

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 Lindero Street San Rafael, California (Address of principal executive offices)	94901 (Zip Code)

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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

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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,” “may,” “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)

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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
				EU MAA
Palynziq in Europe Valoctocogene	PKU	Yes	Yes	regulatory review ⁽¹⁾
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 Roxaparvec for the Treatment of Hemophilia A

On January 7, 2019, we provided an update on our development of valoctocogene roxaparvec, 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 roxaparvec 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 Roxaparvec” below for more information regarding valoctocogene roxaparvec.

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 $\mu\text{mol/L}$), as well as Phe thresholds recommended in the U.S. (<360 $\mu\text{mol/L}$) and the EU (<600 $\mu\text{mol/L}$). 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. Palyntiq 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 five issued U.S. patents and eight foreign patents, and 19 pending applications including one US and 18 foreign applications. These patents will expire between 2021 and 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 Lindero 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 valoctogene roxaparvec 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 valoctogene roxaparvec (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 valoctogene roxaparvec 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 Palyntiq, 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