BIOMARIN PHARMACEUTICAL INC
Form 10-K
February 28, 2019

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2018

Or

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

Commission file number: 000-26727

BioMarin Pharmaceutical Inc.

(Exact name of registrant as specified in its charter)

Delaware (State of other jurisdiction of incorporation or organization)	68-0397820 (I.R.S. Employer Identification No.)
770 Lindaro Street San Rafael, California (Address of principal executive offices)	94901 (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 every Interactive Data File required to be submitted 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 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, a smaller reporting company, or an emerging growth company. See the definitions of “large accelerated filer,” “accelerated filer,” “smaller reporting company,” and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	Accelerated filer
Non-accelerated filer	Smaller reporting company
	Emerging Growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Indicate by check mark whether the registrant is a shell company (as defined 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, 2018 was $8.8 billion, based on the closing price reported for such date on the Nasdaq Global Select Market.

As of February 12, 2019, the registrant had 178,372,202 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 its 2019 annual meeting of stockholders are incorporated by reference into Part III.

BIOMARIN PHARMACEUTICAL INC.

2018 FORM 10-K ANNUAL REPORT

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Unless the context suggests otherwise, references in this Annual Report on Form 10-K to "BioMarin," the "Company," "we," "us," and "our" refer to BioMarin Pharmaceutical Inc. and, where appropriate, its wholly owned subsidiaries.

BioMarin®, Brineura®, Firdapse®, Kuvan®, Naglazyme®, Palynziq® and Vimizim® are our registered trademarks. Kyndrisa™ is our trademark. Aldurazyme® is a registered trademark of BioMarin/Genzyme LLC. All other brand names and service marks, trademarks and other trade names appearing in this report are the property of their respective owners.

Forward-Looking Statements

This Annual Report on Form 10-K contains "forward-looking statements" as defined under securities laws. Many of these statements can be identified by the use of terminology such as "believes," "expects," "intends," "anticipates," "plans," "m "will," "could," would," "projects," "continues," "estimates," "potential," "opportunity" or the negative versions of these terms

other similar expressions. You should not place undue reliance on these types of forward-looking statements, which speak only as of the date that they were made. These forward-looking statements are based on the beliefs and assumptions of our management based on information currently available to management and should be considered in connection with any written or oral forward-looking statements that we may issue in the future as well as other cautionary statements we have made and may make. 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 the section titled “Risk Factors” in Part II, Item 1A of this Annual Report on Form 10-K as well as information provided elsewhere in this Annual Report on Form 10-K. You should carefully consider that information before you make an investment decision. Moreover, we operate in a very competitive and rapidly changing environment. New risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. In light of these risks, uncertainties and assumptions, the forward-looking events and circumstances discussed in this Annual Report on Form 10-K may not occur and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements.

Except as required by law, 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 the occurrence of unanticipated events.

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Part I

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 portfolio consists of several commercial products and multiple clinical and pre-clinical product candidates for the treatment of various diseases. 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.

A summary of our major commercial products is provided below:

Major Commercial Products	Indication	United States Orphan Drug Exclusivity Expiration [1]	United States Biologic Exclusivity Expiration [2]	European Union Orphan Drug Exclusivity Expiration [1]
Aldurazyme (laronidase)	MPS I [3]	Expired	Expired	Expired
Brineura (cerliponase alfa)	CLN2 [4]	2024	2029	2027
Kuvan (sapropterin dihydrochloride)	PKU [5]	Expired	Not Applicable [5]	2020 [5]
Naglazyme (galsulfase)	MPS VI [6]	Expired	Expired	Expired
Palynziq (pegvaliase-pqpz)	PKU [7]	2025	2030	TBD [7]
Vimizim (elosulfase alpha)	MPS IVA [8]	2021	2026	2024

(1) See “Government Regulation—Orphan Drug Designation” below for further discussion
(2) See “Government Regulation— Healthcare Reform” below for further discussion
(3) For the treatment of Mucopolysaccharidosis I (MPS I)
(4) For the treatment of late infantile neuronal ceroid lipofuscinosis type 2 (CLN2)
(5) For the treatment of phenylketonuria (PKU). Kuvan, a small molecule therapy, has been granted orphan drug status in the European Union (EU), which together with pediatric exclusivity, confers 12 years of market exclusivity in the EU that expires in 2020.
(6) For the treatment of Mucopolysaccharidosis VI (MPS VI)
(7) For adult patients with PKU. Palynziq (formerly referred to as pegvaliase) was approved by the United States (U.S.) Food and Drug Administration (FDA) in May 2018 and our European Marketing Authorization Application (MAA) submission for Palynziq was accepted by the European Medicines Agency (EMA) in March 2018. We expect to learn the status of this MAA during the first half of 2019.
(8) For the treatment of Mucopolysaccharidosis IV Type A (MPS IVA)

A summary of our ongoing major development programs, including key metrics, is provided below:

Major Product Candidates in Development	Target Indication	U.S. Orphan Designation	EU Orphan Designation	Stage
Palynziq in Europe	PKU	Yes	Yes	EU MAA regulatory review [1]
Valoctocogene roxaparvovec	Hemophilia A [2]	Yes	Yes	Clinical Phase 3
Vosoritide	Achondroplasia	Yes	Yes	Clinical Phase 3

(1) In May 2018, the FDA granted marketing approval for Palynziq in the U.S., and our MAA submission for Palynziq was accepted by the EMA in March 2018. We expect to learn the status of the MAA during the first half of 2019.

(2) Hemophilia A is also called factor VIII deficiency or classic hemophilia.

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

Recent Developments

EMA Regulatory Review of Palynziq

The EMA accepted our MAA for Palynziq in March 2018. We anticipate an opinion from the Committee for Medicinal Products for Human Use (CHMP), the scientific committee of the EMA, on Palynziq Injection for the treatment of patients 16 and older with PKU in the first quarter of 2019. If the CHMP provides a positive opinion in the first quarter of 2019, then it is possible that the European Commission (EC) could provide marketing authorization for Palynziq in the EU in the second quarter of 2019.

Brineura Data at Three or More Years

On February 7, 2019, we announced that an ongoing open-label extension study treating patients with Brineura continued to show a reduced rate of decline compared to a natural history cohort of CLN2 disease for three years as measured by the CLN2 Clinical Rating Scale. The scale measures performance of motor and language domains, with a score of 0 representing no function and a score of 3 representing normal function for each of the two domains. A response to treatment was defined as the absence of an unreversed (i) two-point decline in the motor-language (ML) scale or (ii) score of 0. The data showed a durability of treatment effect in the primary efficacy endpoint where response to treatment was seen in 19 of 23, or 83%, of treated patients after three years. Natural history patients were 12 times more likely on average to have experienced an unreversed two-point decline in ML score than treated patients at three years. After three years on treatment with Brineura, treated patients’ ML scores were on average 3.8 points better than those of natural history patients. After two years on treatment with Brineura, treated patients’ ML scores were on average 3.3 points better than those of natural history patients. See “Major Commercial Products — Brineura” below for more information regarding Brineura.

Gene Therapy Product Candidate Valoctocogene Roxaparvovec for the Treatment of Hemophilia A

On January 7, 2019, we provided an update on our development of valoctocogene roxaparvovec, a gene therapy program for severe hemophilia A, that we completed enrollment of the initial cohort of patients in our Phase 3 study. Based on the FDA’s Draft Guidance for Human Gene Therapy for Hemophilia issued in July 2018, we expect that Phase 3 data from this cohort available in 2019 could support submission of a Biologics License Application (BLA) for valoctocogene roxaparvovec through an accelerated approval pathway. We plan to decide in the second half of 2019 whether we will submit a BLA through an accelerated approval pathway. The complete Phase 3 study is targeting enrollment of 130 patients by mid-year 2019. See “Major Product Candidates in Development — Valoctocogene Roxaparvovec” below for more information regarding valoctocogene roxaparvovec.

Product Candidate Vosoritide for the Treatment of Achondroplasia

On January 7, 2019, we provided an update on our development of vosoritide, an analog of C-type Natriuretic Peptide (CNP), in children with achondroplasia, the most common form of disproportionate short stature in humans. We announced that enrollment of the Phase 2 study of vosoritide in infants and young children up to age 5 with achondroplasia is on track, and in the early part of the study, vosoritide has been generally well-tolerated.

On November 7, 2018, we provided an update on the open-label Phase 2 study of vosoritide. Vosoritide has demonstrated sustained increase in average growth velocity over 42 months of treatment in a cohort of eight children who completed 42 months of daily dosing at 15 μg/kg/day. The cohort gained a mean of 5.7 cm of cumulative height over what the children’s baseline would have predicted. At 30 months, the same cohort experienced a 4 cm increase

over what the children's baseline growth velocity would have predicted. We also announced that the global Phase 3 study of vosoritide in children was fully enrolled, and we expect top line results by the end of 2019. See "Major Product Candidates in Development — Vosoritide" below for more information regarding vosoritide.

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Palynziq Data at 36 Months

On November 7, 2018, we announced that in an ongoing open-label extension study at 36 months, patients being treated with Palynziq showed durability, and there was an increase in the percentage of patients reaching blood phenylalanine (Phe) thresholds of physiologically normal (<120 µmol/L), as well as Phe thresholds recommended in the U.S. (<360 µmol/L) and the EU (<600 µmol/L). At 36 months, 59% of the participants reached physiologically normal, 67% reached Phe levels as recommended in the U.S. and 74% reached Phe levels as recommended in the EU. See “Major Commercial Products — Palynziq” below for more information regarding Palynziq.

Gene Therapy Product Candidate BMN 307 for the Treatment of PKU

On November 7, 2018, we announced positive, preliminary pre-clinical data for BMN 307, a gene therapy program for PKU. We plan to submit an Investigational New Drug (IND) application and/or a clinical trial application (CTA) for BMN 307 in the second half of 2019.

Summary of Commercial Products and Development Programs

Major Commercial Products

Net Product Revenues related to our major commercial products consisted of the following:

	Years Ended December 31,		
Major Commercial Products	2018	2017	2016
Aldurazyme	$135.1	$90.0	$93.8
Brineura	$39.9	$8.6	$—
Kuvan	$433.6	$407.5	$348.0
Naglazyme	$345.9	$332.2	$296.5
Palynziq	$12.2	$—	$—
Vimizim	$482.0	$413.3	$354.1

Aldurazyme

Aldurazyme is a highly purified protein that is designed to be identical to a naturally occurring form of the human enzyme alpha-L-iduronidase, a lysosomal enzyme normally required for the breakdown of glycosaminoglycans (GAGs). Aldurazyme is approved for marketing in the U.S., the EU and other international markets for patients with 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. 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 Corporation (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 payments ranging from 39.5% to 50% on worldwide net Aldurazyme sales by Genzyme depending on sales volume. 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.

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On January 1, 2018, we adopted Accounting Standards Codification (ASC) 606, Revenue from Contracts with Customers (ASC Topic 606), which superseded nearly all existing revenue recognition guidance under generally accepted accounting principles in the U.S. After adopting ASC Topic 606, we recognize Aldurazyme revenues when the product is shipped to Genzyme and all required quality control certificates are complete, because all of our performance obligations are fulfilled at that point in time. Following the adoption, we record Aldurazyme net product revenues based on the estimated tiered payment that will be in effect when the product is sold through by Genzyme. Prior to the adoption of ASC Topic 606, we recognized product transfer revenues, representing the fixed amount per unit of Aldurazyme that Genzyme was required to pay us if they did not sell the product, at the time of fulfillment of Genzyme purchase orders. Product transfer revenue was subsequently deducted from the calculated variable consideration recognized when the product was sold by Genzyme to third parties. See Note 4 to our accompanying Consolidated Financial Statements for additional discussion of the impact of the adoption.

Brineura

Brineura is a recombinant human tripeptidyl peptidase 1 (TPP1) and is approved for the treatment of patients with CLN2, a form of Batten disease, in the U.S., the EU and other international markets. 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 up to 1,200 to 1,600 cases exist worldwide. On April 27, 2017, Brineura was approved in the U.S. to slow the progression of loss of ambulation in symptomatic pediatric patients three years of age and older with CLN2. Brineura is the first treatment approved to slow the progression of loss of ambulation in children with CLN2 disease.

On June 1, 2017, we announced that the EC granted marketing authorization for Brineura in the EU to treat children with CLN2 disease. Brineura is the first treatment approved in the EU for the treatment of CLN2 disease, and the marketing authorization for Brineura includes all 28 countries of the EU, Norway, Iceland and Liechtenstein. On April 21, 2017, the CHMP, the scientific committee of the EMA adopted a positive opinion for our MAA for Brineura following an accelerated review procedure, reserved for medicinal products expected to be a major public health interest. Brineura is one of the first therapies to go through this process.

Brineura is administered via intracerebroventricular (ICV) infusion and intended to be used in combination with a delivery device, such as an injector or other delivery system. Please see “Government Regulation – Combination Products” below for additional information on combination products.

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 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 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. We commenced the commercial launch of this new form of Kuvan in February 2014. We market Kuvan in the U.S., the EU and other international markets (excluding Japan). 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.

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Two companies previously filed paragraph IV certifications and submitted abbreviated new drug applications (ANDAs) to produce sapropterin dihydrochloride tablets and powder and we subsequently entered into settlement agreements regarding Kuvan with both companies. We expect generic versions of Kuvan to first become available in the U.S. in the fourth quarter of 2020. Please see "Risk Factors" included in Part I, Item 1A of this Annual Report on Form 10-K for more information regarding the settlement agreements and for a discussion of the risks posed by generic versions of Kuvan. Please see "Government Regulation – The Hatch-Waxman Act" below for additional information regarding ANDAs.

Naglazyme

Naglazyme is a recombinant form of N-acetylgalactosamine 4-sulfatase (arylsulfatase B) indicated for patients with 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 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.

Palynziq

Palynziq is a PEGylated recombinant phenylalanine ammonia lyase enzyme, which is delivered through subcutaneous injection to reduce blood Phe concentrations. On May 24, 2018, the FDA approved the use of Palynziq in adult patients with PKU who have uncontrolled blood Phe concentrations greater than 600 micromol/L (10mg/dL) on existing management. Palynziq is our second approved treatment for PKU. Palynziq is only available in the U.S. through the Palynziq Risk Evaluation and Mitigation Strategy (REMS) program, which is required by the FDA to mitigate the risk of anaphylaxis while using the product. Notable requirements of our REMS program include the following:

- prescribers must be certified by enrolling in the REMS program and completing training;
- prescribers must prescribe auto-injectable epinephrine with Palynziq;
- pharmacies must be certified with the REMS program and must dispense Palynziq only to patients who are authorized to receive it;
- patients must enroll in the REMS program and be educated about the risk of anaphylaxis by a certified prescriber to ensure they understand the risks and benefits of treatment with Palynziq; and
- patients must have auto-injectable epinephrine available at all times while taking Palynziq.

Please see "Risk Factors" included in Part I, Item 1A of this Annual Report on Form 10-K for a discussion of the risks posed by the REMS program.

Palynziq was first made commercially available in the U.S. in July 2018. The EMA accepted our MAA for Palynziq in March 2018. We anticipate an opinion from the CHMP, the scientific committee of the EMA, on Palynziq Injection for the treatment of patients 16 and older with PKU in the first quarter of 2019. If the CHMP provides a positive opinion in the first quarter of 2019, then it is possible that the EC could provide marketing authorization for Palynziq in the EU in the second quarter of 2019.

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Vimizim

Vimizim is an enzyme replacement therapy for the treatment of MPS IVA, a lysosomal storage disorder. MPS IVA is a disease characterized by deficient activity of N-acetylgalactosamine-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 IVA and estimate that the total number of patients suffering from MPS IV A worldwide could be as many as 3,000.

Vimizim is approved for marketing in the U.S., the EU and other international markets.

Major Product Candidates in Development

Valoctocogene Roxaparvovec

Valoctocogene roxaparvovec is an adeno associated virus (AAV5) vector drug development candidate designed to restore factor VIII plasma concentrations in patients with severe hemophilia A. Hemophilia A, also called factor VIII deficiency or classic hemophilia, is a genetic disorder caused by missing or defective factor VIII, a clotting protein. 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, the mild hemophilia A range of factor VIII activity levels is between 5% and 40%, the moderate hemophilia A range of factor VIII activity levels is between 1% and 5%, and the severe hemophilia range of factor VIII activity levels is less than 1%. People living with hemophilia A 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.

In July 2016, we announced positive proof-of-concept data from a Phase 1/2 dose-escalation study for valoctocogene roxaparvovec in patients with severe hemophilia A, and we subsequently provided positive updates to our interim results in January, July and December 2017. In May 2018, further updates on valoctocogene roxaparvovec were presented during an oral presentation at the World Federation of Hemophilia (WFH) 2018 World Congress in Glasgow, Scotland by John Pasi, M.B., Ch.B., Ph.D., from Barts and the London School of Medicine and Dentistry and primary investigator for this Phase 1/2 study. The data presented at WFH is the most current data and had a cut off of April 16, 2018. In the 6e13 vg/kg cohort, the data showed continued and substantial reductions in bleeding requiring factor VIII infusions with a 97% reduction in mean Annualized Bleed Rate (ABR), with no spontaneous bleeds and elimination of all bleeds in target joints in the second year. 71% and 86% of participants had zero bleeds requiring factor VIII infusions in years 1 and 2 respectively compared to 14%, who had zero bleeds requiring factor VIII infusions for a year at baseline. There was a 96% reduction in mean factor VIII usage through week 104. Quality of life as measured by the six-domain Haemo-QoL-A instrument rapidly improved across all domains by up to 17.3 points in mean over baseline through the second year. This is well above the 5.2 point increase considered to be the minimal clinically important difference. The 4e13 vg/kg cohort also showed a substantial reduction in bleeding requiring factor VIII infusions with a 92% reduction in ABR. 83% of participants had zero bleeds requiring factor VIII infusions following treatment for a year compared to 17%, who had zero bleeds requiring factor VIII infusions for a year at baseline. Mean factor VIII usage decreased by 98%. Consistent with the reduction in ABR and factor VIII usage, quality of life showed mean improvement by 3.8 to 6.3 points. At 104 weeks post-infusion, mean factor VIII activity level of the 6e13 vg/kg cohort was 59%, and the median was 46%. At 52 weeks post-infusion, mean and median factor VIII activity levels of the 4e13 vg/kg cohort were 32%. These factor VIII activity data were based on

using a one-stage assay. The chromogenic assay tends to result in readings that are approximately 60% of the one-stage assay results. We expect to release both one-stage and chromogenic assay data in the future. Patients in the Phase 1/2 study will be monitored for safety for five years.

On December 19, 2017, we announced that we had dosed the first patient in the global GENEr8-1 Phase 3 study with the 6e13 vg/kg dose for valoctocogene roxaparvovec. This is the first of two Phase 3 studies in the global Phase 3 program to dose a first patient. The global Phase 3 program includes two studies with valoctocogene roxaparvovec, one with the 6e13 vg/kg dose (GENEr8-1) and one with the 4e13 vg/kg dose (GENEr8-2). Both Phase 3 GENEr8 studies are open-label single-arm studies to evaluate the efficacy and safety of valoctocogene roxaparvovec. The primary endpoint in both studies is based on the factor VIII activity level achieved following valoctocogene roxaparvovec, and the secondary endpoints measure annualized factor VIII replacement therapy use rate and annualized bleed rate. In May 2018 we announced that the protocol of global

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GENEr8-1 Phase 3 study was amended to evaluate superiority compared to standard of care with increased enrollment of up to 130 patients. As further described above under "Recent Developments," we have completed enrollment of the initial cohort of patients in our Phase 3 program intended to support a BLA submission through the accelerated approval pathway. We plan to decide in the second half of 2019 whether we will submit a BLA through an accelerated approval pathway. If we decide to submit a BLA through an accelerated approval pathway, then we will disclose additional information on the timing of our plans regarding such BLA submission. The complete Phase 3 study is targeting enrollment of 130 patients by mid-year 2019.

In addition to the two global Phase 3 studies GENEr8-1 and GENEr8-2, we are also conducting a Phase 1/2 Study with the 6E13kg/vg dose of valoctocogene roxaparvovec in approximately 10 participants with pre-existing AAV5 antibodies. In May 2018, we announced that we dosed the first patient in the Phase 1/2 study (BMN 270-203) evaluating our investigational gene therapy, valoctocogene roxaparvovec, in severe hemophilia A patients with pre-existing AAV5 antibodies. Two additional and separate studies, one to study seroprevalence in people with severe hemophilia A and one non-interventional study to determine baseline characteristics in people with hemophilia A, are ongoing around the world.

Valoctocogene roxaparvovec has Orphan Drug designation from the FDA and the EMA. Valoctocogene roxaparvovec has also been accepted for Priority Medicines (PRIME) scheme from the EMA. Additionally, the FDA has granted valoctocogene roxaparvovec Breakthrough Therapy designation.

Vosoritide

Vosoritide is a peptide therapeutic in development for the treatment of achondroplasia, the most common form of disproportionate short stature in humans. 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. In October 2017, we provided an update on the Phase 2 study of vosoritide, which demonstrated sustained increase in average growth velocity over 30 months of treatment in 10 children that completed 30 months of daily dosing at 15 µg/kg/day. Over this period of time, patients experienced mean absolute growth increase of approximately 4 cm over what their baseline growth velocity would have predicted. The sustained increase in annualized growth velocity was accompanied by sustained improvements over time in height compared to age- and gender-matched unaffected children as measured by z-scores. In addition, treatment with vosoritide showed continued improvement over time in proportionality as measured by the U/L ratio.

Our global Phase 3 randomized, placebo-controlled study of vosoritide in approximately 110 children with achondroplasia ages 5-14 for 52 weeks also continued in 2018. The study will be followed by a subsequent open-label extension. Children in this study will have completed a minimum six-month baseline study to determine their respective baseline growth velocity prior to entering the Phase 3 study. Vosoritide is being tested only in children in the age range when their growth plates are still open, which is approximately 25% of people with achondroplasia. Enrollment of the Phase 3 study was completed in 2018 and we expect to have top-line data by the end of 2019. Additionally, we began enrolling an infant/toddler study in 2018 in children with achondroplasia ages 0-5. Finally, we are continuing our natural history program to augment our clinical understanding of outcomes of untreated patients for comparison to patients treated with vosoritide.

Manufacturing

We manufacture the active pharmaceutical ingredients (API) for Aldurazyme, Brineura, Naglazyme, Palynziq, Vimizim and vosoritide in our production facilities located in Novato, California. We currently also manufacture the

API for Brineura and Vimizim 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, packaging, labeling, and release of Vimizim. 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 these products. Vialing and most packaging are performed by contract manufacturers. We believe that we have ample manufacturing capacity in our Novato facilities to support commercial demand for both Aldurazyme and Naglazyme for at least the next five years. We believe that with our Novato, California facility and our Shanbally facility, we have ample manufacturing capacity to support commercial demand for Aldurazyme, Brineura, Naglazyme, Palynziq and Vimizim for at least the next five years.

Firdapse, amifampridine phosphate for Lambert Eaton Myasthenic Syndrome (LEMS), and Kuvan tablets and powder sachets are currently manufactured on a contract basis by third parties. In general, we expect to

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continue to contract with outside service providers for certain manufacturing services, including drug substance, 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 July 2017, we commissioned our commercial-scale gene therapy manufacturing facility, located in Novato, California, and began cGMP production of valoctocogene roxaparvovec to support clinical development activities and anticipated commercial demand. This facility is capable of supporting the manufacturing of product for approximately 2,000 patients per year, and the production process was developed in accordance with International Conference on Harmonisation Technical Requirements for Registration of Pharmaceuticals for Human Use facilitating worldwide registration with health authorities.

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 Brineura, 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 2019, 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, if approved, including Palynziq in the EU and valoctocogene roxaparvovec, will likely require expansion of our commercial organization, including our sales force, in the U.S. and abroad.

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 Brineura, 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 Brineura, Kuvan, 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

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products. However, in certain countries, such as those 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. Palynziq is currently distributed in the U.S. pursuant to the REMS program through a limited number of certified specialty pharmacies. During 2018, 44% of our net product revenues, excluding Aldurazyme, was 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 products and product candidates 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 and product candidates, 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 and product candidates have no direct approved competition currently on the market, however, other companies are in the development phase with new and generic products. Our products and product candidates have potential competition from products under development either using similar technology to our programs or different treatment strategies. The following is a summary of some of the primary possible future competitors for our products and product candidates, but the information below may not include all potential competition.

Products

Aldurazyme, Naglazyme, and Vimizim

In the mucopolysaccharidosis field, several companies are researching treatments using small molecules, gene therapy, and other novel technologies. Aldurazyme, for the treatment of MPS I, has potential competition from clinical stage product candidates from ArmaGen, Inc., RegenxBio Inc., Sangamo Therapeutics, Inc. and earlier stage product candidates, including product candidates from Eloxx Pharmaceuticals Ltd and Immusoft Corporation. Naglazyme, for the treatment of MPS VI, has potential competition from a clinical stage product candidate from Inventiva S.A. and other potential candidates in earlier stages.

Brineura

Brineura, for the treatment of CLN2, has potential competition from preclinical product candidates from RegenxBio Inc. and Spark Therapeutics, Inc.

Firdapse

Firdapse has potential competition from a clinical stage product candidate from Jacobus Pharmaceutical Co. Inc.

Kuvan and Palynziq

There are currently no other approved drugs in the U.S. or the EU for the treatment of PKU. However, two companies previously filed paragraph IV certifications and submitted ANDAs to produce sapropterin dihydrochloride tablets and powder. We entered into settlement agreements regarding Kuvan with both companies, which will allow these companies to market generic versions of sapropterin dihydrochloride. Please see “Risk Factors” included in Part I, Item 1A of this Annual Report on Form 10-K for more information regarding the settlement agreements and for a discussion of the risks posed by generic versions of Kuvan in the U.S. and abroad. Please see “Government Regulation – The Hatch-Waxman Act” below for additional information regarding ANDAs. Kuvan and Palynziq also have potential competition from clinical stage product candidates from Retrophin, Inc. and earlier stage product candidates, including product candidates from Rubius Therapeutics, Inc., and Moderna Therapeutics, Inc. BMN 307 is our preclinical gene therapy program for PKU,

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and other companies are also developing gene therapy candidates for PKU, including a preclinical product candidate from Homology Medicines, Inc.

Clinical Product Candidates

Valoctocogene roxaparvovec

Valoctocogene roxaparvovec, a gene therapy product candidate for severe hemophilia A, could have competition from marketed recombinant factor VIII replacement therapies, a novel bispecific antibody marketed by Roche Holding Ltd, and clinical stage programs, including gene therapy product candidates under development by Bayer AG, Sangamo Therapeutics, Inc., Shire Plc and Spark Therapeutics, Inc., and preclinical product candidates from other companies, including Uniqure NV. In addition, Alnylam Pharmaceuticals, Inc. is developing a novel product candidate in the clinic for the treatment of hemophilia A.

Vosoritide

Vosoritide, for the treatment of achondroplasia, could have competition from clinical stage products under development by Ascendis Pharma A/S and Therachon AG and preclinical product candidates from other companies, including QED Therapeutics, Inc.

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 14, 2019, the number of our worldwide issued patents now stands at 1,747, including 125 patents issued by the U.S. Patent and Trademark Office (the USPTO). Furthermore, our portfolio of pending patent applications totals 548 applications, including 83 pending U.S. applications.

With respect to Aldurazyme, we have rights to 33 issued patents, including six U.S. patents. 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 November 2019 and in 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.

With respect to Brineura, we own or have licensed a number of patents and pending patent applications that relate generally to CLN2/TPP1 protein, use of CLN2/TPP1 protein and methods of treating late infantile neuronal ceroid lipofuscinosis, pharmaceutical compositions and liquid formulations of TPP1 formulations and intrathecal administration of TPP1. We have 13 issued patents, including give issued U.S. patents and eight foreign patents, and 19 pending applications including one US and 18 foreign applications. These patents will expire between 2021and 2036.

With respect to Firdapse, we have patent protection in the European Patent Organization countries. These patents will expire in 2022.

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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 152 issued patents including 17 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 granted licenses to certain of these patents to two companies, as further described in “Major Commercial Products—Kuvan,” above.

With respect to Naglazyme, we have 54 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 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 206 issued patents including 17 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 (NDAs) or BLAs, 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.

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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 IND or a 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. Currently, European clinical trial authorization applications must be submitted to the competent authority in each EU Member State in which the trial will be conducted. Under the new European Regulation on Clinical Trials, which is expected to take effect in 2019, there will be a centralized application procedure where one national authority takes the lead in reviewing the application and the other national authorities have only a limited involvement. Satisfaction of FDA and European 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 becomes effective 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, 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 application is prepared and submitted to the regulatory agency. Approval of the application by the applicable regulatory agency is required before marketing of the product may begin. In Europe, an MAA is prepared and, for all orphan designated products, is submitted to the EMA under the centralized application procedure. EC approval of the MAA under the centralized

application procedure results in a single marketing authorization that is valid across the European Economic Area (i.e., the European Union as well as Iceland, Liechtenstein and Norway).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.

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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 regulatory agency may request additional information rather than accepting an application 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.

Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of an MAA by the EMA is 210 days. This excludes so-called clock stops, during which additional written or oral information is to be provided by the applicant in response to questions asked by the CHMP. At the end of the review period, the CHMP provides an opinion to the EC. If the opinion is favorable, the EC may then adopt a decision to grant marketing authorization. In the event of a negative opinion, the company may request a re-examination of the application within 15 days of receipt of the negative opinion. The company then has 60 days to provide the CHMP with detailed grounds for requesting the re-examination. Within 60 days of providing this information, the CHMP shall re-examine its opinion. The EC follows the recommendation of the CHMP in almost all cases. In exceptional cases, the CHMP might perform an accelerated review of an MAA in no more than 150 days. This is usually when the product is of major interest from the point of view of public health and, in particular, from the viewpoint of therapeutic innovation.

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, such as special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring and the use of patient registries. 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 comprising (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 comprising 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.

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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, 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 becomes the lead evaluator. 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.

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

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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. In the EU, orphan drug designation is available if a sponsor can establish: that the medicine is intended for the diagnosis, prevention or treatment of (1) a life-threatening or chronically debilitating condition affecting no more than five in 10,000 people in the EU, which is equivalent to around 250,000 people or fewer, or (2) a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that the marketing of the medicinal product in the EU would generate sufficient return to justify the necessary investment. For either of these conditions, the applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the EU or, if such method exists, the medicinal product will be of significant benefit to those affected by that condition. Orphan drug designation must be requested before submitting a marketing application.

Orphan drug designation does not shorten 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 (extendable to twelve years for medicines that have complied with an agreed pediatric investigation plan pursuant to Regulation 1901/2006) and, in addition, a range of other benefits during the development and regulatory review process are available in the EU, including scientific assistance for study protocols, authorization through the centralized marketing authorization procedure covering all member countries and a reduction or elimination of registration and marketing authorization fees. Among the benefits of orphan drug designation in the U.S. are tax credits for certain research and a waiver of the NDA/BLA application user fee. 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. In the EU, marketing authorization may be granted to a similar medicinal product with the same orphan indication during the regulatory exclusivity period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if this medicinal product is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if, at the end of the fifth year, it can be demonstrated on the basis of available evidence that the criteria for its designation as an orphan medicine are no longer satisfied, for example if the original orphan medicinal product has become sufficiently profitable not to justify maintenance of market exclusivity.

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.

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PRIME Designation

The EMA launched its 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.

In the EU, companies developing a new medicinal product must agree to a Paediatric Investigation Plan (PIP) with the EMA and must conduct pediatric clinical trials in accordance with that PIP, unless a deferral or waiver applies, (e.g., because the relevant disease or condition occurs only in adults). The MAA for the product must include the results of pediatric clinical trials conducted in accordance with the PIP, unless a waiver applies, or a deferral has been granted, in which case the pediatric clinical trials must be completed at a later date. Products that are granted a marketing authorization on the basis of the pediatric clinical trials conducted in accordance with the PIP are eligible for a six month extension of the protection under a supplementary protection certificate (if any is in effect at the time of approval) or, in the case of orphan medicinal products, a two year extension of the orphan market exclusivity. This pediatric reward is subject to specific conditions and is not automatically available when data in compliance with the PIP are developed and submitted.

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. Moreover, if a company obtains original FDA approval for a product via the accelerated approval pathway, the company may be required to conduct a post-marketing confirmatory trial to verify and describe the clinical benefit in support of full

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approval. An unsuccessful post-marketing study or failure to complete such a study could result in the withdrawal of the FDA's marketing approval for a product.

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 assess 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 manufacturers 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.

Healthcare 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 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

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programs during the preceding year. Other provisions of the law have also affected us and have increased 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 now includes a 70% 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. 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. Effective January 1, 2022, drug manufacturers will also be required to report on payments or transfers of value to physician assistants, nurse practitioners or clinical nurse specialists, certified registered nurse anesthetists, and certified nurse-midwives. 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 current Presidential administration.

Since January 2017, the U.S. President has signed two Executive Orders designed to delay the implementation of any certain provisions of the PPACA or otherwise circumvent some of the requirements for health insurance mandated by the PPACA. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the PPACA. While Congress has not passed legislation repealing the PPACA in its entirety, it has enacted laws that modify certain provisions of the PPACA such as removing penalties, starting January 1, 2019, for not complying with the PPACA's individual mandate to carry health insurance, delaying the implementation of certain ACA-mandated fees, and increasing the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D. Additionally, on December 14, 2018, a Texas U.S. District Court Judge ruled that the PPACA is unconstitutional in its entirety because the individual mandate was repealed by Congress as part of the Tax Cuts and Jobs Act. While the Texas U.S. District Court Judge, as well as the U.S. Presidential administration and the Centers for Medicare and Medicaid Services (CMS), have stated that the ruling will have no immediate effect pending appeal of the decision, it is unclear how this decision, subsequent appeals, and other efforts to repeal and replace the PPACA will impact the PPACA.

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 and enacted state and federal legislation 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. For example, the U.S. Presidential administration released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out of pocket costs of drug products paid by consumers. Although a number of these, and other potential, proposals will require authorization through additional legislation to become effective, Congress and the U.S. Presidential administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and

transparency measures, and, in some cases, to encourage importation from other countries and bulk purchasing.

Brexit and the Regulatory Framework in the United Kingdom

On June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the EU (Brexit). Thereafter, on March 29, 2017, the country formally notified the EU of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. Although it is unclear when or if the United Kingdom will leave the EU if a withdrawal does occur, it is expected to take effect either on the effective date of the withdrawal agreement to be negotiated by the parties or, in the absence of agreement, on March 29, 2019, unless this is extended. Since the regulatory framework for pharmaceutical products in the United Kingdom covering quality, safety and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from EU directives and regulations, immediately following Brexit, it is

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expected that the United Kingdom's regulatory regime will remain aligned with EU regulations. It remains to be seen how, if at all, Brexit will impact regulatory requirements for product candidates and products in the United Kingdom. In the longer term, Brexit could materially impact the future regulatory regime which applies to products and the approval of product candidates in the United Kingdom.

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 certain other 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 exceptions and regulatory safe harbors protecting certain common activities from prosecution or other regulatory sanctions, the exceptions 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 exception 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 their 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 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 from federal healthcare programs, integrity oversight and reporting obligations, 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.

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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 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. Obtaining coverage and adequate reimbursement for our products may be particularly difficult because of the higher prices often associated with drugs administered under the supervision of a physician. 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 high enough price levels to realize sufficient revenues from 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

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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. Since 2017, non-innovator products are also subject to an additional rebate.

The statutory definition of AMP was amended in 2010. CMS 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. Manufacturers are required to report pricing information to the Health Resources and Services Administration (HRSA) on a quarterly basis effective first quarter 2019. HRSA has also issued regulations relating to the calculation of the ceiling price as well as imposition of civil monetary penalties for each instance of knowingly and intentionally overcharging a 340B covered entity.

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%, now 70% since January 1, 2019, 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

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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 significant civil monetary penalties 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 February 13, 2019, we had 2,849 full-time employees, 1,280 of whom were in operations, 713 of whom were in research and development, 419 of whom were in sales and marketing and 437 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.

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 Security and Exchange Commission (the SEC). Such reports and other information may be accessed through the SEC's website at 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. Furthermore, there can be no assurance that approval of one of our product candidates by one regulatory agency will mean that other agencies will also approve the same product candidate. For example, although the FDA approved Palynziq, there can be no assurance that the EMA will also approve Palynziq. Similarly, regulatory authorities may approve a product candidate for fewer or more limited indications than requested or may grant approval subject to the performance of post-marketing studies. In addition, regulatory authorities may not approve the labeling claims that are necessary or desirable for the successful commercialization of our product candidates.

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We have had fewer interactions with regulatory authorities outside the U.S. and the EU as compared to our interactions with the FDA and EMA. The approval procedures vary among countries and can involve additional clinical testing, and the time required to obtain approval may differ from that required to obtain FDA or EMA approval. Moreover, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries. Approval by the FDA or EMA does not ensure approval by regulatory authorities in other countries, and approval by one or more foreign regulatory authorities does not ensure approval by regulatory authorities in other foreign countries or by the FDA or EMA. However, a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory process in others. The foreign regulatory approval process may include all of the risks associated with obtaining FDA or EMA approval. We may not obtain foreign regulatory approvals on a timely basis, if at all. We may not be able to file for regulatory approvals and even if we file we may not receive necessary approvals to commercialize our product candidates in any market.

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 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 are not well-established areas, 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 product candidates, we engage in discussions with the FDA and comparable international regulatory authorities regarding our development programs, including discussions about the regulatory requirements for approval. As part of these discussions, we sometimes seek advice in the design of our clinical programs from various regulatory agencies globally, but we do not always follow

such guidance. This increases the chance of adverse regulatory actions, but we try to always provide appropriate scientific evidence to support approval. For example, although we designed our Phase 3 study of vosoritide in a manner that we believe can demonstrate efficacy and safety of the product candidate for the target patient population, the FDA may ultimately disagree. Moreover, sometimes different regulatory agencies provide different or conflicting advice. While we attempt to harmonize the advice we receive from multiple regulatory authorities, it is not always practical to do so. Also, we may choose not to harmonize conflicting advice when harmonization would significantly delay clinical trial data or is otherwise inappropriate. 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

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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.

Aldurazyme, Brineura, Kuvan, Naglazyme and Vimizim have received regulatory approval to be commercially marketed and sold in the U.S., the EU and certain other countries, Palynziq has received regulatory approval to be commercially marketed in the U.S., and Firdapse has received regulatory approval to be commercially marketed 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, import and export requirements and recordkeeping.

An example of the ongoing regulatory requirements our products are subject to is the Palynziq Risk Evaluation and Mitigation Strategy (REMS) program. In the U.S., Palynziq is only available through the REMS program, which is required by the FDA to mitigate the risk of anaphylaxis while using the product. Notable requirements of our REMS program include the following:

- prescribers must be certified by enrolling in the REMS program and completing training;
- prescribers must prescribe auto-injectable epinephrine with Palynziq;
- pharmacies must be certified with the REMS program and must dispense Palynziq only to patients who are authorized to receive it;
- patients must enroll in the REMS program and be educated about the risk of anaphylaxis by a certified prescriber to ensure they understand the risks and benefits of treatment with Palynziq; and
- patients must have auto-injectable epinephrine available at all times while taking Palynziq.

Failure of prescribers, pharmacies or patients to enroll in our REMS program or to successfully complete and comply with its requirements may result in regulatory action from the FDA or decreased sales of Palynziq. The restrictions and requirements under our REMS program, as well as potential changes to these restrictions and requirements in the future, subject us to increased risks and uncertainties, any of which could harm our business. The requirement for a REMS program can materially affect the potential market for and profitability of a drug. We cannot predict whether the FDA will request, seek to require or ultimately require modifications to, or impose additional requirements on, the Palynziq REMS program, or whether the FDA will permit modifications to the Palynziq REMS program that we consider warranted. Any modifications required or rejected by the FDA could make it more difficult or expensive for us to distribute Palynziq in the U.S., impair the safety profile of Palynziq, disrupt continuity of care for Palynziq patients and/or negatively affect sales of Palynziq.

Moreover, 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. In particular, a product may not be promoted for uses that are not approved by the FDA as reflected in the product’s approved labeling. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant civil, criminal and administrative penalties. 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;

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- 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, our value 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 available if a sponsor can establish: that the medicine is intended for the diagnosis, prevention or treatment of (1) a life-threatening or chronically debilitating condition affecting no more than five in 10,000 people in the EU, which is equivalent to around 250,000 people or fewer or (2) a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that the marketing of the medicinal product in the EU would generate sufficient return to justify the necessary investment. For either of these conditions, the applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the EU or, if such method exists, the medicinal product will be of significant benefit to those affected by that condition. 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. In addition, the FDA may approve another drug during a period of orphan drug exclusivity if the second drug is found to be clinically superior to the first drug. In the EU, a ten-year period of market exclusivity (extendable to twelve years for medicines that have complied with an agreed pediatric investigation plan pursuant to Regulation 1901/2006) is available. Orphan drug marketing exclusivity may be lost in the EU if a manufacturer is unable to supply sufficient quantities and marketing authorization may also be granted to a similar medicinal product with the same orphan indication if this medicinal product is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if, at the end of the fifth year, it can be demonstrated on the basis of available evidence that the criteria for its designation as an orphan medicine are no longer satisfied, for example if the original orphan medicinal product has become sufficiently profitable not to justify maintenance of market exclusivity. 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

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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. Moreover, with respect to biologics and gene therapy, it is uncertain how similarity between product candidates designed to treat the same rare disease or condition may affect such product candidates' orphan drug exclusivities. 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, Brineura, Naglazyme, Palynziq 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. 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. A similar abridged marketing authorization process is available to biosimilar products in the EU. 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. The BPCIA establishes a period of 12 years of exclusivity for reference products. In Europe, a medicinal product containing a new active substance benefits from eight years of data exclusivity, during which biosimilar applications referring to the data of that product may not be accepted by the regulatory authorities, and a further two years of market exclusivity, during which such biosimilar products may not be placed on the market. The two-year period may be extended to three years if during the first eight years a new therapeutic indication with significant clinical benefit over existing therapies is approved. Our products approved under BLAs in the U.S. or MAAs in Europe, as well as products in development that may be approved under those regimes 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. The number of preclinical studies and clinical trials that regulatory authorities require varies 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 have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials. Also, as noted above, we do not always follow the advice of regulatory authorities or comply with all of their requests regarding the design of our clinical programs. In those cases, we may choose a development program that is inconsistent with the advice of regulatory authorities, which may limit the jurisdictions where we conduct clinical trials and/or adversely affect our ability to obtain approval in those jurisdictions where we do not follow the regulatory advice.

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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 valoctocogene roxaparvovec 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 valoctocogene roxaparvovec (formerly referred to as 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 little or too much of the desired protein or RNA. Although a one-time administration of a gene therapy product like our product candidate valoctocogene roxaparvovec is intended to correct an inborn genetic defect for the entire lifetime of a patient, there is a risk that the therapeutic effect will not be durable and production of the desired protein or RNA will decrease over time or cease entirely. Because the treatment is irreversible, there may be challenges in managing side effects, particularly those caused by potential overproduction of the desired protein. 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. Although numerous companies are currently advancing gene therapy product candidates through clinical trials and the FDA has approved several cell-based gene therapy treatments to date, the FDA has only approved one vector-based gene therapy product thus far. Moreover, there are very few approved gene therapy products outside the U.S. As a result, 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 valoctocogene roxaparvovec to market could have a negative effect on our business and financial

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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.

We may decide to submit a BLA for valoctocogene roxaparvovec through the FDA's accelerated approval pathway. If original FDA approval for valoctocogene roxaparvovec is obtained via the accelerated approval pathway, we may be required to conduct a post-marketing confirmatory trial to verify and describe the clinical benefit in support of full approval. An unsuccessful post-marketing study or failure to complete such a study could result in the withdrawal of the FDA's marketing approval for valoctocogene roxaparvovec, which could have a negative effect on our business and financial condition.

Even if we obtain and maintain regulatory approval for valoctocogene roxaparvovec, we may experience delays, and increased costs, in developing, optimizing and operating 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. We invested a considerable amount of capital building our own commercial gene therapy manufacturing facility, which may be subject to significant impairment if our gene therapy programs are unsuccessful. As we develop, seek to optimize and operate the valoctocogene roxaparvovec manufacturing process, we will likely face technical and scientific challenges, considerable capital costs, and potential difficulty in recruiting and hiring experienced, qualified personnel. There may also be unexpected technical or operational issues during clinical or commercial manufacturing campaigns. As a result, we could experience manufacturing delays that prevent us from completing our clinical studies or commercializing valoctocogene roxaparvovec 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 valoctocogene roxaparvovec, 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 valoctocogene roxaparvovec to be substantial. Therefore, we expect that coverage and reimbursement by governments and other third-party payers will be essential for the vast majority of patients to be able to afford valoctocogene roxaparvovec. Accordingly, sales of valoctocogene roxaparvovec, if approved, will depend substantially, both domestically and internationally, on the extent to which its cost will be paid by third-party payers. Even if coverage is provided, the reimbursement amounts approved by third-party payers may not be high enough to allow us to realize sufficient revenues from our investment in the development of valoctocogene roxaparvovec.

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 valoctocogene roxaparvovec, the commercial success of valoctocogene roxaparvovec will depend, in part, on the acceptance of physicians, patients and third-party payers 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 valoctocogene roxaparvovec displays a favorable efficacy and safety profile in clinical trials and is ultimately approved, market acceptance of valoctocogene roxaparvovec will not be fully known until after it is launched. Negative public opinion or more restrictive government regulations could have a negative effect on our business and financial condition and may delay or impair the development and commercialization of, and demand for, valoctocogene roxaparvovec.

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. 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.

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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, 2018, we had cash, cash equivalents and investments totaling $1.3 billion and long-term debt obligations of $870.0 million (undiscounted), which consisted of our 1.50% senior subordinated convertible notes due in 2020 (the 2020 Notes) and our 0.599% senior subordinated convertible notes due in 2024 (the 2024 Notes and, together with the 2020 Notes, the Notes), which, if not converted, will be required to be repaid in cash at maturity in 2020 and 2024, respectively. We will need cash not only to pay the ongoing interest due on the Notes during their term, but also to repay the principal amount of the Notes if not converted.

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 Palynziq, we are obligated to make certain payments to Merck Serono if sales and development milestones are achieved. The remaining milestone payments that may become payable include up to a maximum of €60 million, in cash, if future sales milestones are met with respect to Kuvan and Palynziq, and up to a maximum of €75 million, in cash, if future development milestones are met with respect to Palynziq.

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;
- the time and cost necessary to develop commercial manufacturing processes, including quality systems, and to build or acquire manufacturing capabilities;
- 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 progress of research programs carried out by us;
- our possible achievement of development and commercial milestones under agreements with third parties, such as the termination agreements with Merck Serono related to Kuvan and Palynziq milestones;
- 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;
- Genzyme Corporation’s (Genzyme) ability to continue to successfully commercialize Aldurazyme; 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

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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, 2018, we had $870.0 million (undiscounted) principal amount of indebtedness, including $375.0 million (undiscounted) principal amount of indebtedness under the 2020 Notes and $495.0 million (undiscounted) principal amount of indebtedness under the 2024 Notes. In October 2018, we also entered into an unsecured credit agreement (the 2018 Credit Facility) with Bank of America, N.A., as the administrative agent, swingline lender and a lender, Citibank N.A. as letter of credit issuer and each of Merrill Lynch, Pierce, Fenner & Smith Incorporated, Citibank, N.A. and Wells Fargo Securities, LLC as joint lead arrangers and joint bookrunners, providing up to $200.0 million in revolving loan commitments and terminated the credit facility that we entered into in November 2016, which had provided for up to $100.0 million in revolving loans (the 2016 Credit Facility). The 2018 Credit Facility replaced the 2016 Credit Facility. Our indebtedness may:

- limit our ability to borrow additional funds for working capital, capital expenditures, acquisitions or other general business purposes;
- limit our ability to use our cash flow or obtain additional financing for future working capital, capital expenditures, acquisitions or other general business purposes;
- require us to use a substantial portion of our cash flow from operations to make debt service payments;
- limit our flexibility to plan for, or react to, changes in our business and industry;
- place us at a competitive disadvantage compared to our less leveraged competitors; and
- increase our vulnerability to the impact of adverse economic and industry conditions.

In addition, the 2018 Credit Facility contains, and any future indebtedness that we may incur may contain, financial and other restrictive covenants that limit our ability to operate our business, raise capital or make payments under our other indebtedness. If we fail to comply with these covenants or to make payments under our indebtedness when due, then we would be in default under that indebtedness, which could, in turn, result in that and our other indebtedness becoming immediately payable in full. If we default under the 2018 Credit Facility, the outstanding borrowings thereunder could become immediately due and payable, the 2018 Credit Facility 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 Notes. If we default under any of the Notes, such Notes could become immediately due and payable and it could lead to defaults under the other Notes and/or the 2018 Credit Facility.

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

Our outstanding indebtedness consists primarily of the 2020 Notes and 2024 Notes, which, if not converted, will be required to be repaid in cash at maturity in 2020 and 2024, respectively. In addition, in the event the conditional conversion feature of the 2020 Notes is triggered, holders of the 2020 Notes will be entitled to convert the 2020 Notes at any time during specified periods at their option, and the 2020 Notes will be freely convertible on or after July 15, 2020. We may elect to settle conversions of the 2020 Notes in cash, in whole or in part, which could further affect our liquidity. While we could seek to obtain additional 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.

We could be required under applicable accounting rules to reclassify all or a portion of the outstanding principal of the 2020 Notes as a current rather than long-term liability (for example, if there are 12 months or less remaining until maturity), which would result in a material reduction of our net working capital. 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. In addition, we also may borrow up to $200.0 million in revolving loans under the 2018 Credit Facility, which would be required to be repaid in cash at maturity on October 19, 2021, except that if at least $100.0 million aggregate principal amount of the 2020 Notes remains outstanding on August 1, 2020 and certain

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other conditions have not been met, we may be required to repay all amounts borrowed under the 2018 Credit Facility on August 1, 2020.

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 for the manufacture of Palynziq, and it has been approved by the FDA, the European Commission (EC), and health agencies in other countries for the manufacture of Aldurazyme, Brineura, 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, and it has been approved by the FDA and the EMA as a formulated bulk drug substance manufacturing and quality control facility for Brineura. 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, Brineura, Naglazyme, Palynziq 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

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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.

We have entered into contractual relationships with third-party manufacturers to produce active ingredients in Firdapse, Kuvan and Palynziq. If those manufacturers are unwilling or unable to fulfill their contractual obligations, we may be unable to meet demand for Firdapse, Kuvan and Palynziq, 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, Kuvan and Palynziq. We also currently rely on third parties for portions of the manufacture of Aldurazyme, Brineura, Naglazyme, Palynziq 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.

Any interruption in the supply of finished products could hinder our ability to distribute finished products to meet commercial demand and adversely affect our financial results and financial condition.

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 Brineura, 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

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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 payers, 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 payers. 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 payers, such as government or private healthcare insurers, carefully review and increasingly challenge the prices charged for drugs. Reimbursement rates from private companies vary depending on the third-party payer, the insurance plan and other factors. Obtaining coverage and adequate reimbursement for our products may be particularly difficult because of the higher prices often associated with drugs administered under the supervision of a physician. 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 payers 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 payers 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 payers in the U.S. Therefore, coverage and reimbursement for drug products can differ significantly from payer to payer. 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 payer 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, and we expect a significant portion of our international sales of Brineura will also be through such programs. 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 and may continue to undertake unofficial

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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 in all the markets in which we sell our products. The escalating cost of healthcare has led to increased pressure on the healthcare 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 payers have proposed healthcare reforms and cost reductions. A number of federal and state proposals to control the cost of healthcare, 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 and enacted legislation 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. Further, Congress and the executive branch have each indicated that they will continue to seek new legislative and/or administrative measures to control drug costs. In some international markets, the government controls the pricing, which can affect the profitability of drugs. Current government regulations and possible future legislation regarding healthcare may affect coverage and reimbursement for medical treatment by third-party payers, 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 and continue to propose revenue caps limiting the annual volume of sales of our products. Some of these caps are significantly below the actual demand in certain countries, and if the trend regarding revenue caps continues, 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 healthcare 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. 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 (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. Since its enactment, there have been judicial and Congressional challenges to certain aspects of the PPACA, as well as recent efforts by the U.S. Presidential administration to repeal or replace certain aspects of the PPACA, and we expect there will be additional

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challenges and amendments to the PPACA in the future. Since January 2017, the U.S. President has signed two Executive Orders and other directives designed to delay, circumvent, or loosen certain requirements mandated by the PPACA. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the PPACA. While Congress has not passed legislation repealing the PPACA in its entirety, it has enacted laws that modify certain provisions of the PPACA such as removing penalties, starting January 1, 2019, for not complying with the PPACA's individual mandate to carry health insurance, delaying the implementation of certain ACA-mandated fees, and increasing the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D. Additionally, on December 14, 2018, a Texas U.S. District Court Judge ruled that the PPACA is unconstitutional in its entirety because the individual mandate was repealed by Congress as part of the Tax Cuts & Jobs Act. While the Texas U.S. District Court Judge, as well as the current U.S. Presidential administration and the Centers for Medicare and Medicaid Services (CMS), have stated that the ruling will have no immediate effect pending appeal of the decision, it is unclear how this decision, subsequent appeals, and other efforts to repeal and replace the PPACA will impact the PPACA and our business. In addition, other legislative changes have been adopted since the PPACA was enacted. Some of these changes have resulted 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 in the U.S. or abroad, may result in more rigorous coverage criteria and an additional downward pressure on the reimbursement our customers may receive for our products. Recently there has been heightened governmental scrutiny in countries worldwide over the manner in which manufacturers set prices for their marketed products.

In the U.S., there have been several recent Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the cost of drugs under Medicare, and reform government program reimbursement methodologies for drug products. Moreover, the U.S. Presidential administration released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out of pocket costs of drug products paid by consumers. Although a number of these, and other potential, proposals will require authorization through additional legislation to become effective, Congress and the U.S. Presidential administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. Any reduction in reimbursement from Medicare and other government programs may result in a similar reduction in payments from private payers. In addition, individual states in the United States have also increasingly passed legislation and implemented regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. Moreover, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs.

Likewise, in many EU countries, legislators and other policymakers continue to propose and implement healthcare cost-containing measures in response to the increased attention being paid to healthcare costs in the EU. Certain of these changes could impose limitations on the prices we will be able to charge for our products and any approved product candidates or the amounts of reimbursement available for these products from governmental and private third-party payers, may increase the tax obligations on pharmaceutical companies or may facilitate the introduction of generic competition with respect to our products. Further, an increasing number of EU countries and other foreign countries use prices for medicinal products established in other countries as "reference prices" to help determine the price of the product in their own territory. Consequently, a downward trend in prices of medicinal products in some countries could contribute to similar downward trends elsewhere. Moreover, in order to obtain reimbursement for our products in some countries, we may be required to conduct clinical trials that compare the cost-effectiveness of our

products to other available therapies.

Legally mandated price controls on payment amounts by governmental and private third-party payers or other restrictions could harm our business, results of operations, financial condition and prospects. 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 healthcare reform, see “Government Regulation - Health Reform” in Part I, Item 1 of this Annual Report on Form 10-K for the year ended December 31, 2018.

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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 healthcare laws or privacy and data protection laws, we may be required to pay penalties, be subjected to scrutiny by regulators or governmental entities, or be suspended from participation in government healthcare programs, which may adversely affect our business, financial condition and results of operations.

We are subject to various healthcare laws and regulations in the U.S. and internationally, including anti-kickback laws, false claims laws, data privacy and security laws, and laws related to ensuring compliance. In the U.S., 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 healthcare programs, such as Medicare and Medicaid. Under the federal Anti-Kickback Statute and related regulations, certain arrangements are deemed not to violate the federal Anti-Kickback Statute if they fit within a statutory exception or regulatory safe harbor. However, the exceptions 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 exception 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 healthcare services reimbursed by any source, not just governmental payers.

Federal and state false claims laws, including the civil False Claims Act, prohibit any person or entity 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 healthcare benefit program, including private payers, 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 healthcare benefits, items or services.

In addition, recent healthcare reform legislation has strengthened these laws in the U.S. 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 civil False Claims Act.

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, integrity, availability, 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. The global data protection landscape is rapidly evolving, and implementation standards and enforcement practices are likely to remain uncertain for the foreseeable future. In the United States, California recently enacted the California Consumer Privacy Act (CCPA), which takes effect on January 1, 2020. The CCPA gives California residents expanded rights to access and delete their personal information, opt out of certain personal information sharing, and receive detailed information about how their personal information is used. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that is expected to increase data breach litigation. The CCPA may increase our compliance costs and potential liability. Some observers have noted that the CCPA could mark the beginning of a trend toward more stringent privacy legislation in the U.S., which could increase our potential liability and adversely affect our business.

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The European Regulation 2016/679, known as the General Data Protection Regulation (GDPR), as well as EU Member State implementing legislations, apply to the collection and processing of personal data, including health-related information, by companies located in the EU, or in certain circumstances, by companies located outside of the EU and processing personal information of individuals located in the EU. These laws impose strict obligations on the ability to process personal data, including health-related information, in particular in relation to their collection, use, disclosure and transfer. These include several requirements relating to (i) obtaining, in some situations, the consent of the individuals to whom the personal data relates, (ii) the information provided to the individuals about how their personal information is used, (iii) ensuring the security and confidentiality of the personal data, (iv) the obligation to notify regulatory authorities and affected individuals of personal data breaches, (v) extensive internal privacy governance obligations, and (vi) obligations to honor rights of individuals in relation to their personal data (for example, the right to access, correct and delete their data). The GDPR prohibits the transfer of personal data to countries outside of the European Economic Area (EEA), such as the United States, which are not considered by the European Commission to provide an adequate level of data protection. Switzerland has adopted similar restrictions. Although there are legal mechanisms to allow for the transfer of personal data from the EEA and Switzerland to the United States, they are subject to legal challenges and uncertainty about compliance with EU data protection laws remains.

Potential pecuniary fines for noncompliant companies may be up to the greater of €20 million or 4% of annual global revenue. The GDPR has increased our responsibility and liability in relation to personal data that we process, and we may be required to put in place additional potential mechanisms to ensure compliance with the new EU data protection rules.

Substantial new provisions affecting compliance have also been adopted in the U.S. and certain foreign countries, which may require us to modify our business practices with healthcare practitioners. For example, in the U.S., the PPACA, through the Physician Payments Sunshine Act, requires certain drug, biologicals and medical supply 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. Effective January 1, 2022, manufacturers will also be required to report on payments or transfers of value to physician assistants, nurse practitioners or clinical nurse specialists, certified registered nurse anesthetists, and certified nurse-midwives. In addition, there has been a recent trend of increased state regulation of payments made to physicians. Certain states and/or local jurisdictions 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, the registration of pharmaceutical sales representatives and/or the tracking and reporting of gifts, compensation and other remuneration to physicians. Likewise, in many foreign countries there is an increasing focus on the relationship between drug companies and healthcare practitioners. Recently enacted legislation creates reporting obligations on payments, gifts and benefits made to these professionals; however, implementing regulations enacting such laws are still pending and subject to varying interpretations by courts and government agencies. The shifting regulatory environment and the need to implement systems to comply with multiple jurisdictions with different compliance and/or reporting requirements increases the costs of maintaining compliance and the possibility that we may violate one or more of the requirements and be subject to fines or sanctions.

Due to the breadth of the healthcare and privacy and data protection laws described above, the narrowness of available statutory and regulatory exceptions and safe harbors 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. 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, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar

agreement to resolve allegations of non-compliance with these laws, curtailment of our operations, and debarment, suspension or exclusion from participation in government healthcare programs, any of which could adversely affect our business, financial condition and results of operations.

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. Similarly, we expect a significant portion of the sales of Brineura to be 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

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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
- rapidly evolving global laws and regulations relating to data protection and the privacy and security of 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.

The United Kingdom's withdrawal from the European Union may have a negative effect on global economic conditions, financial markets and our business, which could adversely affect our revenue and results of operations.

In June 2016, a majority of the eligible members of the electorate in the United Kingdom voted to withdraw from the EU in a national referendum (Brexit). The withdrawal of the United Kingdom from the EU will take effect either on the effective date of the withdrawal agreement or, in the absence of agreement, two years after the United Kingdom provides a notice of withdrawal pursuant to Article 50 of the European Union Treaty, unless the European Council, in agreement with the United Kingdom, unanimously decides to extend this period, or if the United Kingdom opts to remain in the EU. On March 29, 2017, the United Kingdom's Prime Minister formally delivered the notice of withdrawal. It appears likely that this withdrawal will continue to involve lengthy negotiations between the United Kingdom and European Union Member States to determine the future terms of the United Kingdom's relationship with the EU, and the wider EEA.

These developments, or the perception that any of them could occur, have had and may continue to have a significant adverse effect on global economic conditions and the stability of global financial markets, and could significantly reduce global market liquidity and restrict the ability of key market participants to operate in certain financial markets. In particular, it could also lead to a period of considerable uncertainty in relation to global financial and banking markets, as well as on regulatory processes in Europe and the EEA. As a result of this uncertainty, global financial markets could experience significant volatility, which could adversely affect the market price of our shares. Asset valuations, currency exchange rates and credit ratings may also be subject to increased market volatility. Lack of

clarity about future United Kingdom laws and regulations as the United Kingdom determines which EU rules and regulations to replace or replicate in the event of a withdrawal, including financial laws and regulations, tax and free trade agreements, intellectual property rights, supply chain logistics, environmental, health and safety laws and regulations, immigration laws and employment laws, could decrease foreign direct investment in all markets, increase costs, depress economic activity and restrict access to capital.

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If the United Kingdom and the EU are unable to negotiate acceptable withdrawal terms or if other EU countries pursue withdrawal, barrier-free access between the United Kingdom and other EU or EEA countries could be diminished or eliminated, which could make our doing business in the EU more difficult. As a result of Brexit, we may face disruptions in our supply chain, inventory management, manufacturing process and product distribution network, which could adversely affect our business and results of operations. Moreover, Brexit may also lead to new regulatory costs and challenges that could have a material adverse effect on our operations. The EMA has issued guidance to marketing authorization holders of centrally authorized medicinal products regarding certain requirements that need to be considered as part of Brexit, such as the requirement for the marketing authorization holder of a product centrally approved by the EC to be established in the EU, and the requirement for some activities relating to centrally approved products, such as batch release and pharmacovigilance, be performed in the EU. Furthermore, there are few indications of the effect Brexit will have on the pathway to obtaining marketing approval for any of our product candidates in the United Kingdom.

If we fail to comply with U.S. export control and economic sanctions, our business, financial condition and operating results may be adversely affected.

Our products are subject to U.S. export control laws and regulations, including the U.S. Export Administration Regulations and various economic and trade sanctions regulations administered by the U.S. Treasury Department's Office of Foreign Assets Control (OFAC). Exports of our products and solutions must be made in compliance with these laws and regulations. Changes to these laws and regulations, or to the countries, governments, persons or activities targeted by such laws, could result in decreased use of our products, or in our decreased ability to export or sell our products to existing or potential customers, which would likely adversely affect our results of operations, financial condition or strategic objectives. If we fail to comply with these laws and regulations, we and certain of our employees could be subject to substantial civil or criminal penalties, including the possible loss of export or import privileges, fines, which may be imposed on us and responsible employees or officers and, in extreme cases, the incarceration of responsible employees or officers.

We rely on a general license from OFAC to sell our medicines for eventual use by hospital and clinic end-users in Iran. The use of this OFAC general license requires us to observe strict conditions with respect to products sold, end-user limitations and payment requirements. Although we believe we have maintained compliance with the general license requirements, there can be no assurance that the general license will not be revoked, be renewed in the future or that we will remain in compliance. A violation of the OFAC general license could result in substantial fines, sanctions, civil or criminal penalties, competitive or reputational harm, litigation or regulatory action and other consequences that might adversely affect our results of operations, financial condition or strategic objectives.

Failure to comply with applicable anti-corruption legislation could result in fines, criminal penalties and materially adversely affect our business, financial condition and results of operations.

We are required to comply with anti-corruption and anti-bribery laws in the jurisdictions in which we operate, including the FCPA in the United States, the UK Bribery Act and other similar laws in other countries in which we do business. We operate in a number of countries that are recognized to have a reputation for corruption and pose an increased risk of corrupt practices. We also regularly interact with government regulators in many countries, including those that are considered higher risk for corruption, in order to secure regulatory approval to manufacture and distribute our products. The anti-corruption and anti-bribery laws to which we are subject generally prohibit companies and their intermediaries from making improper payments to foreign officials or other persons for the purposes of influencing official decisions or obtaining or retaining business and/or other benefits. These laws also require us to make and keep books and records that accurately and fairly reflect our transactions and to devise and maintain an adequate system of internal accounting controls. As part of our business, we deal with state-owned business enterprises, the employees and representatives of which may be considered foreign officials for purposes of

applicable anti-corruption laws.

Although we have adopted policies and procedures designed to ensure that we, our employees and third-party agents will comply with such laws, there can be no assurance that such policies or procedures will work effectively at all times or protect us against liability under these or other laws for actions taken by our employees, partners and other third parties with respect to our business. If we are not in compliance with anti-corruption laws and other laws governing the conduct of business with government entities and/or officials (including local laws), we may be subject to criminal and civil penalties and other remedial measures, which could harm our business, financial condition, results of operations, cash flows and prospects. Investigations of any actual or alleged violations of such laws or policies related to us could harm our business, financial condition, results of operations, cash flows and prospects.

Moreover, there has been enhanced scrutiny of company-sponsored patient assistance programs, including insurance premium and co-pay assistance programs and donations to third-party charities that provide such assistance. There has also been enhanced scrutiny by governments on reimbursement support offerings,

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clinical education programs and promotional speaker programs. If we, our third-party agents or donation recipients are deemed to have failed to comply with laws, regulations or government guidance in any of these areas, we could be subject to criminal or civil sanctions. Any similar violations by our competitors could also negatively impact our industry reputation and increase scrutiny over our business and our products

Changes in funding for the FDA, the EMA and other government agencies or government shutdowns could hinder the ability of such agencies to hire and retain key leadership and other personnel or otherwise prevent those agencies from performing normal functions on which the operation of our business may rely, which could negatively impact our business.

Changes in funding levels of government agencies can affect their ability to hire and retain key personnel and carry out their normal functions that support our business. For example, the ability of the FDA to timely review and approve INDs or marketing authorizations for our product candidates may be hindered by a lack of resources and qualified personnel. In addition, funding of other government agencies on which our operations rely, including those that fund research and development activities, is subject to the political budget process, which is inherently fluid and unpredictable.

Government shutdowns could also impact the ability of government agencies to function normally and support our operations. For example, the U.S. federal government has shut down repeatedly since 1980, including for a period of 35 days beginning on December 22, 2018. During a shutdown, certain regulatory agencies, such as the FDA, have had to furlough key personnel and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

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 United Kingdom Pound, the Canadian Dollar 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 certain 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.

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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.
- Patents have limited duration and expire. For example, our patents related to Aldurazyme expire in November 2019 and in 2020.
- 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.
- 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.

Under policies recently adopted in the EU, clinical trial data submitted to the EMA in MAAs that were traditionally regarded as confidential commercial information are now subject to public disclosure. Subject to our ability to review and redact a narrow sub-set of confidential commercial information, the new EU policies will result in the EMA’s public disclosure of certain of our clinical study reports, clinical trial data summaries and clinical overviews for recently completed and future MAA submissions. 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 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 valoctocogene roxaparvovec, 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.

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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.

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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 depend 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.

If generic manufacturers are successful in their use of litigation or 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 abbreviated new drug applications (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

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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.

We received separate paragraph IV notice letters in 2016, 2015 and 2014 from Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd. (collectively, DRL) and Par Pharmaceutical, Inc. (Par) notifying us that each of DRL and Par had filed ANDAs seeking approval of proposed generic versions of Kuvan (sapropterin dihydrochloride) 100 mg oral powder and Kuvan 100 mg oral tablets prior to the expiration of our Kuvan-related patents listed in the Orange Book. We filed lawsuits alleging patent infringement against DRL and Par, and in 2017, 2016 and 2015 we entered into separate settlement agreements with DRL (the DRL Settlement Agreement) and Par (the Par Settlement Agreement) that resolved the patent litigation in the U.S. Under the terms of the DRL Settlement Agreement, we granted DRL a non-exclusive license to our Kuvan-related patents to allow DRL to market a generic version of sapropterin dihydrochloride in 100 mg oral tablets and oral powder in 100 mg and 500 mg packet formulations in the U.S. for the indications approved for Kuvan beginning on October 1, 2020, or earlier under certain circumstances. Under the Par Settlement Agreement, we granted Par a non-exclusive license to our Kuvan-related patents to allow Par to market a generic version of sapropterin dihydrochloride in 100 mg oral tablets and oral powder in 100 mg and 500 mg packet formulations in the U.S. for the indications approved for Kuvan beginning on: April 1, 2021 if Par is not entitled to the statutory 180-day first filer exclusivity period; October 1, 2020 if Par is entitled to the statutory 180-day first filer exclusivity period; or earlier under certain circumstances.

We expect generic versions of Kuvan to first become available in the U.S. in the fourth quarter of 2020.The DRL Settlement Agreement and the Par Settlement Agreement, 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 any ANDA filer we bring suit against 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 and Par following the settlements described above 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, and there is a process equivalent to the ANDA process under Article 10 of Directive 2001/83/EC in the EU. 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

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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 valoctocogene roxaparvovec, the commercial success of valoctocogene roxaparvovec will still depend, in part, on the acceptance of physicians, patients and healthcare payers 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.

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 operations, 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 or attacks, could harm our ability to operate our business effectively. Our ability to manage and maintain our operations, 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 incidents and attacks in particular are evolving and include, but are not limited to, malicious software, attempts to gain unauthorized access to data, business email compromise and other cyber attacks or cyber incidents that could lead to disruptions in or unavailability of systems, misappropriation of confidential or otherwise protected information, corruption or loss of data, data security breaches and other harm to our business or competitive position. Cybersecurity incidents resulting in the failure of our enterprise resource planning system, production

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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 operations, inventory and internal reports, and result in delays in product fulfillment and reduced efficiency of our operations. Moreover, if such an incident or computer security breach were to result in damage or unauthorized access to, or loss, corruption or unauthorized disclosure of, personally identifiable information, such a breach may require notification to governmental agencies, supervisory bodies, credit reporting agencies, the media or individuals pursuant to various federal, state and foreign data protection, privacy and security laws, regulations and guidelines, if applicable. It could also cause a loss in the confidence of our customers, employees, and partners and other third parties with respect to our business. A breach in security, unauthorized access resulting in misappropriation, theft, or sabotage with respect to our proprietary, personal and confidential information, including research or clinical data and information about patients, employees, contractors and others, could require significant capital investments to remediate and could adversely affect our business, financial condition and results of operations. We would also be exposed to a risk of loss, enforcement measures, penalties, fines, indemnification claims or litigation and potential civil or criminal liability, which could materially 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 currently manufacture Aldurazyme, Brineura, Naglazyme, Palynziq 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, Brineura, Naglazyme and Vimizim or our third-party manufacturers' ability to manufacture Firdapse and Kuvan.

Our Galli Drive facility, located in Novato, California, is currently our only manufacturing facility for Aldurazyme, Naglazyme and Palynziq and is one of two manufacturing facilities for Brineura and Vimizim. Our gene therapy manufacturing facility is also located in Novato, California, and it is currently our only manufacturing facility to support valoctocogene roxaparvovec clinical development activities and the anticipated commercial demand for valoctocogene roxaparvovec, if approved. These facilities are located in the San Francisco Bay Area near known earthquake fault zones and are 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 our products, or to have our products 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.

The impact of the recently passed U.S. comprehensive tax reform bill on us is uncertain and could have a material adverse effect on our business and financial condition.

On December 22, 2017, the U.S. President signed into law new legislation, known as the Tax Cuts & Jobs Act, which significantly revises the Internal Revenue Code of 1986, as amended. The newly enacted federal income tax law, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss carrybacks, one time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation

expense over time, creation of a base erosion and anti-abuse tax and modification or repeal of many business deductions and credits (including reduction of tax credits under the Orphan Drug Act). Many aspects of the new federal tax law are unclear and may not be clarified for some time. Notwithstanding the reduction in the corporate income tax rate, it is possible that the Tax Cuts & Jobs Act, or regulations or interpretations under it, could adversely affect our business and financial condition, and such effect could be material. In addition, it is uncertain if and to what extent various U.S. states will conform to the newly enacted federal tax law.

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

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costs, it may not be feasible to pass price increases on to our customers due to the process by which healthcare 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.

We sell our products in countries that face economic volatility and weakness. Although we have historically collected receivables from customers in those countries, sustained weakness or further deterioration of the local economies and currencies may cause customers in those countries to be unable to pay for our products. Additionally, if one or more of these countries were unable to purchase our products, our revenue would be adversely affected.

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;
- generic competition to Kuvan tablets and powder relating to our settlements with DRL and Par or potential generic competition from future competitors;
- 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 us or the pharmaceutical industry;
- changes in the structure of healthcare payment systems
- cybersecurity incidents experienced by us or others in our 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 stockholders, or members of our management or Board of Directors.

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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 in the future become 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 2020 Notes, we entered into capped call transactions with respect to 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 2020 Notes and are expected generally to reduce potential dilution to the common stock upon conversion of the 2020 Notes in excess of the principal amount of such converted 2020 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 2020 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 2020 Notes (and are likely to do so during the settlement averaging period under the capped call transactions, which precedes the maturity date of the 2020 Notes, and on or around any earlier conversion date related to a conversion of the 2020 Notes).

The effect, if any, of any of these transactions and activities on the market price of our common stock or the 2020 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 2020 Notes and the value of our common stock, if any, that 2020 Note holders receive upon any conversion of the 2020 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 us more difficult, even if a change in control would be beneficial to the stockholders. Our anti-takeover provisions include provisions in our restated certificate of incorporation and amended and restated bylaws providing that stockholders' meetings may only be called by our Chairman, the lead independent director or the majority of our Board of Directors and 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 us. Also, under applicable Delaware law, our Board of Directors may adopt additional anti-takeover measures in the future.

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

The terms of the Notes require us to repurchase the Notes in the event of a fundamental change. A takeover of us 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 us that would otherwise be beneficial to our stockholders or investors in the Notes.

Our amended and restated bylaws provide that the Court of Chancery of the State of Delaware will be the exclusive forum for the adjudication of certain disputes, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers, or employees.

Our amended and restated bylaws provide that the Court of Chancery of the State of Delaware is the sole and exclusive forum for:

- any derivative action or proceeding brought on our behalf;
- any action asserting a claim of breach of a fiduciary duty owed by any director, officer or other employee of BioMarin to us or our stockholders;
- any action asserting a claim against us or any of our directors, officers or other employees arising pursuant to any provision of the General Corporation Law of the State of Delaware, our restated certificate of incorporation or our amended and restated bylaws; and
- any action asserting a claim against us or any of our directors, officers or other employees that is governed by the internal affairs doctrine.

This provision would not apply to suits brought to enforce a duty or liability created by the Exchange Act or any other claim for which the U.S. federal courts have exclusive jurisdiction.

This exclusive-forum provision further provides that any person or entity that acquires any interest in shares of our capital stock will be deemed to have notice of and consented to the provisions of such provision, including consent to the personal jurisdiction of the Court of Chancery of the State of Delaware related to any action covered by such provision.

This exclusive-forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers, or other employees, which may discourage lawsuits against us and our directors, officers, and other employees. If a court were to find this exclusive-forum provision to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving the dispute in other jurisdictions, which could seriously harm our business.

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, 2018:

Location	Approximate Square Feet	Use	Lease Expiration Date
San Rafael facility, San Rafael, California	407,300	Corporate headquarters, laboratory and office	Owned property
Several facilities in Novato, California	275,600	Clinical and commercial manufacturing, laboratory and office	Owned property
Several leased facilities in Novato, California	226,200	Office and warehouse	2020-2023
Shanbally facility, Cork, Ireland	209,600	Manufacturing, laboratory and office	Owned property
Dublin, Ireland	43,500	Office	2030
Brisbane, California	38,300	Office	2029
London, England	22,600	Office	2025

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We expect that these properties, together with our other smaller leased office facilities in various countries, will be adequate for our operations for the foreseeable future.

Item 3. Legal Proceedings

None.

Item 4. Mine Safety Disclosures

Not applicable.

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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.

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 year ended December 31, 2018.

Issuer Purchases of Equity Securities

We did not make any purchases of our common stock during the year ended December 31, 2018.

Holders

As of February 13, 2019, there were 44 holders of record of 178,372,202 outstanding shares of our common stock.

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 $100.00 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

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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, 2013 in stock or index, including reinvestment of dividends.

	Fiscal Year Ending December 31,					
	2013	2014	2015	2016	2017	2018
BioMarin Pharmaceutical Inc.	$100.00	$128.50	$148.91	$117.75	$126.75	$121.04
Nasdaq Composite	100.00	114.62	122.81	133.19	172.11	165.84
Nasdaq Biotechnology	100.00	131.71	140.56	112.25	133.67	121.24

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Item 6. Selected Consolidated Financial Data

We derived the selected consolidated statements of operations data for the years ended December 31, 2018, 2017 and 2016 and the selected consolidated balance sheet data as of December 31, 2018 and 2017 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, 2015 and 2014 and the selected consolidated balance sheet data as of December 31, 2016, 2015 and 2014 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 Part II, 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 millions, except for per share data)				
	2018 (1)	2017 (1)	2016 (1)	2015	2014
Consolidated Statements of Operations data:					
Total revenues	$1,491.2	$1,313.6	$1,116.9	$889.9	$749.3
Total costs and expenses	$1,614.7	$1,328.3	$1,920.3	$1,000.6	$842.2
Loss from operations	$(123.5)	$(14.7)	$(803.4)	$(110.7)	$(92.9)
Provision for (benefit from) income taxes	$(65.5)	$81.2	$(200.8)	$17.1	$9.1
Net loss	$(77.2)	$(117.0)	$(630.2)	$(171.8)	$(134.0)
Net loss per share, basic	$(0.44)	$(0.67)	$(3.80)	$(1.07)	$(0.92)
Net loss per share, diluted	$(0.44)	$(0.67)	$(3.81)	$(1.07)	$(0.92)
Weighted average common shares outstanding, basic	177.1	174.4	166.0	160.0	146.3
Weighted average common shares outstanding, diluted	177.3	174.4	166.2	160.0	146.3

	December 31, (In millions)				
	2018	2017	2016	2015	2014
Consolidated Balance Sheets data:					
Cash, cash equivalents and investments (2)	$1,320.2	$1,781.7	$1,362.4	$1,018.3	$1,043.0
Total assets (1)	$4,427.1	$4,633.1	$4,023.7	$3,729.4	$2,475.4
Convertible senior notes, net (2)	$830.4	$813.5	$660.8	$662.3	$642.9
Other long-term obligations	$105.5	$194.4	$157.3	$220.8	$68.8
Total stockholders' equity	$2,967.9	$2,808.7	$2,766.3	$2,400.8	$1,527.9

(1) See “Management's Discussion and Analysis of Financial Condition and Results of Operations — Results of Operations” in Part II, Item 7 of this Annual Report on Form 10-K for additional discussion of our operating results,

including gains on sales of intangible assets in 2018 and 2017 and impairment of intangible assets in 2016. Also, refer to the Consolidated Financial Statements and related notes thereto included in Item 15 of this Annual Report on Form 10-K for additional discussion of the impact of adoption of new accounting pronouncements in 2018 and 2016 and new tax legislation in 2017.

(2) 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 of our debt.

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Quarterly Financial Data (unaudited)

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 millions, except per share data, unaudited)			
	March 31,	June 30,	September 30,	December 31,
2018:				
Total revenues	$373.4	$372.8	$ 391.7	$ 353.2
Net loss [1]	$(44.1)	$(16.8)	$ (12.6)	$ (3.7)
Net loss per share, basic [1]	$(0.25)	$(0.09)	$ (0.07)	$ (0.02)
Net loss per share, diluted [1]	$(0.26)	$(0.09)	$ (0.07)	$ (0.03)
2017:				
Total revenues	$303.7	$317.4	$ 334.1	$ 358.3
Net loss [1]	$(16.3)	$(36.8)	$ (12.5)	$ (51.4)
Net loss per share, basic [1]	$(0.09)	$(0.21)	$ (0.07)	$ (0.29)
Net loss per share, diluted [1]	$(0.09)	$(0.21)	$ (0.07)	$ (0.30)

(1) Refer to “Management's Discussion and Analysis of Financial Condition and Results of Operations — Results of Operations” in Part II, Item 7 of this Annual Report on Form 10-K for additional discussion of gains on the sale of intangible assets, which impacted the second quarter of 2018 and fourth quarters of 2018 and 2017, and discussion of the incremental income tax expense related to the Tax Cuts and Jobs Act of 2017, which impacted the fourth quarter of 2017.

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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 (MD&A) is intended to help the reader understand our results of operations and financial condition. 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. These risks and uncertainties could cause actual results to differ significantly from those projected in forward-looking statements contained in this report or implied by past results and trends. Forward-looking statements are statements that attempt to forecast or anticipate future developments in our business, financial condition or results of operations. See the section titled "Forward-Looking Statements" that appears at the beginning of this Annual Report on Form 10-K. These statements, like all statements in this report, speak only as of the date of this Annual Report on Form 10-K (unless another date is indicated), and, except as required by law, we undertake no obligation to update or revise these statements in light of future developments. 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 portfolio consists of several commercial therapies and multiple clinical and pre-clinical product candidates. A summary of our major commercial products, including key metrics, as of December 31, 2018, is provided below:

Major Commercial Products	Indication	United States Orphan Drug Exclusivity Expiration [1]	United States Biologic Exclusivity Expiration [2]	European Union Orphan Drug Exclusivity Expiration [1]
Aldurazyme (laronidase)	MPS I [3]	Expired	Expired	Expired
Brineura (cerliponase alfa)	CLN2 [4]	2024	2029	2027
Kuvan (sapropterin dihydrochloride)	PKU [5]	Expired	Not Applicable [5]	2020 [5]
Naglazyme (galsulfase)	MPS VI [6]	Expired	Expired	Expired
Palynziq (pegvaliase-pqpz)	PKU [7]	2025	2030	TBD [7]
Vimizim (elosulfase alpha)	MPS IVA [8]	2021	2026	2024

(1) See "Government Regulation—Orphan Drug Designation" below for further discussion
(2) See "Government Regulation— Healthcare Reform" below for further discussion
(3) For the treatment of Mucopolysaccharidosis I (MPS I)
(4) For the treatment of late infantile neuronal ceroid lipofuscinosis type 2 (CLN2)
(5) For the treatment of phenylketonuria (PKU). Kuvan, a small molecule therapy, has been granted orphan drug status in the European Union (EU), which together with pediatric exclusivity, confers 12 years of market exclusivity in the EU that expires in 2020.
(6) For the treatment of Mucopolysaccharidosis VI (MPS VI)
(7) For adult patients with PKU. Palynziq (formerly referred to as pegvaliase) was approved by the U.S. Food and Drug Administration (FDA) in May 2018 and our European Marketing Authorization Application (MAA)

submission for Palynziq was accepted by the European Medicines Agency (EMA) in March 2018. We expect to learn the status of this MAA during the first half of 2019.

(8) For the treatment of Mucopolysaccharidosis IV Type A (MPS IVA)

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Management's Discussion and Analysis of Financial Condition and Results of Operations (continued)

(In millions of U.S. Dollars, except as otherwise disclosed)

A summary of our ongoing major development programs, including key metrics as of December 31, 2018, is provided below:

Major Product Candidates in Development	Target Indication	U.S. Orphan Designation	EU Orphan Designation	Stage
Palynziq in Europe	PKU	Yes	Yes	EU MAA regulatory review [1]
Valoctocogene roxaparvovec	Hemophilia A [2]	Yes	Yes	Clinical Phase 3
Vosoritide	Achondroplasia	Yes	Yes	Clinical Phase 3

(1) In May 2018, the FDA granted marketing approval for Palynziq in the U.S., and our European MAA submission for Palynziq was accepted by the EMA in March 2018. We expect to learn the status of the MAA during the first half of 2019.

(2) Hemophilia A is also called factor VIII deficiency or classic hemophilia.

Business Developments

We continued to grow our commercial business and advance our product candidate pipeline during 2018. We believe that the combination of our internal research programs, acquisitions and partnerships will allow us to continue to 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:

Product Approval

- Palynziq – In May 2018, the FDA approved Palynziq, a PEGylated recombinant phenylalanine ammonia lyase enzyme product, for the treatment of adults with PKU who have inadequate blood phenylalanine control despite prior management with available treatment options including sapropterin. Palynziq was first made available in the U.S. in July 2018. We anticipate an opinion from the Committee for Medicinal Products for Human Use (CHMP), the scientific committee of the EMA, on Palynziq Injection for the treatment of patients 16 and older with PKU in the first quarter of 2019. If the CHMP provides a positive opinion in the first quarter of 2019, then in the second quarter of 2019 it is possible that the European Commission (EC) could provide marketing authorization in the EU.

Continued Emphasis on Research and Development

- Valoctocogene roxaparvovec – We provided an update on our development of valoctocogene roxaparvovec, a gene therapy program for severe hemophilia A, that we completed enrollment of the initial cohort of patients in our Phase 3 study. Based on the FDA's Draft Guidance for Human Gene Therapy for Hemophilia issued in July 2018, we expect

that Phase 3 data from this cohort available in 2019 could support submission of a Biologics License Application (BLA) for valoctocogene roxaparvovec through an accelerated approval pathway. We plan to decide in the second half of 2019 whether we will submit a BLA through an accelerated approval pathway. The complete Phase 3 study is targeting enrollment of 130 patients by mid-year 2019.

- Vosoritide – We announced that enrollment of the Phase 2 study, a randomized, placebo-controlled study of vosoritide in approximately 70 infants and young children with achondroplasia ages zero to less than 60 months for 52 weeks, is on track, and in the early part of the study, vosoritide has been generally well-tolerated. We provided data from the children in the ongoing Phase 2 study, which demonstrated 5.7 centimeters of cumulative additional height gained at 42 months. We expect to have over 5 years of clinical data from this study to corroborate maintenance of effect at the time of possibly filing for marketing authorization. The global Phase 3 study, which is fully enrolled, is a randomized, placebo-controlled study of vosoritide in approximately 110 children with achondroplasia between the ages of 5-14 years. We expect top line results from the 52-week Phase 3 study by the end of 2019.

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Management's Discussion and Analysis of Financial Condition and Results of Operations (continued)

(In millions of U.S. Dollars, except as otherwise disclosed)

Other Developments

- Brineura – We announced in February 2019 that twenty-three patients in the ongoing open-label extension study treated with Brineura continued to show a reduced rate of decline compared to a natural history cohort of CLN2 disease for three years as measured by the CLN2 Clinical Rating Scale.

Outlook 2019

In 2019, 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 Brineura and Palynziq 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 and Latin America, 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 2019 operating objectives.

2018 Financial Highlights

Key components of our results of operations include the following:

	Years Ended December 31,		
	2018	2017	2016
Net product revenues	$1,470.4	$1,270.4	$1,110.4
Cost of sales	$315.3	$241.8	$209.6
R&D expense	$696.3	$610.8	$661.9
Selling, general and administrative (SG&A) expense	$604.4	$554.3	$476.6
Intangible asset amortization and contingent consideration expense	$48.8	$46.5	$(27.0)

Impairment of intangible assets	$—	$—	$599.1
Gain on sale of intangible assets	$(50.0)	$(125.0)	$—
Provision for (benefit from) income taxes	$(65.5)	$81.2	$(200.8)
Net loss	$(77.2)	$(117.0)	$(630.2)

The decrease in Net Loss for the year ended December 31, 2018 as compared to 2017 was primarily attributed to increased sales across all of our products and the U.S. commercial launch of Palynziq, increased benefit from income taxes, partially offset by increased R&D expense for the expansion of our clinical programs and increased SG&A expense primarily due to the Palynziq U.S. commercial launch and European pre-launch activities, market preparation related to valoctocogene roxaparvovec and the continued expansion of marketing activities related to Brineura, which launched commercially in mid-2017. See “Results of Operations” below for additional information related to the Net Loss fluctuations presented above.

On January 1, 2018, we adopted Accounting Standards Codification (ASC) 606, Revenue from Contracts with Customers (ASC Topic 606) using the modified retrospective method applied to those contracts which were not completed as of January 1, 2018. Results for reporting periods beginning after January 1, 2018 are presented under ASC Topic 606, while prior period amounts are not adjusted and continue to be reported in accordance with our historic accounting under ASC 605, Revenue Recognition. See Note 4 to our accompanying Consolidated Financial Statements for additional information.

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Management's Discussion and Analysis of Financial Condition and Results of Operations (continued)

(In millions of U.S. Dollars, except as otherwise disclosed)

Our cash, cash equivalents and investments totaled $1.3 billion as of December 31, 2018, compared to $1.8 billion as of December 31, 2017. 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, cash equivalents or investments 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, Estimates and Judgments

In preparing our Consolidated Financial Statements in accordance with U.S. GAAP 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. On an ongoing basis, we evaluate our estimates and discuss our critical accounting policies and estimates with the Audit Committee of our Board of Directors. We base our estimates on historical experience and various other assumptions that we believe to be reasonable under the circumstances. Actual results could differ materially from these estimates under different assumptions or conditions.

While our significant accounting policies are more fully described in Note 3 to our accompanying Consolidated Financial Statements included in this Annual Report on Form 10-K, we believe the critical accounting policies below reflect the more significant judgments and estimates used in the preparation of our Consolidated Financial Statements.

- Revenue Recognition and Related Allowances
- Inventory
- Valuation of Goodwill and Acquired Intangible Assets
- Valuation of Contingent Consideration
- Income Taxes

Historically, our assumptions, judgments and estimates relative to our critical accounting policies have not differed materially from actual results.

Revenue Recognition and Related Allowances

Net Product Revenues – Upon adoption of ASC Topic 606, we recognize revenue when the customer obtains control of promised goods or services, in an amount that reflects the consideration which we expect to receive in exchange for those goods or services. For Aldurazyme revenues, 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. Under ASC Topic 606, we recognize our best estimate of the entire revenue that it expects to receive when the product is released and control is transferred to Genzyme. We record Aldurazyme net product revenues based on the estimated variable consideration payable when the product is sold through by Genzyme. Actual amounts of consideration ultimately received may differ from our

estimates. Differences between the estimated variable consideration to be received from Genzyme and actual payments received are not expected to be material. If actual results vary from our estimates, we will make adjustments, which would affect Net Product Revenues and earnings in the period such variances become known.

Prior to adoption of ASC Topic 606, for Aldurazyme revenues, we only recognized a portion of the tiered payment as product transfer revenue when the product was released to Genzyme because all of our performance obligations were fulfilled at that point, the prices were substantially fixed or determinable and title to, and risk of loss for, the product had transferred to Genzyme. The product transfer revenue only represented the fixed amount per unit of Aldurazyme that Genzyme was required to pay us if the product was unsold by Genzyme. The amount of product transfer revenue was eventually deducted from the calculated royalty recognized when the product was subsequently sold by Genzyme. We recorded the Aldurazyme revenues based on net sales information provided by Genzyme and recorded product transfer revenues based on the fulfillment of Genzyme purchase orders in accordance with the terms of the related agreements with Genzyme.

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Management's Discussion and Analysis of Financial Condition and Results of Operations (continued)

(In millions of U.S. Dollars, except as otherwise disclosed)

Revenue Related Allowances – We record product sales net of estimated mandatory and supplemental discounts to government payers, in addition to discounts to private payers, and other related charges. Rebates, cash discounts, and distributor fees represent the majority of our gross to net deductions and are recorded in the same period the related sales occur. Rebates include amounts paid to Medicaid, other government programs, certain managed care providers, as well as foreign government rebates. Rebates, cash discounts and distributor fees are estimates based on contractual arrangements or statutory obligations, which may vary by product and payer. Estimation requires evaluation of our historical experience, customer mix, current contractual and statutory obligations, specific known market events and trends and industry data. We evaluate our customer mix to estimate which sales will be subject to rebates and consider changes to government program guidelines that would impact the actual rebates and/or our estimates of which sales qualify for such rebates.

We update our estimates and assumptions each quarter based on actual historical experience and record any necessary adjustments to our reserves to reflect current information. We believe the methodologies that we use to estimate allowances are reasonable and appropriate given the facts and circumstances. However, actual results may differ significantly from our estimates.

The following table summarizes the consolidated activities and ending balances in our revenue related allowances:

Accrued rebates, cash discounts and distributor fees	Balance at Beginning of Year	Provision for Current Period Sales	Payments	Balance at End of Year
Year ended December 31, 2018	$ 51.8	$ 132.6	$ (123.4)	$ 61.0
Year ended December 31, 2017	43.4	108.5	(100.1)	51.8
Year ended December 31, 2016	$ 39.2	$ 81.2	$ (77.0)	$ 43.4

Inventory Produced Prior to Regulatory Approval

When future commercialization for a product candidate is probable and management expects to realize economic benefit in the future, we capitalize pre-launch inventory costs prior to regulatory approval. For inventories that are capitalized in preparation of product launch, management considers a number of factors, including the product candidate's current status in the regulatory approval process, results from the related pivotal clinical trial, results from meetings with relevant regulatory agencies prior to the filing of regulatory applications, historical experience, as well as potential impediments to the approval process such as product safety or efficacy, commercialization and market trends.

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 and consider the product candidate's stability data for all of the pre-approval production to date to determine whether there is adequate expected shelf life for the capitalized

pre-launch production costs. If the criteria for capitalizing inventory produced prior to regulatory approval are not met, we recognize such costs as R&D expense in the period incurred. As of December 31, 2018, there was no pre-launch inventory on our Consolidated Balance Sheets.

Valuation of Goodwill and Acquired Intangible Assets

We have recorded goodwill and acquired intangible assets primarily related to in-process research and development (IPR&D) projects through acquisitions accounted for as business combinations. When identifiable intangible assets, including IPR&D, are acquired, we determine the fair value of these assets as of the acquisition date. Discounted cash flow models are typically used in these valuations if quoted market prices are not available, and the models require significant estimates and assumptions including but not limited to:

- estimating the time and resources needed to complete the development and approval of product candidate;
- estimating future cash flows from product sales;
- developing appropriate probability of success rates for unapproved product candidates considering their stages of development;
- projecting timing of regulatory approval; and
- risks related to the viability of and potential alternative treatments in any future target markets.

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Management's Discussion and Analysis of Financial Condition and Results of Operations (continued)

(In millions of U.S. Dollars, except as otherwise disclosed)

Goodwill represents the excess of purchase price over fair value of net assets acquired in a business combination accounted for by the acquisition method of accounting and is not amortized, but subject to impairment testing. We review our goodwill and indefinite lived intangible assets for impairment annually in the fourth quarter, or more frequently if warranted by events or changes in circumstances indicate that the carrying amount may not be recoverable.

We assess goodwill impairment by comparing the fair value of our single reporting unit with its carrying amount. If the carrying value of the reporting unit exceeds its fair value, an impairment loss equal to the difference will be recorded.

We assess impairment of indefinite-lived intangible assets first by performing a qualitative assessment. If the qualitative assessment indicates that it is more likely than not that the fair value of our indefinite-lived intangible assets is less than its carrying amount, then we will perform a quantitative assessment and record an impairment loss. We assess definite-lived intangible assets for recoverability when there is an indication of impairment by comparing the estimated undiscounted future cash flows expected to result from the use of the asset or asset group and its eventual disposition to the carrying amount of the asset or asset group. Any excess of the carrying value of the asset or asset group over its estimated fair value is recognized as an impairment loss.

Valuation of Contingent Consideration

Significant estimates and judgments are required in determining the acquisition fair value of any contingent obligations incurred in connection with an acquisition. We estimate the fair value of contingent consideration utilizing a probability-based income approach inclusive of an estimated discount rate. Each period we reassess the fair value of the contingent consideration 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. Changes in the fair value of the contingent consideration can result from changes to one or multiple inputs including the estimated probability 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. Accordingly, subsequent changes in the underlying facts and circumstances could result in changes to our estimates and assumptions, which could have a material impact on the estimated future fair values of contingent consideration.

We believe the fair value used to record contingent consideration incurred in connection with business combinations is based on reasonable estimates and assumptions given the facts and circumstances as of the related valuation date.

Income Taxes

We calculate and provide for income taxes in each of the tax jurisdictions in which we operate. Our Consolidated Balance Sheets reflect net deferred tax assets and liabilities, which are measured using enacted tax rates. The net 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. We utilize financial projections to support our net deferred tax assets, which contain significant assumptions and estimates of future operations. If such assumptions were to differ significantly, it may have a material impact on our ability to realize our deferred tax assets. Changes in our valuation allowance will result in a change to tax expense.

We establish liabilities or reduce assets for certain tax position when we believe certain tax position are not more likely than not to be sustained if challenged. Each quarter, we evaluate these uncertain tax position and adjust the related tax assets and liabilities in light of changing facts and circumstances.

We are subject to income taxes in the U.S. and various foreign jurisdictions, including Ireland. Due to economic and political conditions, various countries are actively considering changes to existing tax laws. We cannot predict the form or timing of potential legislative changes that could have a material adverse impact on our results of operations. In addition, significant judgment is required in determining our worldwide provision for income taxes. Management is not aware of any potential changes that would have a material effect on our Consolidated Financial Statements.

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Management's Discussion and Analysis of Financial Condition and Results of Operations (continued)

(In millions of U.S. Dollars, except as otherwise disclosed)

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, 2018 was $77.2 million, compared to net losses of $117.0 million and $630.2 million for the years ended December 31, 2017 and 2016, respectively. The changes in Net Loss were primarily a result of the following:

	Years Ended December 31,				
	2018	2017	2016	2018 vs. 2017	2017 vs. 2016
Total revenues	$1,491.2	$1,313.6	$1,116.9	$ 177.6	$ 196.7
Cost of sales	315.3	241.8	209.6	73.5	32.2
R&D expense	696.3	610.8	661.9	85.5	(51.1)
SG&A expense	604.4	554.3	476.6	50.1	77.7
Intangible asset amortization and contingent consideration	48.8	46.5	(27.0)	2.3	73.5
Impairment of intangible assets	—	—	599.1	—	(599.1)
Gain on sale of intangible asset	(50.0)	(125.0)	—	75.0	(125.0)
Other, net	(19.1)	(21.0)	(27.7)	1.9	6.7
Provision for (benefit from) income taxes	(65.5)	81.2	(200.8)	(146.7)	282.0
Net loss	$(77.2)	$(117.0)	$(630.2)	$ 39.8	$ 513.2

Net Product Revenues

Net Product Revenues consisted of the following:

	Years Ended December 31,				
	2018	2017	2016	2018 vs. 2017	2017 vs. 2016
Aldurazyme	$135.1	$90.0	$93.8	$ 45.1	$ (3.8)
Brineura	39.9	8.6	—	31.3	8.6

Firdapse	21.7	18.8	18.0	2.9	0.8
Kuvan	433.6	407.5	348.0	26.1	59.5
Naglazyme	345.9	332.2	296.5	13.7	35.7
Palynziq	12.2	—	—	12.2	—
Vimizim	482.0	413.3	354.1	68.7	59.2
Total net product revenues	$1,470.4	$1,270.4	$1,110.4	$ 200.0	$ 160.0

The following is additional discussion of our Net Product Revenue results for our major products:

- Aldurazyme – The increase in 2018 compared to 2017 is attributable to an increase in sales volume and the adoption of ASC Topic 606, which contributed $20.2 million to the increase. Although Genzyme sells Aldurazyme worldwide, the net product revenues earned by us on Genzyme's net sales are denominated in USD.

The decrease in 2017 compared to 2016 was primarily attributable to the decreases in shipments to Genzyme, offset in part by the increase in Aldurazyme revenue reported by Genzyme. Aldurazyme revenues reported by Genzyme totaled $233.8 million and $223.3 million in 2017 and 2016, respectively.

See Note 4 to our accompanying Consolidated Financial Statements for additional information on the impact of ASC Topic 606 on our 2018 results.

- Brineura – The increase in 2018 compared to 2017 was primarily attributable to new patients initiating therapy as the product was commercially launched in mid-2017.

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Management's Discussion and Analysis of Financial Condition and Results of Operations (continued)

(In millions of U.S. Dollars, except as otherwise disclosed)

- Kuvan – The increase in 2018 compared to 2017 was primarily attributable to an increase in patients initiating therapy in North America. The increase in 2017 compared to 2016 was due to an increase in patients initiating therapy in the U.S. and new patients in the ex-North American territories to which we acquired in 2016.
- Naglazyme – The increase in 2018 compared to 2017 was primarily attributable to new patients initiating therapy in Turkey and North America and government ordering patterns in the Middle East, partially offset by a decrease due to the impact of government ordering patterns from certain Latin American countries. The increase in 2017 compared to 2016 was due to new patients initiating therapy, the positive impact of foreign currency exchange rates and the ordering patterns of central government orders from Latin America and Europe.
- Palynziq – The increase in 2018 compared to 2017 was primarily attributable to the conversion of clinical patients to commercial Palynziq in the U.S. in 2018 following the commercial launch of Palynziq in July 2018.
- Vimizim – The increase in 2018 compared to 2017 and in 2017 compared to 2016 was primarily attributable to new patients initiating therapy and government ordering patterns.

In certain countries, such as in Latin America, governments place large periodic orders for Naglazyme and Vimizim. The ordering patterns of these large government orders can be inconsistent and can create significant quarter to quarter variation in our revenues.

We face exposure to movements in foreign currency exchange rates, primarily the Euro. We use foreign currency exchange contracts to hedge a percentage of our foreign currency exposure. The following table shows our Net Product Revenues denominated in USD and foreign currencies:

	Years Ended December 31,				
	2018	2017	2016	2018 vs. 2017	2017 vs. 2016
Sales denominated in USD	$891.7	$748.5	$643.2	$ 143.2	$ 105.3
Sales denominated in foreign currencies	578.7	521.9	467.2	56.8	54.7
Total net product revenues	$1,470.4	$1,270.4	$1,110.4	$ 200.0	$ 160.0

The net impact of foreign currency exchange rates on product sales denominated in currencies other than USD during 2018 was negative by $0.7 million, which was primarily driven by the Brazilian Real. During 2017, the net impact of foreign currency exchange rates was positive by $5.5 million, which was primarily driven by the Brazilian Real and the Euro. During 2016, the net impact of foreign currency exchange rates was negative by $3.6 million, which was primarily driven by the British Pound. See "Quantitative and Qualitative Disclosures about Market Risk" in Part II, Item 7A of this Annual Report on Form 10-K for information on currency exchange rate risk related to our revenues.

Royalty and Other Revenues

Royalty and Other Revenues include royalties on net sales of products to licensees or sublicensees, collaborative agreement revenues and rental income associated with the tenants in our San Rafael, California facility.

	Years Ended December 31,				
	2018	2017	2016	2018 vs. 2017	2017 vs. 2016
Royalty and other revenues	$20.9	$43.2	$6.5	$ (22.3)	$ 36.7

In 2017 we recognized $31.5 million net upfront license revenue from Sarepta Therapeutics (Sarepta) and $3.8 million in royalty revenue earned on Sarepta net sales during 2017. We expect to continue to earn royalties from third parties in the future.

Cost of Sales and Product Gross Margin

Cost of Sales includes raw materials, personnel and facility and other costs associated with manufacturing our commercial products. These costs include production materials, production costs at our manufacturing

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Management's Discussion and Analysis of Financial Condition and Results of Operations (continued)

(In millions of U.S. Dollars, except as otherwise disclosed)

facilities, third-party manufacturing costs, and internal and external final formulation and packaging costs. Cost of Sales also includes royalties payable to third parties based on sales of our products.

The following table summarizes our cost of sales and product gross margin:

	Years Ended December 31,				
	2018	2017	2016	2018 vs. 2017	2017 vs. 2016
Total net product revenues	$1,470.4	$1,270.4	$1,110.4	$ 200.0	$ 160.0
Cost of sales	315.3	241.8	209.6	73.5	32.2
Product gross margin	79 %	81 %	81 %	(2 %)	0 %

The 2018 increase in Cost of Sales was primarily attributable to increased Vimizim manufacturing costs and increased sales volume for Aldurazyme. Gross margin decreased in 2018 compared to 2017 primarily due to the impact of adopting ASC Topic 606 on Aldurazyme net product revenues and increased Vimizim and Naglazyme manufacturing costs. Under ASC 606, which we adopted on January 1, 2018, we recognize the full amount of expected Aldurazyme revenue in the same period as related cost of sales. Prior to adoption Aldurazyme gross margins fluctuated depending on the mix of product transfer revenue and variable consideration recognized in the period. Our product gross margin for the year ended December 31, 2017 remained flat compared to 2016. We expect total product gross margin to remain near 80 percent over the next twelve months.

Research and Development

R&D expense includes costs associated with the research and development of product candidates and post-marketing research commitments related to our approved products. R&D expense primarily includes preclinical and clinical studies, personnel and raw materials costs associated with manufacturing clinical product, quality control and assurance, other R&D activities, facilities and regulatory costs.

We manage our R&D expense by identifying the R&D activities we anticipate will be performed during a given period and then prioritizing efforts based on scientific data, probability of successful development, market potential, available human and capital resources and other similar considerations. We continually review our product pipeline and the development status of product candidates and, as necessary, reallocate resources among the research and development portfolio that we believe will best support the future growth of our business.

We continuously evaluate the recoverability of costs associated with pre-launch or pre-qualification manufacturing activities, and if it is determined that recoverability is highly likely and therefore future revenues are expected, the costs subsequently incurred related to pre-launch or pre-qualification manufacturing activities for purposes of commercial sales will likely be capitalized. When regulatory approval and the likelihood of future revenues for a product candidate are less certain, the related manufacturing costs are expensed as R&D expenses.

R&D expense increased to $696.3 million for the year ended December 31, 2018, compared to $610.8 million and $661.9 million for the years ended December 31, 2017 and 2016, respectively. R&D expense consisted of the following:

	Years Ended December 31,				
	2018	2017	2016	2018 vs. 2017	2017 vs. 2016
Palynziq	$94.8	$122.1	$88.6	$ (27.3)	$ 33.5
Valoctocogene roxaparvovec	161.7	118.2	58.9	43.5	59.3
Vosoritide	89.3	55.1	55.8	34.2	(0.7)
Tralesinidase alfa	82.2	56.0	46.1	26.2	9.9
Brineura	46.9	52.0	77.2	(5.1)	(25.2)
Other approved products	70.6	72.1	65.0	(1.5)	7.1
Early stage programs	68.2	65.4	55.9	2.8	9.5
Other	82.6	69.9	214.4	12.7	(144.5)
Total	$696.3	$610.8	$661.9	$ 85.5	$ (51.1)

2018 compared to 2017

The increase in R&D expense primarily comprised the following:

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Management's Discussion and Analysis of Financial Condition and Results of Operations (continued)

(In millions of U.S. Dollars, except as otherwise disclosed)

- an increase in costs for clinical studies related to our valoctocogene roxaparvovec and vosoritide product candidates;
- an increase in costs of the manufacturing of our tralesinidase alfa clinical product; and
- an increase in costs related to other R&D expenses primarily related to activity for our preclinical programs;
- partially offset by a decrease in costs related to Palynziq, for which capitalization of manufacturing costs began in the second quarter of 2018 following FDA approval; and
- a decrease in clinical manufacturing costs related to Brineura.

During 2019, we expect our R&D spending to increase over 2018 levels primarily due to our valoctocogene roxaparvovec, vosoritide and other programs progressing in their development. We also expect increased spending on preclinical activities for our early development stage programs and we expect to continue incurring R&D expense for the foreseeable future due to long-term clinical activities related to post-approval regulatory commitments for our approved products.

2017 compared to 2016

The decrease in R&D expense primarily comprised the following:

- a decrease in costs related to other R&D expense primarily related to R&D spending in 2016 on the Kyndrisa, other exon-skipping, and reveglucosidase alfa development programs, all of which were terminated in 2016; and
- a decrease in costs related to Brineura, which was approved for marketing in the U.S. and EU in June 2017 and July 2017, respectively. During the second quarter of 2016, we evaluated the facts and circumstances supporting recoverability of pre-launch manufacturing costs related to Brineura and concluded that recoverability was probable, resulting in the decrease in R&D costs as pre-launch manufacturing costs began to be capitalized during 2016. Prior to the second quarter of 2016, Brineura pre-launch manufacturing costs incurred were expensed to R&D expense as significant uncertainty existed over the recoverability of the costs at the time;
- partially offset by an increase in clinical trial activities related to tralesinidase alfa, Palynziq and valoctocogene roxaparvovec product candidates; and
- an increase in pre-clinical activity for our early stage programs.

Selling, General and Administrative

Sales and Marketing (S&M) expense primarily consisted of employee-related expenses for our sales group, brand marketing, patient support groups and pre-commercialization expenses related to our product candidates. General and administrative (G&A) expense primarily consisted of corporate support and other administrative expenses, including employee-related expenses.

SG&A expense increased to $604.4 million for the year ended December 31, 2018, compared to $554.3 million and $476.6 million for the years ended December 31, 2017 and 2016, respectively. SG&A expenses consisted of the following:

	Years Ended December 31,				
	2018	2017	2016	2018 vs. 2017	2017 vs. 2016
S&M expense	$324.2	$291.5	$252.9	$ 32.7	$ 38.6
G&A expense	280.2	262.8	223.7	17.4	39.1
Total SG&A expense	$604.4	$554.3	$476.6	$ 50.1	$ 77.7

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Management's Discussion and Analysis of Financial Condition and Results of Operations (continued)

(In millions of U.S. Dollars, except as otherwise disclosed)

Components of S&M expense were as follows:

	Years Ended December 31,				
S&M expense by product:	2018	2017	2016	2018 vs. 2017	2017 vs. 2016
Brineura	$44.2	$31.6	$15.4	$12.6	$ 16.2
Palynziq	29.4	11.5	3.3	17.9	8.2
Other approved products	208.8	220.8	185.5	(12.0)	35.3
Other	41.8	27.6	48.7	14.2	(21.1)
Total S&M expense	$324.2	$291.5	$252.9	$32.7	$ 38.6

2018 compared to 2017

The increase in S&M expense was primarily a result of the following:

- the Palynziq U.S. commercial launch and European pre-launch activities;
- the continued expansion of marketing activities related to Brineura; and
- pre-launch activities related to our valoctocogene roxaparvovec product candidate;
- partially offset by a decrease in marketing activities related to our mature products as resources were shifted toward activities noted above.

The increase in G&A expense was primarily due to increased personnel-related costs mainly due to increased headcount to support our growth and other administrative-related costs.

We expect SG&A expense to increase in future periods as a result of the continued commercial launch of Palynziq, pre-commercialization efforts related to product candidates, and the continued international expansion of Vimizim and the PKU franchise.

2017 compared to 2016

The increase in S&M expense was primarily a result of the following:

- an increase in costs related to Kuvan and Vimizim due to continued worldwide expansion of commercial activities; and
- an increase in costs related to Brineura primarily due to marketing expense related to the commercial launch of Brineura in 2017;
- partially offset by a decrease in other S&M expenses primarily due to the decrease in S&M activities related to Kyndrisa and other terminated programs.

The increase in G&A expense was primarily due to increased personnel-related costs mainly due to increased headcount.

Intangible Asset Amortization and Contingent Consideration, Impairment of Intangible Assets and Gain on Sale of Intangible Assets

Changes during the periods presented for Intangible Asset Amortization and Contingent Consideration, Impairment of Intangible Assets, and Gain on Sale of Intangible Assets were as follows:

	Years Ended December 31,				
	2018	2017	2016	2018 vs. 2017	2017 vs. 2016
Increases (decreases) in the fair value of contingent consideration	$18.5	$10.3	$(57.2)	$ 8.2	$ 67.5
Amortization of intangible assets	30.3	36.2	30.2	(5.9)	6.0
Total intangible asset amortization and contingent consideration	$48.8	$46.5	$(27.0)	$ 2.3	$ 73.5
Impairment of intangible assets	$—	$—	$599.1	$ —	$ (599.1)
Gain on sale of intangible assets	$(50.0)	$(125.0)	$—	$ 75.0	$ (125.0)

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Management's Discussion and Analysis of Financial Condition and Results of Operations (continued)

(In millions of U.S. Dollars, except as otherwise disclosed)

2018 compared to 2017

Fair value of contingent consideration – the changes in the fair value of the contingent consideration in 2018 were attributable to changes in the estimated probability of achieving development milestones based on the current status of the related development programs, which was primarily related to the continued progress of the Palynziq program to support the filing and progress toward approval of the European MAA.

Amortization of intangible assets – the decrease in 2018 was due to a 2017 impairment of IPR&D assets that we had acquired from Zacharon Pharmaceuticals, Inc. (Zacharon), as the related development program was terminated. It is our policy to report impairment charges that are not material as a component of Intangible Asset Amortization and Contingent Consideration on our Consolidated Statements of Operations.

Impairment of Intangible Assets –no material impairment charges were recorded in 2018 or 2017. See Note 6 to our accompanying Consolidated Financial Statements for additional information regarding our Intangible Assets.

Gain on Sale of Intangible Assets – we recognized a gain of $50.0 million in the year ended December 31, 2018 due to a third party's achievement of development and regulatory approval milestones related to a previously sold intangible asset. See Note 6 to the accompanying Consolidated Financial Statements for additional information.

2017 compared to 2016

Fair value of contingent consideration – The changes in fair value of contingent consideration in 2017 was primarily attributed to the following:

- the continued progress of the Palynziq developmental program; and
- the progress of the talazoparib program being developed by Pfizer Inc.;
- partially offset by the reversal in 2017 of the fair value of the Firdapse FDA approval milestone due to the reduction of the estimated probability of achieving such milestone prior to its expiration date; and
- the termination of the Kyndrisa and reveglucosidase alfa development programs in 2016 resulted in the reversal of the fair value of the remaining contingent consideration related to the Prosensa Holding N.V. and Zystor Therapeutics, Inc. acquisitions, respectively.

Amortization of intangible assets – the increase in amortization of intangible assets during 2017 was primarily attributable to the impairment of IPR&D assets we acquired from Zacharon

Impairment of Intangible Assets – no material impairment charges were recorded in 2017. In 2016, we recorded an impairment charge of $599.1 million related to the Kyndrisa and other exon and reveglucosidase alfa IPR&D assets based on the termination of the internal development of the respective programs.

Gain on Sale of Intangible Assets – In December 2017, we sold the Priority Review Voucher (PRV) that we received in connection with the FDA approval of Brineura. In exchange for the PRV, we received lump sum payment of $125.0 million, which was recognized as a gain on the sale of intangible assets.

Interest Expense

We incur interest expense on our convertible debt. Interest expense consisted of the following:

	Years Ended December 31,				
	2018	2017	2016	2018 vs. 2017	2017 vs. 2016
Coupon interest	$12.5	$10.4	$9.6	$ 2.1	$ 0.8
Amortization of debt issuance costs	3.6	3.7	3.4	(0.1)	0.3
Accretion of discount on convertible notes	27.6	28.6	26.5	(1.0)	2.1
Total interest expense	$43.7	$42.7	$39.5	$ 1.0	$ 3.2

The increased interest expense in 2018 compared to 2017 was primarily due to the issuance of our 0.599% senior subordinated convertible notes due in 2024 (the 2024 Notes) in August 2017, partially offset by the maturity of our 0.75% senior subordinated convertible notes, which matured on October 15, 2018 (the 2018 Notes) in October 2018. The increased interest expense in 2017 compared to 2016 was attributable to the

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Management's Discussion and Analysis of Financial Condition and Results of Operations (continued)

(In millions of U.S. Dollars, except as otherwise disclosed)

issuance of the 2024 Notes. We expect Interest Expense to decrease moderately over the next 12 months due to the maturity of the 2018 Notes. See Note 12 to our accompanying Consolidated Financial Statements for additional information regarding our debt.

Interest Income

We invest our cash equivalents and investments in U.S. government securities and other high credit quality debt securities in order to limit default and market risk. Changes during the periods presented for impairment of intangible assets, gain on sale of intangible assets and interest income were as follows:

	Years Ended December 31,				
	2018	2017	2016	2018 vs. 2017	2017 vs. 2016
Interest income	$22.8	$14.9	$7.5	$ 7.9	$ 7.4

The increase in interest income during 2018 compared to 2017 was primarily due to a higher investment balance during the period and higher average interest rate on investments. The increase in interest income during 2017 compared to 2016 was primarily due to a higher investment balance, which increased due to the investment of the net proceeds of $481.7 million from our August 2017 issuance of the 2024 Notes and higher average interest rate on investments. We expect Interest Income to decrease moderately over the next 12 months due to the repayment of the 2018 Notes.

Provision for (Benefit from) Income Taxes

On December 22, 2017, the 2017 Tax Act was signed into law. The new law has resulted in significant changes to the U.S. corporate income tax system. These changes include a federal statutory rate reduction from 35% to 21% and the elimination or reduction of certain domestic deductions and credits, including a 50% reduction in the orphan drug credit. The 2017 Tax Act changed U.S. international taxation from a worldwide basis to a modified territorial system that includes base erosion prevention measures on foreign earnings. This resulted in our foreign subsidiaries being subject to U.S. taxation in the future. These changes were effective in 2018.

We recognized an income tax benefit of $65.5 million, an income tax expense of $81.2 million and an income tax benefit of $200.8 million in the years ended December 31, 2018, 2017 and 2016, respectively. Changes to tax laws and tax rates are required to be accounted for in the period of the enactment, therefore our 2017 tax provision included the impact of the 2017 Tax Act. Provision for (benefit from) income taxes for 2018, 2017 and 2016 consisted of state, federal and foreign current tax expense which was offset by tax benefits related to stock option exercises and deferred tax benefits from federal orphan drug credits, federal R&D credits and California R&D credits. The provision for (benefit from) income taxes for the years ended December 31, 2018, 2017 and 2016 were further impacted by the

following items:

- 2017 included a provisional expense of $42.3 million related to the 2017 Tax Act primarily consisting of $33.1 million for the re-measurement of the net deferred tax assets at the lower enacted corporate tax rate and $9.2 million related to the new limitations on tax deductible compensation. Our deferred tax assets and liabilities are measured at the enacted tax rate expected to apply when these temporary differences are expected to be realized or settled. Additionally, we established a $41.4 million valuation allowance on state tax credits as management assessed the impact of the 2017 Tax Act on our financial projections and concluded that it is more likely than not that these state tax credits will not be utilized in the foreseeable future because these credits do not expire and we project that we will be generating more credits than we will utilize on an annual basis. The 2017 Tax Act also includes a one-time mandatory deemed repatriation toll tax on accumulated earnings of our foreign subsidiaries that did not impact us due to a net deficit in these foreign subsidiaries.

In December 2017, the Securities and Exchange Commission staff issued Staff Accounting Bulletin No. 118, Income Tax Accounting Implications of the Tax Cuts and Jobs Act (SAB 118), which allowed us to record provisional amounts during a measurement period not to extend beyond one year of the enactment date. As a result, we previously provided a provisional estimate of the effect of the 2017 Tax Act in our financial statements. In the fourth quarter of 2018, we completed our analysis to determine the effect of the 2017 Tax Act and recorded immaterial adjustments as of December 31, 2018. We have elected to account for Global Intangible Low-taxed Income (GILTI) as a current period expense when incurred.

- 2016 included a deferred tax benefit of $143.5 million associated with the GAAP impairment of the Kyndrisa IPR&D.

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(In millions of U.S. Dollars, except as otherwise disclosed)

The consolidated GAAP net loss includes all of our foreign subsidiaries. In accordance with Accounting Standards Codification Topic 740, Income Taxes, we calculate our provision for (benefit from) income taxes on an entity-by-entity and jurisdiction-by-jurisdiction basis as adjusted for differences between book-basis income and tax-basis income, which results in certain foreign entities being profitable and incurring foreign current income tax expense. Certain foreign entities incur significant amounts of R&D expense that results in significant losses that more than offset the income reported by the profitable foreign entities on a consolidated basis. The majority of these material R&D losses are in foreign jurisdictions that do not have net operating loss carryforward provisions that result in deferred tax assets, which results in an effective tax rate of 0% on approximately $142.0 million of foreign net losses during 2018. For the year ended December 31, 2018, our Dutch operations had GAAP income of $36.9 million. For the year ended December 31, 2018, other foreign operations generated GAAP income of approximately $91.1 million with an effective tax rate of approximately 10.6%.

Financial Position, Liquidity and Capital Resources

As of December 31, 2018, we had $1.3 billion in cash, cash equivalents, and investments. We expect to fund our operations with our net product revenues from our commercial products, cash, cash equivalents and investments, supplemented as may become necessary by proceeds from equity or debt financings and loans, or collaborative agreements with corporate partners. We may require additional financing to fund the repayment of our convertible debt, 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 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 timing and mix of our funding options could change depending on many factors, including how much we elect to spend on our development programs, potential licenses and acquisitions of complementary technologies, products and companies or if we elect to settle all or a portion of our convertible debt in cash.

In managing our liquidity needs in the U.S., we do not rely on unrepatriated earnings as a source of funds and we have not provided for U.S. federal or state income taxes on these undistributed foreign earnings. We do not record U.S. tax expense on the undistributed earnings of our controlled foreign subsidiaries as these earnings are intended to be indefinitely reinvested offshore. Currently, we are not subject to the repatriation tax on foreign earnings due to the net deficit in these foreign jurisdictions.

As of December 31, 2018, $156.4 million of our $1.3 billion balance of cash, cash equivalents and investments was held in foreign subsidiaries, a significant portion of which is required to fund the liquidity needs of these foreign subsidiaries. See Note 14 to our accompanying Consolidated Financial Statements for additional discussion regarding income taxes.

We are mindful that conditions in the current macroeconomic environment could affect our ability to achieve our goals. We sell our products in countries that face economic volatility and weakness. Although we have historically collected receivables from customers in such countries, sustained weakness or further deterioration of the local economies and currencies may cause customers in those countries to be unable to pay for our products. We will

continue to monitor these conditions and will attempt to adjust our business processes, as appropriate, to mitigate macroeconomic risks to our business.

Our liquidity and capital resources as of December 31 were as follows:

	2018	2017	2016	2018 vs. 2017	2017 vs. 2016
Cash and cash equivalents	$494.0	$598.0	$408.3	$ (104.0)	$ 189.7
Short-term investments	590.3	797.9	381.3	(207.6)	416.6
Long-term investments	235.9	385.8	572.8	(149.9)	(187.0)
Cash, cash equivalents and investments	$1,320.2	$1,781.7	$1,362.4	$ (461.5)	$ 419.3
Convertible debt, net	$830.4	$1,174.5	$683.2	$ (344.1)	$ 491.3

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Management's Discussion and Analysis of Financial Condition and Results of Operations (continued)

(In millions of U.S. Dollars, except as otherwise disclosed)

Our cash flows for each of the years ended December 31 are summarized as follows:

	2018	2017	2016	2018 vs. 2017	2017 vs. 2016
Cash & cash equivalents at the beginning of the period	$598.0	$408.3	$397.0	$ 189.7	$ 11.3
Net cash provided by (used in) operating activities	20.2	(8.8)	(227.8)	29.0	219.0
Net cash provided by (used in) investing activities	264.4	(305.5)	(484.0)	569.9	178.5
Net cash (used in) provided by financing activities	(388.0)	507.1	727.1	(895.1)	(220.0)
Foreign exchange impact	(0.6)	(3.1)	(4.0)	2.5	0.9
Cash & cash equivalents at the end of the period	$494.0	$598.0	$408.3	$ (104.0)	$ 189.7
Short-term and long-term investments	826.2	1,183.7	954.1	(357.5)	229.6
Cash, cash equivalents and investments	$1,320.2	$1,781.7	$1,362.4	$ (461.5)	$ 419.3

Cash Provided by (Used in) Operating Activities

Cash provided by operating activities for the year ended December 31, 2018 was $20.2 million, compared to cash used in operating activities of $8.8 million for the year ended December 31, 2017. Cash provided by operating activities was primarily attributed to the timing of cash receipts from customers and payments to vendors, partially offset by higher inventory levels. The increase in accounts receivable is primarily due to the increase in Genzyme unbilled receivables due to the adoption of ASC Topic 606.

Cash used in operating activities for the year ended December 31, 2017 was $8.8 million, compared to cash used in operating activities of $227.8 million for the year ended December 31, 2016. Cash used in operating activities was primarily attributed to the timing of cash receipts from customers and payments to vendors, partially offset by higher inventory levels.

Cash Provided by (Used in) Investing Activities

Net cash provided by investing activities for the year ended December 31, 2018 was $264.4 million, compared to net cash used in investing activities of $305.5 million for the year ended December 31, 2017. Net cash provided by investing activities for the year ended December 31, 2018 was primarily attributable to $359.0 million in net maturities of available-for-sale debt securities and $50.0 million in milestone payment receipts related to a previously sold intangible asset, partially offset by $144.6 million in purchases of property, plant and equipment. We expect to continue to make significant capital investments in our manufacturing facilities and our corporate headquarters to accommodate anticipated headcount growth.

Net cash used in investing activities for the year ended December 31, 2017 was $305.5 million, compared to net cash used in investing activities of $484.0 million for the year ended December 31, 2016. Net cash used in investing activities for the year ended December 31, 2017 was primarily attributable to $229.5 million in net purchases of available-for-sale debt securities and $199.2 million in purchases of property, plant and equipment, partially offset by $125.0 million in milestone payment receipts related to a previously sold intangible asset.

Cash (Used in) Provided by Financing Activities

Net cash used in financing activities for the year ended December 31, 2018 was $388.0 million, compared to net cash provided by financing activities of $507.1 million for the year ended December 31, 2017. Net cash used in financing activities for the year ended December 31, 2018 was primarily related to the $375.0 million settlement of the 2018 Notes, which matured in October 2018, partially offset by $31.6 million of net proceeds from issuances under our equity incentive plans.

Net cash provided by financing activities for the year ended December 31, 2017 was $507.1 million, compared to net cash provided by financing activities of $727.1 million for the year ended December 31, 2016. Net cash provided by financing activities for the year ended December 31, 2017 was primarily attributable to $481.7 million of net proceeds from the issuance of the 2024 Notes, issued in August 2017, and $27.4 million of net proceeds from issuances under our equity incentive plans.

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Management's Discussion and Analysis of Financial Condition and Results of Operations (continued)

(In millions of U.S. Dollars, except as otherwise disclosed)

Other Information

Our $870.0 million (undiscounted) of total convertible debt as of December 31, 2018 will impact our liquidity due to the semi-annual cash interest payments. As of December 31, 2018, our indebtedness consisted primarily of our 1.50% senior subordinated convertible notes due in 2020 (the 2020 Notes) and the 2024 Notes (together with the 2020 Notes, the Notes), which, if not converted, will be required to be repaid in cash at maturity in 2020 and 2024, respectively. See Note 12 to our accompanying Consolidated Financial Statements for additional discussion.

Our 2018 Notes matured in October 2018 and were settled with a combination of cash and shares of our common stock, consisting of approximately $375.0 million in cash and 190,220 in shares. The shares issued represented the value of the 2018 Notes in excess of the conversion price of $94.15, as measured over a 25-day averaging period. The cash payment was comprised of the principal, the value of fractional shares and the value of unconverted 2018 Notes. In October 2018, pursuant to a capped call transaction, which was entered into concurrently with the issuance of the 2018 Notes, we received from the capped call counterparties 95,127 shares of our common stock, which was accounted for as treasury shares and subsequently retired. No gain or loss was incurred upon the extinguishment of the 2018 Notes.

In the event the conditional conversion feature of the 2020 Notes is triggered, holders of the 2020 Notes will be entitled to convert the 2020 Notes at any time during specified periods at their option. In addition, the 2020 Notes will be freely convertible on or after July 15, 2020. We intend to use the remaining balance of the net proceeds we received from the issuance of the 2024 Notes to repay, repurchase or settle in cash some or all of the 2020 Notes. We may elect to settle conversions of the 2020 Notes in cash, in whole or in part, which could further affect our liquidity. While we could seek to obtain additional 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. Even if holders of the 2020 Notes do not elect to convert their 2020 Notes, we could be required under applicable accounting rules to reclassify all or a portion of the outstanding principal of such Notes as a current liability rather than long-term liability (for example, when there are twelve months or less remaining until maturity), which would result in a material reduction of our net working capital.

In August 2017, we completed an offering of $495.0 million in aggregate principal amount of the 2024 Notes, which resulted in net proceeds of $481.7 million, after deducting commissions and offering expenses. In August 2016, we sold 7.5 million shares of our common stock at a price of $96.00 per share in an underwritten public offering pursuant to an effective registration statement previously filed with the SEC. We received net proceeds of approximately $712.9 million from this public offering after accounting for the underwriting discount and offering costs.

In October 2018, we entered into an unsecured revolving credit facility of up to $200.0 million (the 2018 Credit Facility) and terminated the credit facility that we entered into in November 2016, which provided for up to $100.0 million in revolving loans (the 2016 Credit Facility). The 2018 Credit Facility includes a letter of credit subfacility and a swingline loan subfacility and is also intended to finance ongoing working capital needs and for other general corporate purposes. Borrowings under the 2018 Credit Facility bear interest, at our option, at a rate equal to either (a) the LIBOR rate (except that if LIBOR is less than zero it shall be deemed to be zero for purposes of the 2018 Credit

Facility), or LIBOR successor rate, plus an applicable margin ranging from 1.00% to 1.95% per annum, based upon our net leverage ratio and EBITDA for each of the two most recently ended four-quarter measurement periods, or (b) the Base Rate, generally the prime lending rate, plus an applicable margin ranging from 0.00% to 0.95%, based upon our net leverage ratio and EBITDA for each of the two most recently ended four-quarter measurement periods. Commitment fees payable on the undrawn amount range from 0.15% to 0.35% per annum based upon our net leverage ratio and EBITDA for each of the two most recently ended four-quarter measurement periods. Our obligations under the Credit Facility are guaranteed by our direct subsidiary, California Corporate Center Acquisition LLC, and such obligations may in the future be guaranteed from time to time by certain other material domestic subsidiaries. The 2018 Credit Facility matures on October 19, 2021 at which time all outstanding amounts become due and payable, except that if at least $100.0 million aggregate principal amount of the 2020 Notes remain outstanding on August 1, 2020 and certain other conditions have not been met, we may be required to repay all amounts borrowed under the 2018 Credit Facility on August 1, 2020. We incurred approximately $1.0 million of issuance costs, which will be amortized to Interest expense over the term of the 2018 Credit Facility. We incurred no gain or loss upon the termination of the 2016 Credit facility. The 2018 Credit Facility contains financial covenants requiring us to maintain a minimum interest coverage ratio and a minimum liquidity requirement. See Note 12 to our accompanying Consolidated Financial Statements for additional discussion.

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Management's Discussion and Analysis of Financial Condition and Results of Operations (continued)

(In millions of U.S. Dollars, except as otherwise disclosed)

Funding Commitments

We cannot estimate with certainty the cost to complete any of our product development programs. Additionally, except as disclosed under "Overview" above, we cannot precisely estimate the time to complete any of our product development programs or when we expect to receive net cash inflows from any of our product development programs. Please see "Risk Factors" included in Part I, Item 1A of this Annual Report on Form 10-K, for a discussion of the reasons we are unable to estimate such information, and in particular the following risk factors:

•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;
•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;
•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.
•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.
Our investment in our product development programs and continued development of our existing commercial products has a major impact on our operating performance. Our R&D expenses for the period since inception as of December 31, 2018 for certain of our key programs were as follows:

	Since Program Inception
Palynziq	$ 617.7
Valoctocogene roxaparvovec	401.0
Vosoritide	319.0
Brineura	287.1
Other approved products	1,050.4
Other	Not meaningful

We may need or elect to increase our spending above our current long-term plans to be able to achieve our long-term goals. This may increase our capital requirements, including: costs associated with the commercialization of our

products additional clinical trials investments in the manufacturing of our commercial products preclinical studies and clinical trials for our other product candidates potential licenses and other acquisitions of complementary technologies, products and companies and general corporate purposes.

Our future capital requirements will depend on many factors, including, but not limited to:

- our ability to successfully market and sell our products;
- the time and cost necessary to develop commercial manufacturing processes, including quality systems, and to build or acquire manufacturing capabilities;
- 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 progress of research programs carried out by us.

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Management's Discussion and Analysis of Financial Condition and Results of Operations (continued)

(In millions of U.S. Dollars, except as otherwise disclosed)

Off-Balance Sheet Arrangements

We do not have any off-balance sheet arrangements that are currently material or reasonably likely to be material to our consolidated financial position or results of operations.

Contractual and Commercial Obligations

We have contractual and commercial obligations under our convertible debt, operating leases and other obligations related to R&D activities, purchase commitments, licenses and sales royalties with annual minimums. Our contractual obligations as of December 31, 2018 are presented in the table below.

	Payments Due within				
	1 Year or Less	>1 -3 Years	> 3 - 5 Years	More Than 5 Years	Total
2020 Notes and related interest	$5.6	$380.6	$—	$—	$386.2
2024 Notes and related interest	3.0	5.9	5.9	498.0	512.8
Operating leases	13.0	23.7	20.6	27.7	85.0
R&D and purchase commitments	88.3	3.5	—	—	91.8
Total	$109.9	$413.7	$26.5	$525.7	$1,075.8

We are also subject to contingent payments related to certain development and regulatory activities and commercial sales and licensing milestones totaling approximately $477.3 million as of December 31, 2018, which are due upon achievement of certain development and commercial milestones, and if they occur before certain dates in the future. Of this amount, $154.5 million relates to remaining amounts due to Ares Trading S.A. (Merck Serono), from whom in 2016 we acquired certain rights and other assets with respect to Kuvan and Palynziq, and $80.7 million relates to programs that are no longer being developed.

As of December 31, 2018, we have recorded $132.8 million of contingent consideration on our Consolidated Balance Sheets.

Any outstanding amounts due under the 2018 Credit Facility will be due in full in October 2021 with related interest, if any, due on a quarterly basis, except that if at least $100.0 million aggregate principal amount of the 2020 Notes remain outstanding on August 1, 2020 and certain other conditions have not been met, we may be required to repay all amounts borrowed under the 2018 Credit Facility on August 1, 2020. As of December 31, 2018, there was no outstanding balance.

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Item 7A. Quantitative and Qualitative Disclosure About Market Risk

We are exposed to market risks that may result from changes in foreign currency exchange rates, interest rates and credit risks. To reduce certain of these risks, we enter into foreign currency derivative hedging transactions, follow investment guidelines and monitor outstanding trade receivables as part of our risk management program.

Foreign Currency Exchange Rate Risk

Our operations include manufacturing and sales activities in the U.S. as well as sales activities in regions outside the U.S, including Europe, Latin America and Asia Pacific. As a result, our financial results may be significantly affected by factors such as changes in foreign currency exchange rates or weak economic conditions in the foreign markets in which we sell our products. Our operating results are exposed to changes in foreign currency exchange rates between the U.S. Dollar (USD) and various foreign currencies, primarily the Euro. When the USD strengthens against these currencies, the relative value of the sales made in the respective foreign currency decreases. Conversely, when the USD weakens against these currencies, the relative value of such sales increases. Overall, we are a net receiver of foreign currencies and, therefore, benefit from a weaker USD and are adversely affected by a stronger USD relative to those foreign currencies in which we transact significant business.

During 2018, approximately 39% of our net product sales were denominated in foreign currencies and 17% of our operating expenses were denominated in foreign currencies. To partially mitigate the impact of changes in currency exchange rates on net cash flows from our foreign currency denominated sales and operating expenses, we may enter into forward foreign currency exchange contracts (forward contracts). We also hedge certain monetary assets and liabilities, primarily those denominated in Euros, using forward contracts, which reduces but does not eliminate our exposure to currency fluctuations between the date the transaction is recorded and the date the cash is collected or paid. Generally, the market risks of these contracts are offset by the corresponding gains and losses on the transactions being hedged.

We do not use derivative financial instruments for speculative trading purposes, nor do we hedge foreign currency exchange rate exposure in a manner that entirely offsets the effects of changes in foreign currency exchange rates. The counterparties to these forward contracts are creditworthy multinational commercial banks, which minimizes the risk of counterparty nonperformance. We regularly review our hedging program and may, as part of this review, make changes to the program.

As of December 31, 2018, we had open forward contracts with notional amounts of $418.4 million. A hypothetical 10% strengthening in foreign currency exchange rates compared with the USD relative to exchange rates at December 31, 2018 would have resulted in a reduction in the value received over the remaining life of these contracts by approximately $43.7 million on this date and, if realized, would negatively affect earnings during the remaining life of the contracts. The estimated fair value change was determined by measuring the impact of the hypothetical exchange rate movement on outstanding forward contracts. This analysis does not consider the impact of the hypothetical changes in foreign currency rates would have on the forecasted transactions that these foreign currency sensitive instruments were designated to offset. Our use of this methodology to quantify the market risk of such instruments is subject to assumptions and actual impact could be significantly different.

Based on our overall foreign currency exchange rate exposures at December 31, 2018, we believe that a near-term 10% fluctuation of the USD exchange rate could result in a potential change in the fair value of our foreign currency sensitive assets, excluding our investments and open forward contracts by approximately $3.3 million. We expect to continue to enter into transactions based in foreign currencies that could be impacted by changes in exchange rates.

Interest Rate Market Risk

Our exposure to market risk for changes in interest rates relates primarily to our investment portfolio, which includes our cash equivalents and marketable debt securities. By policy, we place our investments with highly rated credit issuers and limit the amount of credit exposure to any one issuer. As stated in our investment policy, we seek to improve the safety and likelihood of preservation of our invested funds by limiting default risk and market risk.

We mitigate default risk by investing in high credit quality securities and by positioning our portfolio to respond appropriately to a significant reduction in a credit rating of any investment issuer or guarantor. The portfolio includes only marketable securities with active secondary or resale markets to ensure portfolio liquidity.

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We have outstanding $375.0 million (undiscounted) of the 2020 Notes and $495.0 million (undiscounted) of the 2024 Notes. The interest rates on these notes are fixed and therefore they do not expose us to risk related to rising interest rates. As of December 31, 2018, the fair value of our convertible debt was $911.3 million.

In connection with the October 2013 offering of the 2018 Notes, which matured in October 2018, and the 2020 Notes, we paid $29.8 million to purchase a capped call covering 3,982,988 shares of our common stock, with 50% related to the 2018 Notes and 50% related to the 2020 Notes. If the per share price of our common stock remains below $94.15, the capped call transaction would be not applicable and, therefore, would provide us no benefit in offsetting potential dilution from the 2020 Notes. If the per share price of our common stock exceeds $121.05, then, to the extent of the excess, the capped call transaction would result in additional dilution from conversion of the 2020 Notes.

As of December 31, 2018, our investment portfolio did not include any investments with significant exposure to countries that face economic volatility and weakness. Although not predictive in nature, we believe a hypothetical 100 basis point threshold reflects a reasonably possible near-term change in interest rates. Based on our investment portfolio and interest rates at December 31, 2018, we believe that a 100 basis point increase in interest rates could result in a potential loss in fair value of our investment portfolio of approximately $5.6 million. Changes in interest rates may affect the fair value of our investment portfolio. However, we will not recognize such gains or losses in our Consolidated Statements of Operations unless the investments are sold or we determine that the decline in the investment’s value is other than temporary.

The table below summarizes the expected maturities and average interest rates of our interest-generating investments at December 31, 2018 (in millions):

	Expected Maturity						
	2019	2020	2021	2022	2023	Thereafter	Total
Available-for-sale debt securities	$649.7	$182.3	$53.4	$—	$—	$0.2	$885.6
Average interest rate	2.8%	3.1%	3.2%	—	—	5.3%	2.9%

Counterparty credit risks

Our financial instruments, including derivatives, are subject to counterparty credit risk that we consider as part of the overall fair value measurement. Our financial risk management policy limits derivative transactions by requiring transactions to be with institutions with minimum credit ratings of A or equivalent by Standards & Poor’s, Moody's or Fitch. In addition, we have an investment policy that limits investments to certain types of debt and money market instruments issued by institutions primarily with investment grade credit ratings and places restriction on maturities and concentrations by asset class and issuer.

Item 8. Financial Statements and Supplementary Data

The information required to be filed in this item appears under “Exhibits, Financial Statement Schedules” in Part IV, Item 15 of this Annual Report on Form 10-K and is set forth on pages F-1 to F-41.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

An evaluation was carried out, under the supervision of and with the participation of our management, including our Chief Executive Officer and our Chief Financial Officer, of the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act) as of the end of the period covered by this report. Based on the evaluation, our Chief Executive Officer and our Chief Financial Officer have concluded that our disclosure controls and procedures were effective as of December 31, 2018.

Management’s Annual Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining an adequate internal control structure and procedures for financial reporting. Under the supervision of and with the participation of our management,

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including our Chief Executive Officer and our Chief Financial Officer, our management has assessed the effectiveness of our internal control over financial reporting as defined in Rule 13a-15(f) under the Exchange Act as of December 31, 2018. Our management's assessment was based on criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO), Internal Control-Integrated Framework (2013).

Based on the COSO criteria, our management has concluded that our internal control over financial reporting as of December 31, 2018 was effective.

Our independent registered public accounting firm, KPMG LLP, has audited the financial statements included in this Annual Report on Form 10-K and has issued a report on the effectiveness of our internal control over financial reporting. The report of KPMG LLP is incorporated by reference to Item 8 of this Annual Report on Form 10-K.

Changes in Internal Control Over Financial Reporting

There were no changes in our internal control over financial reporting during our most recently completed quarter that have materially affected or are reasonably likely to materially affect our internal control over financial reporting, as defined in Rule 13a-15(f) under the Exchange Act.

Effective January 1, 2019, we adopted Financial Accounting Standards Board (FASB) Accounting Standards Codification (ASC) Topic 842, Leases (ASC Topic 842). During the year ended 2018, we evaluated internal controls necessary to ensure that we adequately evaluated our contracts and properly assessed the impact of ASC Topic 842 on our financial statements to facilitate the adoption on January 1, 2019. We have implemented new internal controls. No new systems were implemented and we do not expect significant changes to our internal control over financial reporting due to the adoption of ASC Topic 842.

Scope of the Effectiveness of Controls

Our internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with GAAP. Our internal control over financial reporting includes those policies and procedures that:

- pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect our transactions and dispositions of our assets;
- provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with GAAP, and that our receipts and expenditures are being made only in accordance with authorizations of our management and our board of directors; and
- provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of our assets that could have a material effect on our financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions or that the degree of compliance with the policies or procedures may deteriorate.

Item 9B. Other Information

None.

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Part III

Item 10. Directors, Executive Officers and Corporate Governance

The information required by this Item regarding our directors, executive officers and corporate governance is incorporated into this section by reference to the sections captioned “Election of Directors” and “Executive Officers” in the proxy statement for our 2019 annual meeting of stockholders.

Item 11. Executive Compensation

The information required by this Item regarding executive compensation is incorporated into this section by reference to the section captioned “Executive Compensation” in the proxy statement for our 2019 annual meeting of stockholders.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this Item regarding security ownership of our beneficial owners, management and related stockholder matters is incorporated into this section by reference to the section captioned “Security Ownership of Certain Beneficial Owners and Management” in the proxy statement for our 2019 annual meeting of stockholders.

The information required by this Item regarding the securities authorized for issuance under our equity compensation plans is incorporated into this section by reference to the section captioned “Equity Compensation Plan Information” in the proxy statement for our 2019 annual meeting of stockholders.

Item 13. Certain Relationships and Related Transactions and Director Independence

The information required by this Item regarding certain relationships, related transactions and director independence is incorporated into this section by reference to the sections captioned “Transactions with Related Persons, Promoters and Certain Control Persons,” “Review, Approval and Ratification of Transactions with Related Parties” and “Director Independence” in the proxy statement for our 2019 annual meeting of stockholders.

Item 14. Principal Accounting Fees and Services

The information required by this Item regarding our principal accountant fees and services is incorporated into this section by reference to the section captioned “Independent Registered Public Accounting Firm” in the proxy statement for our 2019 annual meeting of stockholders.

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Part IV

Item 15. Exhibits, Financial Statement Schedules

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Exhibit Index

2.1	Purchase Agreement, dated as of November 23, 2014, among BioMarin Falcons B.V., BioMarin Pharmaceutical Inc. and Prosensa Holding N.V., previously filed with the SEC on November 26, 2014 as Exhibit 2.01 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
2.2	Amended and Restated Termination and Transition Agreement, dated as of December 23, 2015, between BioMarin Pharmaceutical Inc. and Ares Trading S.A., previously filed with the SEC on January 7, 2016 as Exhibit 2.1 to the Company's

		Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference. Portions of this exhibit (indicated by asterisks) have been omitted pursuant to a request for confidential treatment. Omitted portions have been filed separately with the SEC.
2.3	Termination Agreement, dated as of October 1, 2015, between BioMarin Pharmaceutical Inc. and Ares Trading S.A., previously filed with the SEC on January 7, 2016 as Exhibit 2.2 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference. Portions of this exhibit (indicated by asterisks) have been omitted	

		pursuant to a request for confidential treatment. Omitted portions have been filed separately with the SEC.
2.4		Termination and Transition Agreement, dated as of October 1, 2015, between BioMarin Pharmaceutical Inc. and Ares Trading S.A., previously filed with the SEC on January 7, 2016 as Exhibit 2.3 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference. Portions of this exhibit (indicated by asterisks) have been omitted pursuant to a request for confidential treatment. Omitted portions have been filed separately with the SEC.
2.5		First Amendment,

		dated as of December 12, 2016, to the Amended and Restated Termination and Transition Agreement, dated as of December 23, 2015 and effective as of October 1, 2015, between BioMarin Pharmaceutical Inc. and Ares Trading S.A., previously filed with the SEC on February 27, 2017 as Exhibit 2.6 to the Company's Annual Report on Form 10-K (File No. 000-26727), which is incorporated herein by reference. Portions of this exhibit (indicated by asterisks) have been omitted pursuant to a request for confidential treatment. Omitted portions have been filed separately with the SEC.
2.6	Asset Purchase Agreement between BioMarin	

		Pharmaceutical Inc. and Medivation, Inc., dated August 21, 2015, previously filed with the SEC on October 7, 2015 as Exhibit 2.1 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference. The SEC has granted confidential treatment with respect to certain portions of this exhibit. Omitted portions have been filed separately with the SEC.
3.1		Restated Certificate of Incorporation of BioMarin Pharmaceutical Inc., previously filed with the SEC on June 12, 2017 as Exhibit 3.2 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by

		reference.
3.2		Amended and Restated Bylaws of BioMarin Pharmaceutical Inc., previously filed with the SEC on September 24, 2018 as Exhibit 3.1 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
4.1		Indenture dated as of March 29, 2006, between BioMarin Pharmaceutical Inc. and Wilmington Trust Company, previously filed with the SEC on March 29, 2006 as Exhibit 4.1 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
4.2		Second Supplemental Indenture, dated as of April 23, 2007, between

	BioMarin Pharmaceutical Inc. and Wilmington Trust Company, previously filed with the SEC on April 23, 2007 as Exhibit 4.1 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.

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4.3	Indenture, dated as of October 15, 2013, between BioMarin Pharmaceutical Inc. and Wilmington Trust, National Association, previously filed with the SEC on October 15, 2013 as Exhibit 4.1 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
4.4	First Supplemental Indenture, dated as of October 15, 2013, between BioMarin Pharmaceutical Inc. and Wilmington Trust, National Association (including the form of 0.75% Senior Subordinated Convertible Notes due 2018), previously filed with the SEC on October 15, 2013 as Exhibit 4.2 to the

		Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
4.5		Second Supplemental Indenture, dated as of October 15, 2013, between BioMarin Pharmaceutical Inc. and Wilmington Trust, National Association (including the form of 1.50% Senior Subordinated Convertible Notes due 2020), previously filed with the SEC on October 15, 2013 as Exhibit 4.3 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
4.6		Base Indenture, dated August 11, 2017, between the Company and Wilmington Trust, National

		Association, as Trustee, previously filed with the SEC on August 11, 2017 as Exhibit 4.1 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
4.7		First Supplemental Indenture, dated August 11, 2017, between the Company and Wilmington Trust, National Association, as Trustee (including the form of 0.599% Senior Subordinated Convertible Note due 2024), previously filed with the SEC on August 11, 2017 as Exhibit 4.2 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.1†		Form of Indemnification Agreement for Directors and Officers,

		previously filed with the SEC on December 19, 2016 as Exhibit 10.1 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.2†		BioMarin Pharmaceutical Inc. Amended and Restated 2006 Employee Stock Purchase Plan, as adopted on June 21, 2006 and amended on March 5, 2014, previously filed with the SEC on June 10, 2014 as Exhibit 10.1 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.3†		BioMarin Pharmaceutical Inc. Amended and Restated 2006 Share Incentive Plan, as adopted on May 2, 2006 and as amended and restated on April 16, 2015,

		previously filed with the SEC on June 15, 2015 as Exhibit 10.1 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.4†		Form of Agreement Regarding Restricted Share Units for the BioMarin Pharmaceutical Inc. 2006 Share Incentive Plan, previously filed with the SEC on May 16, 2013 as Exhibit 10.1 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.5†		Form of Amendment to Agreement Regarding Restricted Share Units for the BioMarin Pharmaceutical Inc. 2006 Share Incentive Plan, previously filed with the SEC on December 9, 2016 as Exhibit

		10.1 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.6†	Amended and Restated BioMarin Pharmaceutical Inc. Nonqualified Deferred Compensation Plan, as adopted on December 1, 2005 and as amended and restated on January 1, 2009 and further amended and restated on December 19, 2013 and October 7, 2014, previously filed with the SEC on October 14, 2014 as Exhibit 10.2 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.	
10.7†	Summary of Bonus Plan, previously filed with the SEC on February 27,	

		2009 as Exhibit 10.33 to the Company's Annual Report on Form 10-K (File No. 000-26727), which is incorporated herein by reference.

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10.8†	Amended and Restated Employment Agreement with Jean-Jacques Bienaimé effective December 13, 2016 previously filed with the SEC on December 19, 2016 as Exhibit 10.2 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.9	Grant Terms and Conditions Agreement between BioMarin Pharmaceutical Inc. and Harbor-UCLA Research and Education Institute dated April 1, 1997, as amended, previously filed with the SEC on July 21, 1999 as Exhibit 10.17 to the Company's Amendment No. 3 to Registration Statement on Form S-1 (File No. 333-77701), which is incorporated herein by reference. The SEC has granted confidential treatment with respect to certain portions of this exhibit. Omitted portions have been filed separately with the SEC.

10.10	License Agreement dated July 30, 2004, between BioMarin Pharmaceutical Inc. and Daiichi Suntory Pharma Co., Ltd., as amended by Amendment No. 1 to License Agreement dated November 19, 2004, previously filed with the SEC on March 16, 2005 as Exhibit 10.25 to the Company's Annual Report on Form 10-K (File No. 000-26727), which is incorporated herein by reference. The SEC has granted confidential treatment with respect to certain portions of this exhibit. Omitted portions have been filed separately with the SEC.
10.11	Operating Agreement with Genzyme Corporation, previously filed with the SEC on July 6, 1999 as Exhibit 10.30 to the Company's Amendment No. 2 to Registration Statement on Form S-1 (File No. 333-77701), which is incorporated herein by reference.
10.12	Manufacturing, Marketing and Sales

	Agreement dated as of January 1, 2008, by and among BioMarin Pharmaceutical Inc., Genzyme Corporation and BioMarin/Genzyme LLC previously filed with the SEC on February 28, 2008 as Exhibit 10.30 to the Company's Annual Report on Form 10-K (File No. 000-26727), which is incorporated herein by reference. The SEC has granted confidential treatment with respect to certain portions of this exhibit. Omitted portions have been filed separately with the SEC.
10.13	Amended and Restated Collaboration Agreement dated as of January 1, 2008, by and among BioMarin Pharmaceutical Inc., Genzyme Corporation and BioMarin/Genzyme LLC previously filed with the SEC on February 28, 2008 as Exhibit 10.31 to the Company's Annual Report on Form 10-K (File No. 000-26727), which is incorporated herein by reference.

		The SEC has granted confidential treatment with respect to certain portions of this exhibit. Omitted portions have been filed separately with the SEC.
10.14		Members Agreement dated as of January 1, 2008 by and among BioMarin Pharmaceutical Inc., Genzyme Corporation, BioMarin Genetics Inc., and BioMarin/Genzyme LLC previously filed with the SEC on February 28, 2008 as Exhibit 10.32 to the Company's Annual Report on Form 10-K (File No. 000-26727), which is incorporated herein by reference. The SEC has granted confidential treatment with respect to certain portions of this exhibit. Omitted portions have been filed separately with the SEC.
10.15†		BioMarin Pharmaceutical Inc. 2012 Inducement Plan, adopted May 8, 2012, previously filed with the SEC on May 9, 2012 as Exhibit 10.2 to the Company's Current

		Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.16†		Form of Stock Options Agreement for the BioMarin Pharmaceutical Inc. 2006 Share Incentive Plan. (as Amended and Restated 2010), previously filed with the SEC on August 2, 2012 as Exhibit 10.11 to the Company's Quarterly Report on Form 10-Q (File No. 000-26727), which is incorporated herein by reference.
10.17†		Form of Stock Options Agreement for the BioMarin Pharmaceutical Inc. 2012 Inducement Plan, previously filed with the SEC on August 2, 2012 as Exhibit 10.13 to the Company's Quarterly Report on Form 10-Q (File No. 000-26727), which is incorporated herein by reference.
10.18†		Form of Agreement Regarding Restricted Stock Units for the BioMarin Pharmaceutical Inc. 2012 Inducement Plan, previously filed with the SEC on August 2, 2012

	as Exhibit 10.14 to the Company's Quarterly Report on Form 10-Q (File No. 000-26727), which is incorporated herein by reference.

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10.19	Capped Call Confirmation for the 2018 Notes, dated October 8, 2013, between BioMarin Pharmaceutical Inc. and Bank of America, N.A., previously filed with the SEC on October 11, 2013 as Exhibit 10.1 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.20	Capped Call Confirmation for the 2020 Notes, dated October 8, 2013, between BioMarin Pharmaceutical Inc. and Bank of America, N.A., previously filed with the SEC on October 11, 2013 as Exhibit 10.2 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated

	herein by reference.
10.21	Capped Call Confirmation for the 2018 Notes, dated October 8, 2013, between BioMarin Pharmaceutical Inc. and Morgan Stanley & Co. LLC, previously filed with the SEC on October 11, 2013 as Exhibit 10.3 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.22	Capped Call Confirmation for the 2020 Notes, dated October 8, 2013, between BioMarin Pharmaceutical Inc. and Morgan Stanley & Co. LLC, previously filed with the SEC on October 11, 2013 as Exhibit 10.4 to the Company's Current Report on Form 8-K (File No. 000-26727), which is

		incorporated herein by reference.
10.23		Capped Call Confirmation for the 2018 Notes, dated October 8, 2013, between BioMarin Pharmaceutical Inc. and Barclays Bank PLC, previously filed with the SEC on October 11, 2013 as Exhibit 10.5 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.24		Capped Call Confirmation for the 2020 Notes, dated October 8, 2013, between BioMarin Pharmaceutical Inc. and Barclays Bank PLC, previously filed with the SEC on October 11, 2013 as Exhibit 10.6 to the Company's Current Report on Form 8-K (File No. 000-26727),

		which is incorporated herein by reference.
10.25		Additional Capped Call Confirmation for the 2018 Notes, dated October 9, 2013, between BioMarin Pharmaceutical Inc. and Bank of America, N.A., previously filed with the SEC on October 11, 2013 as Exhibit 10.7 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.26		Additional Capped Call Confirmation for the 2020 Notes, dated October 9, 2013, between BioMarin Pharmaceutical Inc. and Bank of America, N.A., previously filed with the SEC on October 11, 2013 as Exhibit 10.8 to the Company's Current Report

		on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.27		Additional Capped Call Confirmation for the 2018 Notes, dated October 9, 2013, between BioMarin Pharmaceutical Inc. and Morgan Stanley & Co. LLC, previously filed with the SEC on October 11, 2013 as Exhibit 10.9 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.28		Additional Capped Call Confirmation for the 2020 Notes, dated October 9, 2013, between BioMarin Pharmaceutical Inc. and Morgan Stanley & Co. LLC, previously filed with the SEC on October 11, 2013 as Exhibit

		10.10 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.29		Additional Capped Call Confirmation for the 2018 Notes, dated October 9, 2013, between BioMarin Pharmaceutical Inc. and Barclays Bank PLC, previously filed with the SEC on October 11, 2013 as Exhibit 10.11 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.30		Additional Capped Call Confirmation for the 2020 Notes, dated October 9, 2013, between BioMarin Pharmaceutical Inc. and Barclays Bank PLC, previously filed

			with the SEC on October 11, 2013 as Exhibit 10.12 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.

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10.31	Contract of Purchase and Sale and Joint Escrow Instructions, dated December 17, 2013, for the San Rafael Corporate Center, by and among BioMarin Pharmaceutical Inc., through its wholly-owned subsidiary, California Corporate Center Acquisition, LLC, SR Corporate Center Phase One, LLC, and SR Corporate Center Phase Two, previously filed with the SEC on February 26, 2014 as Exhibit 10.68 to the Company's Annual Report on Form 10-K (File No. 000-26727), which is incorporated herein by reference.
10.32	Convertible Promissory Note, dated as of November 26, 2014, between Prosensa Holding N.V. and BioMarin Falcons B.V., previously filed

		with the SEC on November 26, 2014 as Exhibit 10.3 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.33†		BioMarin Pharmaceutical Inc. 2014 Inducement Plan, adopted December 17, 2014, previously filed with the SEC on December 23, 2014 as Exhibit 10.1 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.34		Form of Contingent Value Rights Agreement, dated as of January 14, 2015, by and between BioMarin Pharmaceutical Inc., BioMarin Falcons B.V. and American Stock Transfer & Trust Company, LLC,

		previously filed with the SEC on January 16, 2015 as Exhibit 10.1 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.35†		Form of Stock Options Agreement for the BioMarin Pharmaceutical Inc. 2014 Inducement Plan, previously filed with the SEC on March 2, 2015 as Exhibit 10.60 to the Company's Annual Report on Form 10-K (File No. 000-26727), which is incorporated herein by reference.
10.36†		Form of Agreement Regarding Restricted Share Units for the BioMarin Pharmaceutical Inc. 2014 Inducement Plan, previously filed with the SEC on March 2, 2015 as Exhibit 10.61 to the Company's Annual Report on Form 10-K

		(File No. 000-26727), which is incorporated herein by reference.
10.37†		Form of Amended and Restated Employment Agreement for the Company's Executive Officers (other than the Company's Chief Executive Officer) previously filed with the SEC on June 15, 2015 as Exhibit 10.2 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.38		Settlement and License Agreement among BioMarin Pharmaceutical Inc., Merck & Cie, Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd., dated September 14, 2015, previously filed with the SEC on November 2, 2015 as Exhibit 10.2 to the

		Company's Quarterly Report on Form 10-Q (File No. 000-26727), which is incorporated herein by reference. The SEC has granted confidential treatment with respect to certain portions of this exhibit. Omitted portions have been filed separately with the SEC.
10.39		Credit Agreement by and among BioMarin Pharmaceutical Inc., as the Borrower, Bank of America, N.A., as Administrative Agent, Swing Line Lender, L/C Issuer and a Lender, and the Lenders party thereto, dated as of November 29, 2016, previously filed with the SEC on February 27, 2017 as Exhibit 10.49 to the Company's Annual Report on Form 10-K (File No. 000-26727), which is incorporated herein by reference.

10.40	Settlement and License Agreement among BioMarin Pharmaceutical Inc., Merck & Cie and Par Pharmaceutical, Inc., dated as of April 12, 2017, previously filed with the SEC on November 13, 2017 as Exhibit 10.1 to the Company's Amendment No. 1 to Quarterly Report on Form 10-Q/A (File No. 000-26727), which is incorporated herein by reference. The SEC has granted confidential treatment with respect to certain portions of this exhibit. Omitted portions have been filed separately with the SEC.
10.41†	Form of Agreement Regarding Performance Stock Award in the Form of Restricted Stock Units for the BioMarin Pharmaceutical Inc. 2006 Share Incentive Plan, previously filed with the SEC on

		February 27, 2017 as Exhibit 10.50 to the Company's Annual Report on Form 10-K (File No. 000-26727), which is incorporated herein by reference.

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10.42†	BioMarin Pharmaceutical Inc. 2017 Equity Incentive Plan, adopted April 10, 2017, previously filed with the SEC on June 12, 2017 as Exhibit 10.1 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.43†	Form of Stock Options Agreement for the BioMarin Pharmaceutical Inc. 2017 Equity Incentive Plan, previously filed with the SEC on June 12, 2017 as Exhibit 10.2 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.44†	Form of Agreement Regarding Restricted Stock Units for the BioMarin Pharmaceutical Inc. 2017 Equity Incentive Plan, previously filed with the SEC on June 12, 2017 as Exhibit 10.3 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.

10.45†	Form of Agreement Regarding Performance Stock Award in the Form of Restricted Stock Units for the BioMarin Pharmaceutical Inc. 2017 Equity Incentive Plan, previously filed with the SEC on June 12, 2017 as Exhibit 10.4 to the Company's Current Report on Form 8-K (File No. 000-26727), which is incorporated herein by reference.
10.46†	BioMarin Pharmaceutical Inc. Summary of Independent Director Compensation, previously filed with the SEC on October 31, 2017 as Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q (File No. 000-26727), which is incorporated herein by reference.
10.47	Asset Purchase Agreement by and between Novartis Pharma AG, BioMarin Pharmaceutical Inc. and BioMarin Commercial Ltd., dated as of November 21, 2017, previously filed with the SEC on February 26, 2018 as Exhibit 10.47 to the Company's Annual Report on Form 10-K

	(File No. 000-26727), which is incorporated by reference herein.
10.48*	Credit Agreement by and among BioMarin Pharmaceutical Inc., as the Borrower, Bank of America, N.A., as Administrative Agent, Swing Line Lender and a Lender, and Citibank N.A. as L/C Issuer, and the Lenders party thereto, dated as of October 19, 2018.
21.1*	Subsidiaries of BioMarin Pharmaceutical Inc.
23.1*	Consent of KPMG LLP, Independent Registered Public Accounting Firm for BioMarin Pharmaceutical Inc.
24.1*	Power of Attorney (Included in Signature Page to this Report)
31.1*	Certification of Chief Executive Officer pursuant to Rules 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended.
31.2*	Certification of Chief Financial Officer pursuant to Rules 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended.

32.1*	Certification of Chief Executive Officer and Chief Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002. This Certification accompanies this report and shall not, except to the extent required by the Sarbanes-Oxley Act of 2002, be deemed filed for purposes of §18 of the Securities Exchange Act of 1934, as amended.
101.INS	XBRL Instance Document
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase
101.LAB	XBRL Taxonomy Extension Labels Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Link Document

* Filed herewith

† Management contract or compensatory plan or arrangement

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Item 16. Form 10-K Summary

None.

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SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

BIOMARIN PHARMACEUTICAL INC.

Dated: February 27, 2019 By: /S/ DANIEL SPIEGELMAN
Daniel Spiegelman
Executive Vice President and Chief Financial Officer

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POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Jean-Jacques Bienaimé and Daniel Spiegelman, his or her attorney-in-fact, with the power of substitution, for him or her in any and all capacities, to sign any amendments to the Report on Form 10-K and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, hereby ratifying and confirming all that each of said attorneys-in-fact, or his substitute or substitutes, may do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated:

Signature	Title	Date
/S/ JEAN-JACQUES BIENAIMÉ Jean-Jacques Bienaimé	Chairman and Chief Executive Officer (Principal Executive Officer)	February 27, 2019
/S/ DANIEL SPIEGELMAN Daniel Spiegelman	Executive Vice President and Chief Financial Officer (Principal Financial Officer)	February 27, 2019
/S/ BRIAN R. MUELLER Brian R. Mueller	Senior Vice President, Finance and Chief Accounting Officer (Principal Accounting Officer)	February 27, 2019
/S/ WILLARD H. DERE, M.D. Willard H. Dere, M.D.	Director	February 27, 2019
/S/ MICHAEL G. GREY Michael G. Grey	Director	February 27, 2019
/S/ ELAINE J. HERON Elaine J. Heron	Director	February 27, 2019
/S/ ROBERT J. HOMBACH Robert J. Hombach	Director	February 27, 2019
/S/ V. BRYAN LAWLIS V. Bryan Lawlis	Director	February 27, 2019
/S/ ALAN J. LEWIS Alan J. Lewis	Director	February 27, 2019
/S/ RICHARD A. MEIER Richard A. Meier	Lead Independent Director	February 27, 2019

/S/ DAVID PYOTT David Pyott	Director	February 27, 2019
/S/ DENNIS J. SLAMON Dennis J. Slamon	Director	February 27, 2019

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BIOMARIN PHARMACEUTICAL INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

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Report of Independent Registered Public Accounting Firm

To the stockholders and the Board of Directors

BioMarin Pharmaceutical Inc.:

Opinion on the Consolidated Financial Statements

We have audited the accompanying consolidated balance sheets of BioMarin Pharmaceutical, Inc. and subsidiaries (the Company) as of December 31, 2018 and 2017, the related consolidated statements of operations, comprehensive loss, stockholders' equity, and cash flows for each of the years in the three-year period ended December 31, 2018 and the related notes (collectively, the consolidated financial statements). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2018 and 2017, and the results of its operations and its cash flows for each of the years in the three-year period ended December 31, 2018, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2018, based on criteria established in Internal Control – Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission, and our report dated February 27, 2019 expressed an unqualified opinion on the effectiveness of the Company's internal control over financial reporting.

Change in Accounting Principle

As discussed in Note 4 to the consolidated financial statements, the Company has changed its method of accounting for Revenue effective January 1, 2018, due to the adoption of Accounting Standards Codification 606 (ASC 606), Revenue from Contracts with Customers.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these consolidated financial statements based on our audits. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ KPMG LLP

We have served as the Company’s auditor since 2002.

San Francisco, California
February 27, 2019

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Report of Independent Registered Public Accounting Firm

The Board of Directors and Stockholders

BioMarin Pharmaceutical Inc.:

Opinion on Internal Control Over Financial Reporting

We have audited BioMarin Pharmaceutical, Inc. and subsidiaries' (the Company) internal control over financial reporting as of December 31, 2018, based on criteria established in Internal Control – Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission. In our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2018, based on criteria established in Internal Control – Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2018 and 2017, the related consolidated statements of operations, comprehensive loss, stockholders' equity, and cash flows for each of the years in the three-year period ended December 31, 2018, and the related notes (collectively, the "consolidated financial statements"), and our report dated February 27, 2019 expressed an unqualified opinion on those consolidated financial statements.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting, included in the accompanying Management's Annual Report on Internal Control Over Financial Reporting in Item 9a. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audit also included performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control Over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance

with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ KPMG LLP

San Francisco, California
February 27, 2019

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BIOMARIN PHARMACEUTICAL INC.

CONSOLIDATED BALANCE SHEETS

December 31, 2018 and 2017

(In thousands of U.S. Dollars, except share and per share amounts)

	December 31, 2018	December 31, 2017
ASSETS		
Current assets:		
Cash and cash equivalents	$ 493,982	$ 598,028
Short-term investments	590,326	797,940
Accounts receivable, net	342,633	261,365
Inventory	530,871	475,775
Other current assets	98,403	74,036
Total current assets	2,056,215	2,207,144
Noncurrent assets:		
Long-term investments	235,864	385,785
Property, plant and equipment, net	948,682	896,700
Intangible assets, net	491,808	517,510
Goodwill	197,039	197,039
Deferred tax assets	460,952	399,095
Other assets	36,568	29,852
Total assets	$ 4,427,128	$ 4,633,125
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable and accrued liabilities	$ 437,290	$ 401,921
Short-term convertible debt, net	—	360,949
Short-term contingent consideration	85,951	53,648
Total current liabilities	523,241	816,518
Noncurrent liabilities:		
Long-term convertible debt, net	830,417	813,521
Long-term contingent consideration	46,883	135,318
Other long-term liabilities	58,647	59,105
Total liabilities	1,459,188	1,824,462
Stockholders' equity:		
Common stock, $0.001 par value: 500,000,000 shares authorized;		
178,252,954 and 175,843,749 shares issued and outstanding,		
respectively.	178	176
Additional paid-in capital	4,669,926	4,483,220
Company common stock held by Nonqualified Deferred Compensation	(13,301)	(14,224)

Plan (the NQDC)		
Accumulated other comprehensive income (loss)	5,271	(22,961)
Accumulated deficit	(1,694,134)	(1,637,548)
Total stockholders' equity	2,967,940	2,808,663
Total liabilities and stockholders' equity	$4,427,128	$4,633,125

The accompanying notes are an integral part of these Consolidated Financial Statements.

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BIOMARIN PHARMACEUTICAL INC.

CONSOLIDATED STATEMENTS OF OPERATIONS

Years Ended December 31, 2018, 2017 and 2016

(In thousands of U.S. Dollars, except per share amounts)

	2018	2017	2016
REVENUES:			
Net product revenues	$1,470,356	$1,270,445	$1,110,381
Royalty and other revenues	20,856	43,201	6,473
Total revenues	1,491,212	1,313,646	1,116,854
OPERATING EXPENSES:			
Cost of sales	315,264	241,786	209,620
Research and development	696,328	610,753	661,905
Selling, general and administrative	604,353	554,336	476,593
Intangible asset amortization and contingent consideration	48,791	46,471	(26,953)
Impairment of intangible assets	—	—	599,118
Gain on sale of intangible assets	(50,000)	(125,000)	—
Total operating expenses	1,614,736	1,328,346	1,920,283
LOSS FROM OPERATIONS	(123,524)	(14,700)	(803,429)
Equity in the loss of BioMarin/Genzyme LLC	(553)	(1,291)	(538)
Interest income	22,831	14,853	7,487
Interest expense	(43,664)	(42,707)	(39,499)
Other income, net	2,205	7,970	4,929
LOSS BEFORE INCOME TAXES	(142,705)	(35,875)	(831,050)
Provision for (benefit from) income taxes	(65,494)	81,167	(200,840)
NET LOSS	$(77,211)	$(117,042)	$(630,210)
NET LOSS PER SHARE, BASIC	$(0.44)	$(0.67)	$(3.80)
NET LOSS PER SHARE, DILUTED	$(0.44)	$(0.67)	$(3.81)
Weighted average common shares outstanding, basic	177,061	174,427	165,985
Weighted average common shares outstanding, diluted	177,268	174,427	166,219

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BIOMARIN PHARMACEUTICAL INC.

CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS

Years Ended December 31, 2018, 2017 and 2016

(In thousands of U.S. Dollars)

	2018	2017	2016
NET LOSS	$(77,211)	$(117,042)	$(630,210)
OTHER COMPREHENSIVE INCOME (LOSS):			
Available-for-sale debt securities:			
Unrealized holding gain (loss) arising during the period, net of tax impact of $(413), $272 and $4,412, respectively.	1,391	(483)	(7,692)
Less: reclassifications to net loss, net of tax impact of $0, $(1,191) and $42, respectively.	—	2,061	(73)
Net change in unrealized holding gain (loss), net of tax	1,391	(2,544)	(7,619)
Cash flow hedges:			
Unrealized holding gain (loss) arising during the period, net of tax impact of $0.	25,386	(38,351)	9,677
Less: reclassifications to net loss, net of tax impact of $0.	(2,047)	(5,113)	10,273
Net change in unrealized holding gain (loss), net of tax	27,433	(33,238)	(596)
Other	(6)	5	(2)
OTHER COMPREHENSIVE INCOME (LOSS), NET OF TAX	28,818	(35,777)	(8,217)
COMPREHENSIVE LOSS	$(48,393)	$(152,819)	$(638,427)

The accompanying notes are an integral part of these Consolidated Financial Statements.

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BIOMARIN PHARMACEUTICAL INC.

CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY

Years Ended December 31, 2018, 2017 and 2016

(In thousands of U.S. Dollars and share amounts in thousands)

	Common stock		Additional Paid-in	Company Stock Held by	Accumulated Other Comprehensive Income	Accumulated	Total Stockholders'
	Shares	Amount	Capital	NQDC	(Loss)	Deficit	Equity
Balance at December 31, 2015	161,526	$ 162	$3,414,837	$(13,616)	$ 21,033	$(1,021,569)	$2,400,847
Net loss						(630,210)	(630,210)
Cumulative-effect adjustment of new share-based compensation guidance						131,273	131,273
Other comprehensive loss, net of tax					(8,217)		(8,217)
Issuance of common stock, net of offering costs	7,500	8	712,930				712,938
Issuances under equity incentive plans, net of tax	3,184	3	14,755				14,758
Conversion of convertible notes, net	438		8,928				8,928
Company stock held by NQDC				(705)			(705)
Stock-based compensation			136,663				136,663
Balance at December 31, 2016	172,648	$ 173	$4,288,113	$(14,321)	$ 12,816	$(1,520,506)	$2,766,275
Net loss						(117,042)	(117,042)
Other comprehensive loss, net of tax					(35,777)		(35,777)
Issuances under equity	2,092	2	27,350				27,352

incentive plans, net of tax							
Conversion of convertible notes, net	1,104	1	22,476				22,477
Company stock held by NQDC				97			97
Stock-based compensation			145,281				145,281
Balance at December 31, 2017	175,844	$ 176	$4,483,220	$(14,224)	$ (22,961)	$(1,637,548)	$2,808,663
Impact of change in accounting principle - ASC Topic 606						20,039	20,039
Impact of change in accounting principle - ASU 2018-02					(586)	586	—
Adjusted balance at January 1, 2018	175,844	$ 176	$4,483,220	$(14,224)	$ (23,547)	$(1,616,923)	$2,828,702
Net loss						(77,211)	(77,211)
Other comprehensive income, net of tax					28,818		28,818
Issuances under equity incentive plans, net of tax	2,314	2	31,583				31,585
Conversion of convertible notes, net	95		(16)				(16)
Company stock held by NQDC				923			923
Stock-based compensation			155,139				155,139
Balance at December 31, 2018	178,253	$ 178	$4,669,926	$(13,301)	$ 5,271	$(1,694,134)	$2,967,940

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BIOMARIN PHARMACEUTICAL INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS

Years Ended December 31, 2018, 2017 and 2016

(In thousands of U.S. dollars)

	2018	2017	2016
CASH FLOWS FROM OPERATING ACTIVITIES:			
Net loss	$(77,211)	$(117,042)	$(630,210)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	95,671	87,861	96,912
Non-cash interest expense	31,186	32,300	29,930
Accretion of discount on investments	358	3,077	1,300
Stock-based compensation expense	148,819	140,263	134,641
Gain on sale of intangible assets	(50,000)	(125,000)	—
(Gain) loss on sale of equity investment	—	(3,252)	108
Impairment of assets	—	—	599,118
Deferred income taxes	(68,378)	44,464	(228,054)
Unrealized foreign exchange loss (gain)	(17,766)	6,258	(14,481)
Non-cash changes in the fair value of contingent consideration\	9,296	10,342	(57,161)
Other	(2,347)	5,935	336
Changes in operating assets and liabilities:			
Accounts receivable, net	(54,274)	(25,256)	(51,483)
Inventory	(23,747)	(96,890)	(64,512)
Other current assets	(17,767)	(20,687)	19,316
Other assets	(935)	(2,439)	(4,979)
Accounts payable and accrued liabilities	38,389	45,517	(53,205)
Other long-term liabilities	8,914	5,792	(5,413)
Net cash provided by (used in) operating activities	20,208	(8,757)	(227,837)
CASH FLOWS FROM INVESTING ACTIVITIES:			
Purchases of property, plant and equipment	(144,620)	(199,219)	(148,380)
Maturities and sales of investments	993,734	425,960	367,569
Purchase of available-for-sale debt securities	(634,753)	(655,447)	(699,749)
Proceeds from sale of intangible asset	50,000	125,000	—
Business acquisitions, net of cash acquired	—	—	(2,789)
Other	(10)	(1,753)	(698)
Net cash provided by (used in) investing activities	264,351	(305,459)	(484,047)
CASH FLOWS FROM FINANCING ACTIVITIES:			