change of control, as such term is defined in the MMS Agreement, or has declared bankruptcy and also is in breach of the MMS Agreement. Although we are not currently in breach of the MMS Agreement, there is a risk that either party could breach the MMS Agreement in the future. Either party may also terminate the MMS Agreement upon one year prior written notice for any reason.

If the MMS Agreement is terminated for breach, the breaching party will transfer its interest in the BioMarin/Genzyme LLC to the non-breaching party, and the non-breaching party will pay a specified buyout amount for the breaching party's interest in Aldurazyme and in the BioMarin/Genzyme LLC. If we are the breaching party, we would lose our rights to Aldurazyme and the related intellectual property and regulatory approvals. If the MMS Agreement is terminated without cause, the non-terminating party would have the option, exercisable for one year, to buy out the terminating party's interest in Aldurazyme and in the BioMarin/Genzyme LLC at a specified buyout amount. If such option is not exercised, all rights to Aldurazyme will be sold and the BioMarin/Genzyme LLC will be

dissolved. In the event of termination of the buyout option without exercise by the non-terminating party as described above, all right and title to Aldurazyme is to be sold to the highest bidder, with

the proceeds to be split between Genzyme and us in accordance with our percentage interest in the BioMarin/Genzyme LLC.

If the MMS Agreement is terminated by either party because the other party declared bankruptcy, the terminating party would be obligated to buy out the other party and would obtain all rights to Aldurazyme exclusively. If the MMS Agreement is terminated by a party because the other party experienced a change of control, the terminating party shall notify the other party, the offeree, of its intent to buy out the offeree's interest in Aldurazyme and the BioMarin/Genzyme LLC for a stated amount set by the terminating party at its discretion. The offeree must then either accept this offer or agree to buy the terminating party's interest in Aldurazyme and the BioMarin/Genzyme LLC on those same terms. The party who buys out the other party would then have exclusive worldwide rights to Aldurazyme. The Amended and Restated Collaboration Agreement between us and Genzyme will automatically terminate upon the effective date of the termination of the MMS Agreement and may not be terminated independently from the MMS Agreement.

If we were obligated or given the option to buy out Genzyme's interest in Aldurazyme and the BioMarin/Genzyme LLC, and thereby gain exclusive rights to Aldurazyme, we may not have sufficient funds to do so and we may not be able to obtain the financing to do so. If we fail to buy out Genzyme's interest, we may be held in breach of the agreement and may lose any claim to the rights to Aldurazyme and the related intellectual property and regulatory approvals. We would then effectively be prohibited from developing and commercializing Aldurazyme. If this happened, not only would our product revenues decrease, but our share price would also decline.

If we fail to develop new products and product candidates or compete successfully with respect to acquisitions, joint ventures, licenses or other collaboration opportunities, our ability to continue to expand our product pipeline and our growth and development would be impaired.

Our future growth and development depends in part on our ability to successfully develop new products from our research and development activities. The development of biopharmaceutical products is very expensive and time intensive and involves a great degree of risk. The outcomes of research and development programs, especially for innovative biopharmaceuticals, are inherently uncertain and may not result in the commercialization of any products.

Our competitors compete with us to attract organizations for acquisitions, joint ventures, licensing arrangements or other collaborations. To date, several of our former and current product programs have been acquired through acquisitions and several of our former and current product programs have been developed through licensing or collaborative arrangements, such as Aldurazyme, Firdapse, Kuvan and Naglazyme. These collaborations include licensing proprietary technology from, and other relationships with, academic research institutions. Our future success will depend, in part, on our ability to identify additional opportunities and to successfully enter into partnering or acquisition agreements for those opportunities. If our competitors successfully enter into partnering arrangements or license agreements with academic research institutions, we will then be precluded from pursuing those specific opportunities. Because each of these opportunities is unique, we may not be able to find a substitute. Several pharmaceutical and biotechnology companies have already established themselves in the field of genetic diseases. These companies have already begun many drug development programs, some of which may target diseases that we are also targeting, and have already entered into partnering and licensing arrangements with academic research institutions, reducing the pool of available opportunities.

Universities and public and private research institutions also compete with us. While these organizations primarily have educational or basic research objectives, they may develop proprietary technology and acquire patents that we may need for the development of our product candidates. We will attempt to license this proprietary technology, if available. These licenses may not be available to us on acceptable terms, if at all. If we are unable to compete successfully with respect to acquisitions, joint venture and other collaboration opportunities, we may be limited in our ability to develop new products and to continue to expand our product pipeline.

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If generic manufacturers use litigation and regulatory means to obtain approval for generic versions of Kuvan, our revenue and results of operations would be adversely affected.

The Drug Price Competition and Patent Term Restoration Act of 1984, known as the Hatch-Waxman Act, permits the FDA to approve ANDAs for generic versions of branded drugs. We refer to this process as the ANDA process. The ANDA process permits competitor companies to obtain marketing approval for a drug with the same active ingredient as a branded drug, but does not generally require the conduct and submission of clinical efficacy studies for the generic product. In place of such clinical studies, an ANDA applicant usually needs only to submit data demonstrating that its product is bioequivalent to the branded product.

Pursuant to the Hatch-Waxman Act, companies were permitted to file ANDA applications for proposed generic versions of Kuvan at any time after December 2011. We own several patents that cover Kuvan, and we have listed those patents in conjunction with that product in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book). The Hatch-Waxman Act requires an ANDA applicant seeking FDA approval of its proposed generic product prior to the expiration of our Orange Book-listed patents to certify that the applicant believes that our patents are invalid or will not be infringed by the manufacture, use or sale of the drug for which the application has been submitted (a paragraph IV certification) and notify us of such certification (a paragraph IV notice). Upon receipt of a paragraph IV notice, the Hatch-Waxman Act allows us, with proper basis, to bring an action for patent infringement against the ANDA filer, asking that the proposed generic product not be approved until after our patents expire. If we commence a lawsuit within 45 days from receipt of the paragraph IV notice, the Hatch-Waxman Act provides a 30-month stay, during which time the FDA cannot finally approve the generic's application. If the litigation is resolved in favor of the ANDA applicant during the 30-month stay period, the stay is lifted and the FDA may approve the ANDA if it is otherwise ready for approval. The discovery, trial and appeals process in such a lawsuit is costly, time consuming, and may result in generic competition if the ANDA applicant prevails. In addition to our patent protection, we have received three-year Hatch-Waxman exclusivity for a New Patient Population for Kuvan that expires in October 2017, including pediatric exclusivity. Thus, depending on the proposed labeling of a generic product, generic versions of Kuvan may be prohibited until October 2017, though it is possible that an ANDA applicant could propose to carve out information in the Kuvan labeling protected by the New Patient Population exclusivity and obtain approval earlier.

We received a paragraph IV notice letter, dated January 22, 2015, from Par Pharmaceutical, Inc. (Par), notifying us that Par had filed an ANDA seeking approval of a proposed generic version of Kuvan (sapropterin dihydrochloride) 100 mg oral tablets prior to the expiration of our patents listed in the FDA's Orange Book. Together with Merck & Cie, on March 6, 2015, we filed a lawsuit against Par in the U.S. District Court for the District of New Jersey alleging infringement of our patents relating to Kuvan tablets and seeking an injunction to prevent Par from introducing a generic version of Kuvan tablets that would infringe our patents prior to their expiration. The filing of that lawsuit triggered the automatic 30-month stay on the approval of Par's ANDA in accordance with the Hatch-Waxman Act, which expires in July 2017. In response, Par alleged, inter alia, that the asserted patents are not infringed and/or are invalid.

We also received a paragraph IV notice letter, dated January 14, 2016, from Par, notifying us that Par has filed a separate ANDA seeking approval of a proposed generic version of Kuvan 100 mg oral powder prior to the expiration of our patents listed in the FDA's Orange Book. On February 22, 2016, we filed a lawsuit against Par in the U.S. District Court for the District of New Jersey alleging infringement of our patents relating to Kuvan powder and seeking an injunction to prevent Par from introducing a generic version of Kuvan powder that would infringe our patents prior to their expiration. The filing of that lawsuit triggered the automatic 30-month stay on the approval of Par's ANDA in accordance with the Hatch-Waxman Act, which expires in July 2018. In response, Par alleged, inter alia, that the asserted patents are not infringed and/or are invalid.

The two cases against Par have been consolidated in the District of New Jersey for all purposes, including pretrial and trial. The Court held a claim construction hearing on May 5, 2016 but has not yet issued its ruling. Fact discovery

closed on September 22, 2016, and expert discovery closes on March 31, 2017. No trial date has been set, but the Court has indicated that trial is likely to occur in May or June 2017.

In September 2015, we entered into a settlement agreement with Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd. (collectively, DRL) that resolved patent litigation with DRL in the U.S. related to DRL's

ANDA seeking approval of a proposed generic version of Kuvan 100 mg oral tablets. Under the terms of the settlement agreement, we have granted DRL a non-exclusive license to our Kuvan-related patents to allow DRL to market a generic version of sapropterin dihydrochloride 100 mg tablets in the U.S. for the indications approved for Kuvan beginning at a confidential date in the future, but which is more than five years from the settlement date, or earlier under certain circumstances.

We also received a paragraph IV notice letter, dated December 23, 2016, from DRL, notifying us that DRL has filed a separate ANDA seeking approval of a proposed generic version of Kuvan 100 mg oral powder prior to the expiration of our patents listed in the FDA's Orange Book. On February 6, 2017, we filed a lawsuit against DRL in the U.S. District Court for the District of New Jersey alleging infringement of our patents relating to Kuvan powder and seeking an injunction to prevent DRL from introducing a generic version of Kuvan powder that would infringe our patents prior to their expiration. The filing of that lawsuit triggered the automatic 30-month stay on the approval of DRL’s ANDA in accordance with the Hatch-Waxman Act, which expires in June 2019. DRL has not yet answered the complaint, and no schedule has been set by the Court to date.

The settlement with DRL relating to Kuvan tablets does not affect the consolidated cases against Par, or the recently-filed case against DRL relating to Kuvan powder. Those two litigation matters are still pending. For more information regarding these matters, see “Legal Proceedings” in Part I, Item 3 of this Annual Report on Form 10-K.

The settlement with DRL relating to tablets, the filing of Par’s purported ANDAs with respect to Kuvan tablets and powder, and the filing of DRL’s purported ANDA with respect to Kuvan powder, as well as any future ANDA or related legal proceeding, could have an adverse impact on our stock price, and litigation to enforce our patents has, and is likely to continue to, cost a substantial amount and require significant management attention. If the patents covering Kuvan and its use are not upheld in litigation, or if Par and/or DRL is found to not infringe our asserted patents, the resulting generic competition following the expiration of regulatory exclusivity would have a material adverse effect on our revenue and results of operations. Moreover, generic competition from DRL following the settlement described above relating to Kuvan tablets could have a material adverse effect on our revenue and results of operations.

We also face potential generic competition for Kuvan in certain foreign countries, including, without limitation, Russia, South Korea, Taiwan, and Turkey. Our ability to successfully market and sell Kuvan in many countries in which we operate is based upon patent rights or certain regulatory forms of exclusivity, or both. The scope of our patent rights and regulatory exclusivity for Kuvan vary from country to country and are dependent on the availability of meaningful legal remedies in each country. If our patent rights and regulatory exclusivity for Kuvan are successfully challenged, expire, or otherwise terminate in a particular country, the resulting generic competition could have a material adverse effect on our revenue and results of operations.

If we do not achieve our projected development goals in the timeframes we announce and expect, the commercialization of our product candidates may be delayed and the credibility of our management may be adversely affected and, as a result, our stock price may decline.

For planning purposes, we estimate the timing of the accomplishment of various scientific, clinical, regulatory and other product development goals, which we sometimes refer to as milestones. These milestones may include the commencement or completion of scientific studies and clinical trials and the submission of regulatory filings. From time to time, we publicly announce the expected timing of some of these milestones. All of these milestones are based on a variety of assumptions. The actual timing of these milestones can vary dramatically compared to our estimates, in many cases for reasons beyond our control. If we do not meet these milestones as publicly announced, the commercialization of our products may be delayed and the credibility of our management may be adversely affected and, as a result, our stock price may decline.

We depend upon our key personnel and our ability to attract and retain employees.

Our future growth and success will depend in large part on our continued ability to attract, retain, manage and motivate our employees. The loss of the services of any member of our senior management or the inability to hire or retain experienced management personnel could adversely affect our ability to execute our business plan and harm our operating results.

Because of the specialized scientific and managerial nature of our business, we rely heavily on our ability to attract and retain qualified scientific, technical and managerial personnel. In particular, the loss of one or more of our senior executive officers could be detrimental to us if we do not have an adequate succession plan or if we cannot recruit suitable replacements in a timely manner. While our senior executive officers are parties to employment agreements with us, these agreements do not guarantee that they will remain employed with us in the future. In addition, in many cases, these agreements do not restrict our senior executive officers' ability to compete with us after their employment is terminated. The competition for qualified personnel in the pharmaceutical field is intense, and there is a limited pool of qualified potential employees to recruit. Due to this intense competition, we may be unable to continue to attract and retain qualified personnel necessary for the development of our business or to recruit suitable replacement personnel. If we are unsuccessful in our recruitment and retention efforts, our business may be harmed.

Our success depends on our ability to manage our growth.

Product candidates that we are currently developing or may license or acquire in the future may be intended for patient populations that are significantly larger than any of the patient populations we currently target. In order to continue development and marketing of these products, if approved, we will need to significantly expand our operations. To manage expansion effectively, we need to continue to develop and improve our research and development capabilities, manufacturing and quality capacities, sales and marketing capabilities, financial and administrative systems and standard processes for global operations. Our staff, financial resources, systems, procedures or controls may be inadequate to support our operations and may increase our exposure to regulatory and corruption risks and our management may be unable to manage successfully future market opportunities or our relationships with customers and other third-parties.

Changes in methods of treatment of disease could reduce demand for our products and adversely affect revenues.

Even if our product candidates are approved, if doctors elect a course of treatment which does not include our products, this decision would reduce demand for our products and adversely affect revenues. For example, if gene therapy becomes widely used as a treatment of genetic diseases, the use of enzyme replacement therapy, such as Aldurazyme, Naglazyme, and Vimizim in MPS diseases, could be greatly reduced. Moreover, if we obtain regulatory approval for BMN 270, the commercial success of BMN 270 will still depend, in part, on the acceptance of physicians, patients and health care payors of gene therapy products in general, and our product candidate in particular, as medically necessary, cost-effective and safe. Changes in treatment method can be caused by the introduction of other companies' products or the development of new technologies or surgical procedures which may not directly compete with ours, but which have the effect of changing how doctors decide to treat a disease.

If product liability lawsuits are successfully brought against us, we may incur substantial liabilities.

We are exposed to the potential product liability risks inherent in the testing, manufacturing and marketing of human pharmaceuticals. We currently maintain insurance against product liability lawsuits for the commercial sale of our products and for the clinical trials of our product candidates. Pharmaceutical companies must balance the cost of insurance with the level of coverage based on estimates of potential liability. Historically, the potential liability associated with product liability lawsuits for pharmaceutical products has been unpredictable. Although we believe that our current insurance is a reasonable estimate of our potential liability and represents a commercially reasonable balancing of the level of coverage as compared to the cost of the insurance, we may be subject to claims in connection with our clinical trials and commercial use of our products and product candidates for which our insurance coverage may not be adequate and we may be unable to avoid significant liability if any product liability lawsuit is brought against us. If we are the subject of a successful product liability claim that exceeds the limits of any insurance coverage we obtain, we may incur substantial charges that would adversely affect our earnings and require the commitment of capital resources that might otherwise be available for the development and commercialization of our product programs.

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We rely significantly on information technology and any failure, inadequacy, interruption or security lapse of that technology, including any cybersecurity incidents, could harm our ability to operate our business effectively.

We rely significantly on our information technology and manufacturing infrastructure to effectively manage and maintain our inventory and internal reports, to manufacture and ship products to customers and to timely invoice them. Any failure, inadequacy or interruption of that infrastructure or security lapse of that technology, including cybersecurity incidents, could harm our ability to operate our business effectively. Our ability to manage and maintain our inventory and internal reports, to manufacture and ship our products to customers and timely invoice them depends significantly on our enterprise resource planning, production management and other information systems. Cybersecurity attacks in particular are evolving and include, but are not limited to, malicious software, attempts to gain unauthorized access to data and other electronic security breaches that could lead to disruptions in systems, misappropriation of our confidential or otherwise protected information and corruption of data. Cybersecurity incidents resulting in the failure of our enterprise resource planning system, production management or other systems to operate effectively or to integrate with other systems, or a breach in security or other unauthorized access of these systems, may affect our ability to manage and maintain our inventory and internal reports, and result in delays in product fulfillment and reduced efficiency of our operations. A breach in security, unauthorized access resulting in misappropriation, theft, or sabotage with respect to our proprietary and confidential information, including research or clinical data, could require significant capital investments to remediate and could adversely affect our business, financial condition and results of operations.

If a natural disaster or terrorist or criminal activity caused significant damage to our facilities or the facilities of our third-party manufacturers and suppliers, we may be unable to meet demand for our products and lose potential revenue, have reduced margins, or be forced to terminate a program.

We manufacture Aldurazyme, Naglazyme and a portion of Vimizim in a manufacturing facility located near known earthquake fault zones, and the occurrence of an earthquake or other catastrophic disaster could cause damage to our facility and equipment, or that of our third-party manufacturers or single-source suppliers, which could materially impair our ability to manufacture Aldurazyme, Naglazyme and Vimizim or our third-party manufacturers' ability to manufacture Firdapse or Kuvan.

Our Galli Drive facility located in Novato, California is currently our only manufacturing facility for Aldurazyme and Naglazyme and is one of two manufacturing facilities for Vimizim. It is located in the San Francisco Bay Area near known earthquake fault zones and is vulnerable to significant damage from earthquakes. We, the third-party manufacturers with whom we contract and our single-source suppliers of raw materials, which include many of our critical raw materials, are also vulnerable to damage from other types of disasters, including fires, explosions, floods, power loss and similar events. If any disaster were to occur, or any terrorist or criminal activity caused significant damage to our facilities or the facilities of our third-party manufacturers and suppliers, our ability to manufacture Aldurazyme, Naglazyme and Vimizim, or to have Firdapse or Kuvan manufactured, could be seriously, or potentially completely, impaired, and our commercialization efforts and revenue could be seriously impaired. The insurance that we carry, the inventory that we maintain and our risk mitigation plans may not be adequate to cover our losses resulting from disasters or other business interruptions.

Our business is affected by macroeconomic conditions.

Various macroeconomic factors could adversely affect our business and the results of our operations and financial condition, including changes in inflation, interest rates and foreign currency exchange rates and overall economic conditions and uncertainties, including those resulting from the current and future conditions in the global financial markets. For instance, if inflation or other factors were to significantly increase our business costs, it may not be feasible to pass price increases on to our customers due to the process by which health care providers are reimbursed for our products by the government. Interest rates, the liquidity of the credit markets and the volatility of the capital markets could also affect the value of our investments and our ability to liquidate our investments in order to fund our

operations. We purchase or enter into a variety of financial instruments and transactions, including investments in commercial paper, the extension of credit to corporations, institutions and governments and hedging contracts. If any of the issuers or counter parties to these instruments were to default on their obligations, it could materially reduce the value of the transaction and adversely affect our cash flows.

For the year ended December 31, 2016, 6% of our net product revenues were from Italy, Spain, Portugal, Greece and Russia. Approximately 11% of our total accounts receivable as of December 31, 2016, are related to these countries. If the financial conditions of these countries continues to decline, a substantial portion of the receivables may be uncollectable, which would mean we would have to provide for additional allowances for doubtful accounts or cease selling products in these countries, either of which could adversely affect our results of operations. Additionally, if one or more of these countries were unable to purchase our products, our revenue would be adversely affected. We also sell our products in other countries that face economic crises and local currency devaluation. Although we have historically collected receivables from customers in those countries, sustained weakness or further deterioration of the local economies and currencies may cause our customers in those countries to be unable to pay for our products with the same negative effect on our operations.

Interest rates and the ability to access credit markets could also adversely affect the ability of our customers/distributors to purchase, pay for and effectively distribute our products. Similarly, these macroeconomic factors could affect the ability of our contract manufacturers, sole-source or single-source suppliers to remain in business or otherwise manufacture or supply product. Failure by any of them to remain a going concern could affect our ability to manufacture products.

Risks Related to Ownership of Our Securities

Our stock price may be volatile, and an investment in our stock could suffer a decline in value.

Our valuation and stock price have no meaningful relationship to current or historical earnings, asset values, book value or many other criteria based on conventional measures of stock value. The market price of our common stock will fluctuate due to factors including:

- product sales and profitability of our products;
- manufacturing, supply or distribution of our product candidates and commercial products;
- progress of our product candidates through the regulatory process and our ability to successfully commercialize any such products that receive regulatory approval;
- results of clinical trials, announcements of technological innovations or new products by us or our competitors;
- results relating to our lawsuits against Par and DRL to protect our patents relating to Kuvan tablets and powder and generic competition to Kuvan relating to our settlement with DRL related to Kuvan tablets;
- government regulatory action affecting our product candidates, our products or our competitors' product candidates and products in both the U.S. and non-U.S. countries;
- developments or disputes concerning patent or proprietary rights;
- general market conditions and fluctuations for the emerging growth and pharmaceutical market sectors;
- economic conditions in the U.S. or abroad;
- negative publicity about our company or the pharmaceutical industry;
- broad market fluctuations in the U.S., the EU or in other parts of the world;
- actual or anticipated fluctuations in our operating results, including due to timing of large order for our products, in particular in Latin America, where governments place large periodic orders for Naglazyme and Vimizim;
- changes in company assessments or financial estimates by securities analysts;
- acquisitions of products, businesses, or other assets; and
- sales of our shares of stock by us, our significant shareholders, or members of our management or Board of Directors.

In the past, following periods of large price declines in the public market price of a company's securities, securities class action litigation has often been initiated against that company. Litigation of this type could result in substantial costs and diversion of management's attention and resources, which would hurt our business. Any adverse determination in litigation could also subject us to significant liabilities. In addition, our stock price can be materially adversely affected by factors beyond our control, such as disruptions in global financial markets or negative trends in the biotechnology sector of the economy, even if our business is operating well.

Conversion of the Notes will dilute the ownership interest of existing stockholders, including holders who had previously converted their Notes, or may otherwise depress the price of our common stock.

The conversion of some or all of the Notes will dilute the ownership interests of existing stockholders to the extent we deliver shares upon conversion of any of the Notes. The Notes may become in the future convertible at the option of their holders prior to their scheduled terms under certain circumstances. Any sales in the public market of the common stock issuable upon such conversion could adversely affect prevailing market prices of our common stock. In addition, the existence of the Notes may encourage short selling by market participants because the conversion of the Notes could be used to satisfy short positions, or anticipated conversion of the Notes into shares of our common stock could depress the price of our common stock.

The capped call transactions may affect the value of the Notes and our common stock.

In connection with the issuance of the 2018 Notes and 2020 Notes, we entered into capped call transactions with respect to 50% of the principal amount of the 2018 Notes and 50% of the principal amount of the 2020 Notes with certain hedge counterparties. The capped call transactions will cover, subject to customary anti-dilution adjustments, the aggregate number of shares of common stock underlying 50% of the principal amount of the relevant Notes and are expected generally to reduce potential dilution to the common stock upon conversion of the relevant Notes in excess of the principal amount of such converted Notes. In connection with establishing their initial hedges of the capped call transactions, the hedge counterparties (or their affiliates) entered into various derivative transactions with respect to the common stock concurrently with, and/or purchased the common stock shortly after, the pricing of the relevant notes. The hedge counterparties (or their affiliates) are likely to modify their hedge positions by entering into or unwinding various derivative transactions with respect to the common stock and/or by purchasing or selling the common stock or other securities of ours in secondary market transactions prior to the maturity of the relevant Notes (and are likely to do so during the settlement averaging period under the relevant capped call transactions, which precedes the maturity date of the relevant Notes, and on or around any earlier conversion date related to a conversion of the relevant Notes).

The effect, if any, of any of these transactions and activities on the market price of our common stock or the Notes will depend in part on market conditions and cannot be ascertained at this time, but any of these activities could adversely affect the value of our common stock, which could affect the value of the Notes and the value of our common stock, if any, that Note holders receive upon any conversion of the Notes.

Anti-takeover provisions in our charter documents and under Delaware law may make an acquisition of us, which may be beneficial to our stockholders, more difficult.

We are incorporated in Delaware. Certain anti-takeover provisions of Delaware law and our charter documents as currently in effect may make a change in control of our company more difficult, even if a change in control would be beneficial to the stockholders. Our anti-takeover provisions include provisions in our certificate of incorporation providing that stockholders' meetings may only be called by our Chairman or the majority of our Board of Directors and provisions in our bylaws providing that the stockholders may not take action by written consent and requiring that stockholders that desire to nominate any person for election to our Board of Directors or to make any proposal with respect to business to be conducted at a meeting of our stockholders be submitted in appropriate form to our Secretary within a specified period of time in advance of any such meeting. Additionally, our Board of Directors has the

authority to issue shares of preferred stock and to determine the terms of those shares of stock without any further action by our stockholders. The rights of holders of our common stock are subject to the rights of the holders of any preferred stock that may be issued. The issuance of preferred stock could make it more difficult for a third-party to acquire a majority of our outstanding voting stock. Delaware law also prohibits corporations from engaging in a business combination with any holders of 15% or more of their capital stock until

the holder has held the stock for three years unless, among other possibilities, our Board of Directors approves the transaction. Our Board of Directors may use these provisions to prevent changes in the management and control of our company. Also, under applicable Delaware law, our Board of Directors may adopt additional anti-takeover measures in the future.

The fundamental change repurchase feature of the Notes may delay or prevent an otherwise beneficial attempt to take over our company.

The terms of the Notes require us to repurchase the Notes in the event of a fundamental change. A takeover of our company would trigger options by the respective holders of the applicable Notes to require us to repurchase such Notes. This may have the effect of delaying or preventing a takeover of our company that would otherwise be beneficial to our stockholders or investors in the Notes.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

The following table contains information about our current significant owned and leased properties as of December 31, 2016:

Location	Approximate Square Feet	Use	Lease Expiration Date
San Rafael facility, San Rafael, California	391,700	Corporate headquarters, laboratory and office	NA: owned property
Several locations in Novato, California	225,000	Office, laboratory and warehouse	2016-2021
Shanbally facility, Cork, Ireland	166,900	Manufacturing, laboratory and office	NA: owned property
Galli Drive facility, Novato, California	98,200	Clinical and commercial manufacturing and laboratory	NA: owned property
Bel Marin Keys facilities, Novato, California	83,000	Technical operations, finance, administration, and laboratory	NA: owned property
Digital Drive facility, Novato, California	47,000	Office and laboratory	NA: owned property
Leveroni Drive facility, Novato, California	38,300	Manufacturing (construction in progress)	NA: owned property
London, England	22,600	Office	2025
Dublin, Ireland	11,800	Office	2024

In addition to the above, we also maintain small offices in a variety of locations around the world. We expect our facilities to be adequate for our operations for the foreseeable future. We believe that, to the extent required, we will be able to lease or buy additional facilities at commercially reasonable rates. We plan to use contract manufacturing when appropriate to provide product for both clinical and commercial requirements until such time as we believe it prudent to develop additional in-house clinical and/or commercial manufacturing capacity.

Item 3. Legal Proceedings

Paragraph IV Notices

We received a paragraph IV notice letter, dated October 3, 2014, from Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd. (collectively, DRL), notifying us that DRL had filed an ANDA seeking approval of a proposed generic version of Kuvan 100 mg oral tablets prior to the expiration of our patents listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book). Together with Merck & Cie, on November 17, 2014, we filed a lawsuit against DRL in the U.S. District Court for the District of New Jersey alleging infringement of our patents relating to Kuvan tablets and seeking an injunction to prevent DRL from

introducing a generic version of Kuvan tablets that would infringe our patents prior to their expiration. In September 2015, we entered into a settlement agreement with DRL that resolved the patent litigation with DRL in the U.S. related to Kuvan 100 mg oral tablets. Under the terms of the settlement agreement, we have granted DRL a non-exclusive license to our Kuvan-related patents to allow DRL to market a generic version of sapropterin dihydrochloride 100 mg tablets in the U.S. for the indications approved for Kuvan beginning at a confidential date in the future, but which is more than five years from the settlement date, or earlier under certain circumstances.

Additionally, we received a paragraph IV notice letter, dated January 22, 2015, from Par Pharmaceutical, Inc. (Par), notifying us that Par has filed an ANDA seeking approval of a proposed generic version of Kuvan 100 mg oral tablets prior to the expiration of our patents listed in the FDA's Orange Book. Together with Merck & Cie, on March 6, 2015 we filed a lawsuit against Par in the U.S. District Court for the District of New Jersey alleging infringement of our patents relating to Kuvan tablets and seeking an injunction to prevent Par from introducing a generic version of Kuvan tablets that would infringe our patents prior to their expiration. The filing of that lawsuit triggered the automatic 30-month stay on the approval of Par's ANDA in accordance with the Hatch-Waxman Act, which expires in July 2017. In response, Par alleged, inter alia, that the asserted patents are not infringed and/or are invalid.

We also received a paragraph IV notice letter, dated January 14, 2016, from Par, notifying us that Par has filed a separate ANDA seeking approval of a proposed generic version of Kuvan 100 mg oral powder prior to the expiration of our patents listed in the FDA's Orange Book. On February 22, 2016, we filed a lawsuit against Par in the U.S. District Court for the District of New Jersey alleging infringement of our patents relating to Kuvan powder and seeking an injunction to prevent Par from introducing a generic version of Kuvan powder that would infringe our patents prior to their expiration. The filing of that lawsuit triggered the automatic 30-month stay on the approval of Par's ANDA in accordance with the Hatch-Waxman Act, which expires in July 2018. In response, Par alleged, inter alia, that the asserted patents are not infringed and/or are invalid.

The two cases against Par have been consolidated in the District of New Jersey for all purposes, including pretrial and trial. The Court held a claim construction hearing on May 5, 2016 but has not yet issued its ruling. Fact discovery closed on September 22, 2016, and expert discovery closes on March 31, 2017. No trial date has been set, but the Court has indicated that trial is likely to occur in May or June 2017.

We also received a paragraph IV notice letter, dated December 23, 2016, from DRL, notifying us that DRL has filed a separate ANDA seeking approval of a proposed generic version of Kuvan 100 mg oral powder prior to the expiration of our patents listed in the FDA's Orange Book. On February 6, 2017, we filed a lawsuit against DRL in the U.S. District Court for the District of New Jersey alleging infringement of our patents relating to Kuvan powder and seeking an injunction to prevent DRL from introducing a generic version of Kuvan powder that would infringe our patents prior to their expiration. The filing of that lawsuit triggered the automatic 30-month stay on the approval of DRL's ANDA in accordance with the Hatch-Waxman Act, which expires in June 2019. DRL has not yet answered the complaint, and no schedule has been set by the Court to date.

The settlement with DRL relating to Kuvan tablets does not affect the consolidated cases against Par, or the recently-filed case against DRL relating to Kuvan powder. Those two litigation matters are still pending.

SEC Subpoena

In August 2016, we received a subpoena from the staff of the Securities and Exchange Commission (SEC) requesting that we produce documents in connection with a non-public, fact-finding inquiry related to our former drisapersen program. The letter enclosing the subpoena states that the investigation and the subpoena do not mean that the Company or anyone else has broken the law, or that the SEC has a negative opinion of any person, entity or security. We intend to cooperate fully with the SEC in this matter. We are not able to predict whether any proceeding may be instituted in connection with the subpoena, or the outcome of any proceeding that may be instituted.

Item 4. Mine Safety Disclosures

Not applicable.

Part II

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

Our common stock is listed under the symbol "BMRN" on the NASDAQ Global Select Market. The following table sets forth the range of high and low quarterly sales prices for our common stock for the periods noted, as reported by NASDAQ.

		Prices	
Year	Period	High	Low
2016	Fourth Quarter	$98.34	$78.42
	Third Quarter	$102.49	$77.04
	Second Quarter	$94.08	$73.45
	First Quarter	$105.61	$62.12
2015	Fourth Quarter	$118.48	$91.21
	Third Quarter	$151.75	$95.09
	Second Quarter	$141.51	$110.50
	First Quarter	$133.54	$88.51

On February 13, 2017, the last reported sale price on the NASDAQ Global Select Market for our common stock was $90.89. We have never paid any cash dividends on our common stock and we do not anticipate paying cash dividends in the foreseeable future.

Recent Sales of Unregistered Securities

We did not sell any unregistered securities during the three years ended December 31, 2016.

Issuer Purchases of Equity Securities

We did not make any purchases of our common stock during the year ended December 31, 2016.

Holders

As of February 13, 2017, there were 47 holders of record of 172,866,495 outstanding shares of our common stock. Additionally, on such date, options to acquire 8.7 million shares of our common stock were outstanding.

Performance Graph

The following is not deemed “filed” with the Securities and Exchange Commission and is not to be incorporated by reference into any filing we make under the Securities Act of 1933, as amended, whether made before or after the date hereof and irrespective of any general incorporation by reference language in such filing.

The following graph shows the value of an investment in BioMarin common stock, the NASDAQ Composite Index (U.S.) and the NASDAQ Biotechnology Index, assuming the investment of $100 at the beginning of the period and the reinvestment of dividends, if any. Our common stock is traded on the NASDAQ Global Select Market and is a component of both the NASDAQ Composite Index and the NASDAQ Biotechnology Index. The comparisons shown in the graph are based upon historical data and we caution that the stock price performance shown in the graph is not indicative of, nor intended to forecast, the potential future performance of our stock.

*$100 invested on December 31, 2011 in stock or index, including reinvestment of dividends.

	Fiscal Year Ending December 31,					
	2011	2012	2013	2014	2015	2016
BioMarin Pharmaceutical Inc.	$100.00	$143.11	$204.62	$262.94	$304.71	$240.95
NASDAQ Composite	100.00	116.41	165.47	188.69	200.32	216.54
NASDAQ Biotechnology	100.00	134.68	232.37	307.67	328.76	262.08

Item 6. Selected Consolidated Financial Data

We derived the selected consolidated statements of operations data for the years ended December 31, 2016, 2015 and 2014 and the selected consolidated balance sheet data as of December 31, 2016 and 2015 from the audited Consolidated Financial Statements appearing elsewhere in this Annual Report on Form 10-K. We derived the selected consolidated statements of operations data for the years ended December 31, 2013 and 2012 and the selected consolidated balance sheet data as of December 31, 2014, 2013 and 2012 from audited Consolidated Financial Statements not included in this Annual Report on Form 10-K. The information set forth below is not necessarily indicative of results of future operations, and should be read in conjunction with Item 7, Management's Discussion and Analysis of Financial Condition and Results of Operations and the Consolidated Financial Statements and related notes thereto included in Item 15 of this Annual Report on Form 10-K to fully understand factors that may affect the comparability of the information presented below:

	Years Ended December 31, (In thousands, except for per share data)				
	2016 (1)	2015	2014	2013	2012
Consolidated Statements of Operations data:					
Total revenues (2)	$1,116,854	$889,895	$749,284	$548,485	$500,723
Total costs and expenses (2)	1,920,283	1,000,597	842,175	704,492	610,938
Loss from operations	(803,429)	(110,702)	(92,891)	(156,007)	(110,215)
Provision for (benefit from) income taxes	(200,840)	17,075	9,101	(150)	(3,931)
Net loss	(630,210)	(171,799)	(133,969)	(176,353)	(114,347)
Net loss per share, basic	$(3.80)	$(1.07)	$(0.92)	$(1.28)	$(0.95)
Net loss per share, diluted	$(3.81)	$(1.07)	$(0.92)	$(1.28)	$(0.95)
Weighted average common shares outstanding, basic	165,985	160,025	146,349	137,755	120,271
Weighted average common shares outstanding, diluted	166,219	160,025	146,349	137,755	120,271

	December 31, (in thousands)				
	2016 (1) (3)	2015	2014	2013	2012
Consolidated Balance Sheets data:					
Cash, cash equivalents and investments (4)	$1,362,388	$1,018,271	$1,043,048	$1,052,423	$563,798
Total assets	4,023,690	3,729,368	2,475,379	2,225,497	1,564,645
Other long-term obligations	157,344	220,778	68,845	64,182	90,588
Long-term convertible senior notes, net (5)	660,761	662,286	642,902	637,003	321,157
Total stockholders' equity	2,766,275	2,400,847	1,527,894	1,341,041	1,015,763

(1) In the fourth quarter of 2016, we elected to early adopt Accounting Standards Update No. 2016-09, Compensation-Stock Compensation (Topic 718) "Improvement to Employee Share-based Payment Accounting" (ASU 2016-09), which requires us to record, among other items, excess tax benefits as a reduction of the

provision for income taxes in the income statements. We are required to reflect any adoption adjustments as of January 1, 2016, the beginning of the annual period that includes the interim period of adoption. As such, certain Consolidated Statements of Operations data for the year ended December 31, 2016 included the impact of the ASU 2016-09 adoption. See Note 4 to the accompanying Consolidated Financial Statements for additional information related to this adoption.

(2) See “Management's Discussion and Analysis of Financial Condition and Results of Operations” in Part II, Item 7 of this Annual Report on Form 10-K for a description of our results of operations for 2016.

(3) Certain Consolidated Balance Sheets data as of December 31, 2016, include the impact of ASU 2016-09, which we early adopted in 2016. For instance, the net cumulative-effect adjustment of $131.3 million decrease to Accumulated deficit, which was recorded as of January 1, 2016, mostly related to the recognition of the previously unrecognized excess tax benefits using the modified retrospective

method. See Note 4 to the accompanying Consolidated Financial Statements for additional information related to this adoption.

(4) See “Management's Discussion and Analysis of Financial Condition and Results of Operations— Financial Position, Liquidity and Capital Resources” in Part II, Item 7 of this Annual Report on Form 10-K for additional discussion.

(5) During 2013, we issued $750.0 million principal amount of convertible senior notes in a registered offering.

You should read the following tables presenting our unaudited quarterly results of operations in conjunction with the Consolidated Financial Statements and related notes contained elsewhere in this Annual Report on Form 10-K. We have prepared this unaudited information on the same basis as our audited Consolidated Financial Statements. Our quarterly operating results have fluctuated in the past and may continue to do so in the future as a result of a number of factors, including, but not limited to, the timing and nature of research and development activities.

	Three Months Ended (In thousands, except per share data, unaudited)			
	March 31,	June 30,	September 30,	December 31,
2016:				
Total revenues	$236,736	$300,131	$ 279,896	$ 300,091
Net loss (1)	(83,051)	(419,014)	(37,425)	(90,720)
Net loss per share, basic and diluted (1)	(0.51)	(2.58)	(0.22)	(0.53)
2015:				
Total revenues	$202,920	$250,135	$ 208,904	$ 227,936
Net income (loss)	(67,501)	(81,989)	(90,926)	68,617
Net income (loss) per share, basic	(0.43)	(0.51)	(0.57)	0.43
Net income (loss) per share, diluted	(0.43)	(0.51)	(0.60)	0.39

(1) We elected to early adopt ASU 2016-09 in the fourth quarter of 2016. As such, certain Consolidated Statements of Operations data for the three months ended December 31, 2016, September 30, 2016, June 30, 2016, and March 31, 2016 included the impacts of early adoption of ASU 2016-09. See Note 4 of the accompanying notes to our Consolidated Financial Statements for additional information related to this adoption. In the opinion of management, the financial information reflects all adjustments, consisting only of normal recurring adjustments, which we consider necessary for a fair presentation of this data.

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

The following Management's Discussion and Analysis of Financial Condition and Results of Operations (the MD&A) is intended to help the reader understand our results of operations and financial condition. The MD&A is provided as a supplement to, and should be read in conjunction with, our audited Consolidated Financial Statements and the accompanying notes to the Consolidated Financial Statements and other disclosures included in this Annual Report on Form 10-K, including the disclosures under "Risk Factors" in Part I, Item 1A of this Annual Report on Form 10-K. Our Consolidated Financial Statements have been prepared in accordance with United States (U.S.) generally accepted accounting principles (GAAP) and are presented in U.S. dollars (USD).

Overview

We are a global biotechnology company that develops and commercializes innovative therapies for people with serious and life-threatening rare diseases and medical conditions. We select product candidates for diseases and conditions that represent a significant unmet medical need, have well-understood biology and provide an opportunity to be first-to-market or offer a significant benefit over existing products.

Our therapy portfolio consists of five products and multiple clinical and pre-clinical product candidates. Our commercial products are Aldurazyme (laronidase) for Mucopolysaccharidosis I (MPS I), Firdapse (amifampridine phosphate) for Lambert Eaton Myasthenic Syndrome (LEMS), Kuvan (sapropterin dihydrochloride) for phenylketonuria (PKU), Naglazyme (galsulfase) for Mucopolysaccharidosis VI (MPS VI) and Vimizim (elosulfase alpha) for Mucopolysaccharidosis IV Type A (MPS IV A).

Business Developments

We continued to grow our commercial business and advance our product pipeline during 2016. We believe that the combination of our internal research programs, acquisitions and partnerships will allow us to continue develop and commercialize innovative therapies for people with serious and life-threatening rare diseases and medical conditions. Below is a summary of key business developments to date:

- In January 2017, we announced an update to positive interim clinical results of an open-label Phase 1/2 study of BMN 270, an investigational gene therapy treatment for severe hemophilia A. In February 2017, we announced that the European Medicines Agency (EMA) has granted BMN 270 access to its Priority Medicines (PRIME) regulatory initiative. To be accepted for PRIME, an investigational therapy has to show its potential to benefit patients with unmet medical needs based on early clinical data. Earlier in the year, we received Orphan Drug Designation from the Food and Drug Administration (FDA) for BMN 270 for hemophilia A.
- In January 2017, we announced preliminary results Phase 1/2 trial, which began enrolling patients in April 2016, demonstrating that BMN 250, an investigational enzyme replacement therapy using a novel fusion of recombinant human alpha-N-acetyglucosaminidase with a peptide derived from insulin-like growth factor 2 (IGF2), for the treatment of Sanfilippo B syndrome or mucopolysaccharidosis IIIB (MPS IIIB), reduced heparan sulfate levels to normal range in cerebral spinal fluid of MPS IIIB patients. Additionally, patients have safely escalated to 100mg dosage.
- In December 2016, we announced the enrollment of the first patient in our Phase 3 trial for vosoritide, for the treatment of children with achondroplasia. In October 2016, we provided an update on our Phase 2 study of vosoritide, an analog of C-type Natriuretic peptide, in children with achondroplasia, the most common form of dwarfism. Results from eight children in cohort 4, who completed six months of daily dosing at 30 µg/kg/daily, experienced a 46% or 2.1 cm/year increase in mean annualized growth velocity from baseline. These data are comparable to those observed at the lower dose of 15 µg/kg/day in cohort 3. Results from 10 children in cohort 3, who completed six months of daily dosing at 15 µg/kg/day, experienced a 50% or 2.0 cm/year increase in mean annualized growth velocity from baseline.
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In September 2016, we announced that the EMA validated the Marketing Authorization Application (MAA) for Brineura, an investigational therapy to treat children with CLN2 disease, a form of Batten disease. Validation of the MAA confirmed that the submission was accepted and starts the formal

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review process by the EMA's Committee for Human Medicinal Products (CHMP). The EMA previously granted our request for accelerated assessment for the MAA. The CHMP opinion and decision from the European Commission (EC) is expected in the third quarter of 2017. Accelerated assessments are granted on the grounds that a product may satisfy an unmet medical need and is of major interest from the point of view of therapeutic innovation and public health.

- In July 2016, we announced that the FDA accepted for review the submission of a Biologics License Application (BLA) for Brineura. During their initial review of the BLA, the FDA requested updated efficacy data from the ongoing extension study, which we provided. In September 2016, the FDA designated this submission as a major amendment to the application, thus extending the Prescription Drug User Fee Act (PDUFA) action date by three months to April 27, 2017. The FDA granted Brineura Priority Review status, which is designated to drugs that, if approved, would be a significant improvement in treatment or provide a treatment where no adequate therapy exists. Brineura was previously granted Orphan Drug Designation by the FDA and EMA and Breakthrough Therapy Designation by the FDA.
- In June 2016, we announced that the reveglucosidase alfa development program has been terminated. We recognized an impairment charge of $25.0 million in the second quarter of 2016 related to the reveglucosidase alfa in-process research and development (IPR&D) assets.
- In May 2016, we withdrew our MAA from the EMA for Kyndrisa (drisapersen). We discontinued clinical and regulatory development of Kyndrisa as well as the three other first generation follow-on products, BMN 044, BMN 045 and BMN 053 (other exons). We recognized an impairment charge of $574.1 million in the second quarter of 2016 related to the Kyndrisa and other exon IPR&D assets.
- In March 2016, we announced that our pivotal Phase 3 PRISM-2 study of pegvaliase met the primary endpoint of change in blood Phe compared with placebo ($p<0.0001$). Based on the supportive data results, we plan to submit a BLA to the FDA in the second quarter of 2017.
- In January 2016, we acquired all global rights to Kuvan and pegvaliase, with the exception of Kuvan in Japan, (collectively, the Merck PKU Business) from Ares Trading S.A. (Merck Serono), an indirectly wholly-owned affiliate of Merck KGaA, in exchange for cash payments of $374.5 million. We also agreed to pay Merck Serono up to a maximum of €60.0 million in milestones if certain sales milestones are met and up to a maximum of €125.0 million if certain pegvaliase development milestones are met. See Note 5 to our accompanying Consolidated Financial Statements for additional discussion.
- We reported total revenues of $1.1 billion for the year ended December 31, 2016, compared to $889.9 million and $749.3 million for the years ended December 31, 2015 and 2014, respectively.

Outlook 2017

In 2017, we will continue to focus on our key operating objectives which include continued progression of our product pipeline and continued uptake of our commercial products. From a research and development (R&D) perspective, we expect to continue to invest in our various ongoing clinical studies, which support both our commercial products and pipeline of new product candidates. We expect to move forward on a number of late-stage clinical studies for new product candidates and plan to file marketing applications for various therapeutic areas.

From a commercial perspective, we expect to continue to build-out our commercial organization to support the commercialization of Vimizim and the international expansion of Kuvan.

We continue to monitor conditions in the macroeconomic environment that could affect our ability to achieve our goals, such as changes in the reimbursement and payer landscape, a worsening of economic conditions in certain key markets, particularly in Europe, patent expirations of competitive products and the launch of generic competitors, government pricing pressures internationally and the potential volatility in foreign currency exchange rates. We will adjust our business processes, as appropriate, to attempt to mitigate these risks to our business.

We expect that our product pipeline investments and expanding commercial infrastructure will enable us to execute on our 2017 operating objectives.

2016 Financial Highlights

Key components of our results of operations include the following (in millions):

	Years Ended December 31,		
	2016	2015	2014
Net product revenues	$1,110.4	$884.5	$738.4
Cost of sales (excluding amortization of intangible assets)	209.6	152.0	122.3
R&D expense	661.9	634.8	461.5
Selling, general and administrative (SG&A) expense	476.6	402.3	302.2
Intangible asset amortization and contingent consideration expense	(27.0)	(17.7)	23.7
Net loss	(630.2)	(171.8)	(134.0)
Stock-based compensation expense	134.6	111.5	86.4

See "Results of Operations" below for a discussion of the detailed components and analysis of the amounts above.

Total net product revenues were as follows (in millions):

	Years Ended December 31,		
	2016	2015	2014
Aldurazyme	$93.8	$98.0	$105.6
Firdapse	18.0	16.0	18.1
Kuvan	348.0	239.3	203.0
Naglazyme	296.5	303.1	334.4
Vimizim	354.1	228.1	77.3
Total net product revenues	$1,110.4	$884.5	$738.4

Net product revenues are generated from the five approved products in our product portfolio. In the U.S., our commercial products are generally sold to specialty pharmacies or end-users, such as hospitals, which act as retailers. Outside the U.S., our commercial products are sold to our authorized distributors or directly to government purchasers or hospitals, which act as the end-users. Collaborative agreement revenues include both license revenue and contract research revenue. Royalty and Other Revenues include royalties on net sales of products to licensees or sublicensees and rental income associated with the tenants in our San Rafael, California facility.

Our cash, cash equivalents and investments totaled $1.4 billion as of December 31, 2016, compared to $1.0 billion as of December 31, 2015. We have historically financed our operations primarily through our cash flows from operating activities and the issuance of common stock and convertible debt. We will be highly dependent on our net product revenues to supplement our current liquidity and fund our operations for the foreseeable future. We may in the future

elect to supplement this with further debt or equity offerings or commercial borrowing. Further, depending on market conditions, our financial position and performance and other factors, we may in the future choose to use a portion of our cash or cash equivalents to repurchase our convertible debt or other securities. See “Financial Position, Liquidity and Capital Resources” below for a further discussion of our liquidity and capital resources.

Critical Accounting Policies and Estimates

In preparing our Consolidated Financial Statements in accordance with GAAP in the U.S. and pursuant to the rules and regulations promulgated by the Securities and Exchange Commission (the SEC), we make assumptions, judgments and estimates that can have a significant impact on our net income/loss and affect the reported amounts of certain assets, liabilities, revenue and expenses, and related disclosures. We base our assumptions, judgments and estimates on historical experience and various other factors that we believe to be reasonable under the circumstances. Actual results could differ materially from these estimates under different assumptions or conditions.

On a regular basis, we evaluate our assumptions, judgments and estimates. We also discuss our critical accounting policies and estimates with the Audit Committee of our Board of Directors.

We believe that the assumptions, judgments and estimates involved in the accounting for business combinations, contingent acquisition consideration payable, income taxes, long-lived assets and revenue recognition have the greatest impact on our Consolidated Financial Statements, so we consider these to be our critical accounting policies. Historically, our assumptions, judgments and estimates relative to our critical accounting policies have not differed materially from actual results.

Business Combinations

We allocate the purchase price of acquired businesses to the tangible and intangible assets acquired and liabilities assumed based upon their estimated fair values on the acquisition date. The purchase price allocation process requires management to make significant estimates and assumptions, especially at the acquisition date with respect to intangible assets and IPR&D. In connection with the purchase price allocations for acquisitions, we estimate the fair value of contingent acquisition consideration payments utilizing a probability-based income approach inclusive of an estimated discount rate.

Although we believe the assumptions and estimates made are reasonable, they are based in part on historical experience and information obtained from the management of the acquired businesses and are inherently uncertain. Examples of critical estimates in valuing any contingent acquisition consideration issued or that may be issued and the intangible assets we have acquired or may acquire in the future include but are not limited to:

- the feasibility and timing of achievement of development, regulatory and commercial milestones;
- expected costs to develop the IPR&D into commercially viable products; and
- future expected cash flows from product sales.

Unanticipated events and circumstances may occur that may affect the accuracy or validity of such assumptions, estimates or actual results.

Valuation of Contingent Acquisition Consideration Payable

Each period we reassess the fair value of the contingent acquisition consideration payable associated with certain acquisitions and record increases in the fair value as contingent consideration expense and record decreases in the fair value as a reduction of contingent consideration expense. Increases or decreases in the fair value of the contingent acquisition consideration payable can result from changes in estimated probability adjustments with respect to regulatory approval, changes in the assumed timing of when milestones are likely to be achieved and changes in assumed discount periods and rates. Significant judgment is employed in determining the appropriateness of these assumptions each period. Accordingly, future business and economic conditions, as well as changes in any of the assumptions described in the accounting for business combinations above can materially impact the amount of contingent consideration expense that we record in any given period.

Income Taxes

Our Consolidated Balance Sheets reflect net deferred tax assets and liabilities. The deferred tax assets primarily represent the tax benefit of tax credits and timing differences between book and tax recognition of certain revenue and expense items, net of a valuation allowance. When it is more likely than not that all or some portion of deferred tax

assets may not be realized, we establish a valuation allowance for the amount that may not be realized. Each quarter, we evaluate the need to retain all or a portion of the valuation allowance on our net deferred tax assets. Our evaluation considers historical earnings, estimated future taxable income and ongoing prudent and feasible tax planning strategies. Adjustments to the valuation allowance increase or decrease net income/loss in the period such adjustments are made. The deferred tax liabilities primarily represent the timing differences between book and tax recognition of certain revenue and expense items. If our estimates require adjustments, it could have a significant impact on our Consolidated Financial Statements. We continually review the adequacy and necessity of the valuation allowance. Changes in tax laws and rates could also

affect recorded deferred tax assets in the future. Management is not aware of any such changes that would have a material effect on our Consolidated Financial Statements.

Impairment of Long-Lived Assets

Our long-lived assets include property, plant and equipment, intangible assets and goodwill. We review the carrying value of plant and equipment and finite-lived intangible assets for impairment whenever events or changes in circumstances indicate that the carrying amount of an asset may not be recoverable. If such circumstances exist, an estimate of undiscounted future cash flows to be generated by the long-lived asset is compared to the carrying value to determine whether an impairment exists. If an asset is determined to be impaired, the loss is measured based on the difference between the asset's fair value and its carrying value.

Indefinite-lived intangible assets, composed primarily of IPR&D projects acquired in business combinations that have not reached technological feasibility, are reviewed annually for impairment and whenever events or changes in circumstances indicate that the carrying amount may not be recoverable. We determine impairment by comparing the fair value of the asset to its carrying value. If the asset's carrying value exceeds its fair value, an impairment charge is recorded for the difference and its carrying value is reduced accordingly.

Estimating future cash flows of an IPR&D product candidate for purposes of an impairment analysis requires us to make significant estimates and assumptions regarding the amount and timing of costs to complete the project and the amount, timing and probability of achieving revenues from the completed product similar to how the acquisition date fair value of the project was determined, as described above. There are often major risks and uncertainties associated with IPR&D projects as we are required to obtain regulatory approvals in order to be able to market these products. Such approvals require completing clinical trials that demonstrate a product candidate is safe and effective. Consequently, the eventual realized value of the acquired IPR&D project may vary from its estimated fair value at the date of acquisition, and IPR&D impairment charges may occur in future periods which could have a material adverse effect on our results of operations.

We believe our estimations of future cash flows used for assessing impairment of long-lived assets are based on reasonable assumptions given the facts and circumstances as of the related dates of the assessments.

When reviewing goodwill for impairment, we assess whether goodwill should be allocated to operating levels lower than our single operating segment for which discrete financial information is available and reviewed for decision-making purposes. These lower levels are referred to as reporting units. Currently, we have identified only one reporting unit as per Financial Accounting Standards Board (FASB) Accounting Standards Codification (ASC) Topic 350-20, Intangibles—Goodwill and Other.

We perform our annual impairment review of goodwill and long-lived assets during the fourth quarter and whenever events or circumstances indicate that the carrying amount of an asset may not be recoverable. Our impairment review was based on a qualitative assessment or performing a quantitative analysis in determining whether it is more likely than not that the fair value of the net assets are below their carrying amounts. Examples of qualitative factors assessed in 2016 include industry and market considerations and other entity specific factors that may have a significant impact on the fair value of our goodwill or long-lived assets. Based on our qualitative assessment, we determined that the fair value of our goodwill is greater than its carrying amount at December 31, 2016 and that no long-lived assets, other than those impaired in the second quarter of 2016, were impaired at December 31, 2016. See "Results of Operations" for further discussion.

Revenue Recognition

We recognize revenue when persuasive evidence of an arrangement exists, delivery has occurred, the price to the buyer is fixed or determinable and collection from the customer is reasonably assured.

Net Product Revenues—We recognize revenues from product sales when title and risk of loss have passed to the customer, which typically occurs upon delivery. Product sales transactions are evidenced by customer purchase orders, customer contracts, invoices and/or the related shipping documents. Amounts collected from customers and

remitted to governmental authorities, which primarily consists of value-added taxes related to product sales in foreign jurisdictions, are presented on a net basis in our Consolidated Statements of Operations, in that taxes billed to customers are not included as a component of net product revenues.

In the U.S., our commercial products are generally sold to specialty pharmacies or end-users, such as hospitals, which act as retailers. Through December 31, 2015, we sold Kuvan to Merck Serono at a price near its manufacturing cost, and Merck Serono resold the product to end users outside the U.S., Canada and Japan. The royalty earned from Kuvan product sold by Merck Serono in the EU was included as a component of Net Product Revenues in the period earned and approximates 4% of Merck Serono's world-wide sales. Outside the U.S., our commercial products are sold to our authorized distributors or directly to government purchasers or hospitals, which act as the end-users.

We receive a payment ranging from 39.5% to 50% on worldwide net Aldurazyme sales by Genzyme Corporation (Genzyme) depending on sales volume, which is included in Net Product Revenues in our Consolidated Statements of Operations. We recognize a portion of this amount as product transfer revenue when the product is released to Genzyme because all of our performance obligations are fulfilled at that point and title to, and risk of loss for, the product has transferred to Genzyme. The product transfer revenue represents the fixed amount per unit of Aldurazyme that Genzyme is required to pay us if the product is unsold by Genzyme. The amount of product transfer revenue will eventually be deducted from the calculated royalty recognized when the product is sold by Genzyme. We record the Aldurazyme revenues based on net sales information provided by Genzyme and record product transfer revenue based on the fulfillment of Genzyme purchase orders in accordance with the terms of the related agreements with Genzyme and when the title and risk of loss for the product is transferred to Genzyme. Although described as royalties in our agreements with Genzyme, the revenues that we receive for Aldurazyme and, for the periods through 2015, for Kuvan are similar to direct product sales because we manufacture the product and the revenue is highly dependent on substantial operational activities performed by us, including responsibility for global regulatory compliance. These responsibilities, and the operational risk that could reduce or eliminate our receipt of these percentage of net sales amounts, are similar to many of the responsibilities and risks associated with our direct sales of other commercial products. Due to the significant role we play in the operations of Aldurazyme and, through 2015, Kuvan as well as the rights and responsibilities to deliver the products to Genzyme and previously to Merck Serono, respectively, we include Aldurazyme revenues as a component of Net Product Revenues in our Consolidated Statements of Operations. As of December 31, 2016 and 2015, accounts receivable included $30.7 million and $36.1 million, respectively, of unbilled accounts receivable related to net incremental Aldurazyme product transfers to Genzyme.

We record reserves for rebates payable under Medicaid and other government programs as a reduction of revenue at the time product revenues are recorded. Our reserve calculations require estimates, including estimates of customer mix, to determine which sales will be subject to rebates and the amount of such rebates. We update our estimates and assumptions each quarter and record any necessary adjustments to our reserves. We record fees paid to distributors and cash discounts as a reduction of revenue.

We record allowances for product returns, if appropriate, as a reduction of revenue at the time product sales are recorded. Several factors are considered in determining whether an allowance for product returns is required, including market exclusivity of the products based on their orphan drug status, the patient population, the customers' limited return rights and our experience with returns. Because of the pricing of our products, the limited number of patients and customers' limited return rights, most customers and retailers carry a limited inventory.

Certain international customers, usually government entities, tend to purchase larger quantities of product less frequently. Although such buying patterns may result in revenue fluctuations from quarter to quarter, we have not experienced an increase in product returns and do not believe these buying patterns increase the risk of product

returns. We rely on historical return rates to estimate returns for our commercial products. Genzyme's contractual return rights for Aldurazyme are limited to defective product. Based on these factors and the fact that we have not experienced significant product returns to date, management has concluded that product returns will be minimal. In the future, if any of these factors and/or the history of product returns changes, an allowance for product returns may be required.

Bad debt reserves are based on estimated uncollectible accounts receivable. Given our historical experience with bad debts, combined with our credit management policies and practices, we do not presently maintain significant bad debt reserves. However some of our customers are based in countries where the economic conditions continue to present challenges. We continue to monitor these conditions and associated impacts on the financial performance and credit worthiness of our large customers so that we can properly assess and respond to changes in customer credit profiles. As of December 31, 2016 and 2015, our allowance for doubtful accounts was $0.1 million and $0.1 million, respectively.

The nature and amount of our current estimates of the applicable revenue dilution items that are currently applied to aggregate world-wide gross product sales of our commercial products to derive net sales are described in the table below.

Weighted Average Gross Revenue to Net Revenue Adjustments	Years Ended December 31,		Description
	2016	2015	
Rebates	3.5%	5.3%	Rebates payable to state Medicaid, other government programs and certain managed care providers
Distributor Fees	3.0%	3.4%	Fees paid to authorized distributors
Cash Discounts	0.8%	1.0%	Discounts offered to customers for prompt payment of accounts receivable
Total	7.3%	9.7%	

Royalty and Other Revenues—Royalty and other revenues includes royalties on net sales of products with which we have no direct involvement, collaborative agreement revenues and rental income.

Royalty revenue is recognized as earned in accordance with the contract terms at the time the royalty amount is fixed or determinable based on information received from the licensees and sublicensees and at the time collectibility is reasonably assured.

Collaborative agreement revenues includes both license revenue and contract research revenue. Activities under collaborative agreements are evaluated to determine if they represent a multiple element revenue arrangement. We allocate the arrangement consideration to those units of accounting. The amount of allocable arrangement consideration is limited to amounts that are fixed or determinable. Arrangement consideration is allocated at the inception of the arrangement to the identified units of accounting based on their relative estimated selling price. Revenue is recognized for each unit of accounting when the appropriate revenue recognition criteria are met.

Revenue from non-refundable up-front license fees and milestone payments, such as under a development collaboration or an obligation to supply product, is recognized as performance occurs and our obligations are completed. In accordance with the specific terms of our obligations under these arrangements, revenue is recognized as the obligation is fulfilled or ratably over the development or manufacturing period. Revenue associated with substantive at-risk milestones is recognized based upon the achievement of the milestones set forth in the respective agreements. Advance payments received in excess of amounts earned are classified as deferred revenue on our Consolidated Balance Sheets.

Inventories Produced in Preparation for Product Launches

We capitalize inventories produced in preparation for product launches sufficient to support estimated initial market demand. Typically, capitalization of such inventory begins when positive results have been obtained for the clinical trials that we believe are necessary to support regulatory approval, uncertainties regarding ultimate

regulatory approval have been significantly reduced and we have determined it is probable that these capitalized costs will provide future economic benefit in excess of capitalized costs. The factors considered by us in evaluating these uncertainties include the receipt and analysis of positive pivotal clinical trial results for the underlying product candidate, results from meetings with the relevant regulatory authorities prior to the filing of regulatory applications, and the compilation of the regulatory application. We closely monitor the status of each respective product within the regulatory approval process, including all relevant communication with regulatory authorities. We also consider our historical experience with manufacturing and commercializing similar products and the relevant product candidate. If we are aware of any specific material risks or contingencies other than the normal regulatory review and approval process or if there are any specific issues identified relating to safety, efficacy, manufacturing, marketing or labeling, the related inventory would generally not be capitalized.

For inventories that are capitalized in preparation of product launch, anticipated future sales, expected approval date and shelf lives are evaluated in assessing realizability. The shelf life of a product is determined as part of the regulatory approval process; however in evaluating whether to capitalize pre-launch inventory production costs, we consider the product stability data of all of the pre-approval production to date to determine whether there is adequate expected shelf life for the capitalized pre-launch production costs. In applying the lower of cost or net realizable value to pre-launch inventory, we estimate a range of likely commercial prices based on our comparable commercial products.

Recent Accounting Pronouncements

See Note 4 to our accompanying Consolidated Financial Statements for a full description of recent accounting pronouncements and our expectation of their impact, if any, on our results of operations and financial condition.

Results of Operations

Net Loss

Our net loss for the year ended December 31, 2016 was $630.2 million, compared to a net loss of $171.8 million and $134.0 million for the years ended December 31, 2015 and 2014, respectively. The increase in net loss was primarily a result of the following (in millions):

	Years Ended December 31,				
	2016	2015	2014	2016 vs. 2015	2015 vs. 2014
Total revenues	$1,116.9	$889.9	$749.3	$ 227.0	$ 140.6
Cost of sales	209.6	152.0	122.3	57.6	29.7
R&D expense	661.9	634.8	461.5	27.1	173.3
SG&A expense	476.6	402.3	302.2	74.3	100.1
Intangible asset amortization and contingent consideration	(27.0)	(17.7)	23.7	(9.3)	(41.4)
Impairment of intangible asset	599.1	198.7	—	400.4	198.7
Gain on sale of intangible asset	—	(369.5)	(67.5)	369.5	(302.0)
Other, net	(27.7)	(44.0)	(32.0)	16.3	(12.0)
Provision for (benefit from)	(200.8)	17.1	9.1	(217.9)	8.0

income taxes	
Net loss	$(630.2) $