Risk Factors Comparison 2024-02-26 to 2023-02-27 Form: 10-K

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• If we fail to obtain and maintain 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. • **As compared to our other, more traditional products, gene therapy products may present additional challenges with respect to the pricing, coverage, reimbursement, and acceptance of the product. •** Because the target patient populations for our products are relatively small, we must achieve significant market share and maintain high per- patient prices for our products to achieve and maintain profitability. • 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 revenues could be adversely affected. • Changes in methods of treatment of disease could reduce demand for our products and adversely affect revenues. • If we fail to develop new products and product candidates or compete successfully with respect to acquisitions, joint ventures, licenses or other collaboration opportunities, our ability to continue to expand our product pipeline and our growth and development would be impaired. • The sale of generic versions of KUVAN by generic manufacturers has adversely affected and will continue to adversely affect our revenues and may cause a decline in KUVAN revenues faster than expected. • If we do not achieve our projected development goals in the timeframes we announce or fail to achieve such goals, the commercialization of our product candidates may be delayed or never occur and the credibility of our management may be adversely affected and, as a result, our stock price may decline. Regulatory Risks • 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 revenues 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. • 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 U. S. Food and Drug Administration (FDA **), the European Commission (EC**), the European Medicines Agency (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 revenues 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. • 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. Likewise, preliminary, initial or interim data from clinical trials should be considered carefully and with caution because the final data may be materially different from the preliminary, initial or interim data, particularly as more patient data become available. • 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 revenues and results of operations. • Government healthcare reform could increase our costs and adversely affect our revenues and results of operations ~~. Risks Related to Our Gene Therapy Programs • Our gene therapy products and product candidates are based on a novel technology, which presents additional development, manufacturing, regulatory and treatment risks in relation to our other, more traditional drug development programs. • As compared to our other, more traditional products, gene therapy products may present additional problems with respect to the pricing, coverage, and reimbursement and acceptance of the product~~ . Financial and Financing Risks • If we incur operating losses or are unable to sustain positive cash flows for a period longer than anticipated, we may be unable to continue our operations at planned levels and may be forced to reduce our operations. Manufacturing Risks • If we fail to comply with manufacturing regulations, our financial results and financial condition will be adversely affected. • If we are unable to successfully develop and maintain manufacturing processes for our product candidates to produce sufficient quantities at acceptable costs, we may be unable to support a clinical trial or be forced to terminate a program, or if we are unable to produce sufficient quantities of our products at acceptable costs, we may be unable to meet commercial demand, lose potential revenue, have reduced margins or be forced to terminate a program. • 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. Risks Related to International 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 revenues and results of operations. • 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 revenues in these countries. • Our international operations pose currency risks, which may adversely affect our operating results and net income. Intellectual Property Risks • If we are unable to protect our intellectual property, we may not be able to compete effectively or preserve our market shares. • Competitors and other third parties may have developed intellectual property that could limit our ability to market and commercialize our products and product candidates, if approved. Part I Item 1. Business Overview Founded in 1997, BioMarin Pharmaceutical Inc. (BioMarin, we, us or our) is a global biotechnology company dedicated to transforming lives through genetic discovery. We develop and commercialize targeted therapies that address the root cause of genetic conditions. Our robust research and development capabilities have resulted in multiple innovative commercial therapies for patients with rare genetic disorders. Our distinctive approach to drug discovery has produced a diverse pipeline of commercial, clinical, and pre- clinical candidates that address a significant unmet medical need, have well- understood biology, and provide an opportunity to be first- to- market or offer a substantial benefit over existing treatment options. Recent Developments In ~~2022~~ **2023** , we achieved ~~nearly~~ $ 2. ~~1~~ **4** billion in total revenues, including a significant contribution from our ongoing ~~launch~~ **expansion** of VOXZOGO, and we continued making important advancements in our product development pipeline. Our key business developments **in** ~~since the beginning of 2022~~ **2023** include ~~the conditional~~ **U. S. Food and Drug Administration (FDA)** approval of ~~ROCTAVIAN~~ **VOXZOGO for children with achondroplasia of all ages with open growth plates in the United States, European Commission** (**EC** ~~formerly referred to as valoctocogene roxaparvovec~~) **approval to expand the indication for VOXZOGO to treat children with achondroplasia aged four months and older with open growth plates** in the European Union (EU) ~~for the treatment of severe hemophilia A in adult patients~~ , **and FDA approval** ~~our release of positive three- year data from our Phase 3 study~~ of ROCTAVIAN **in** ~~, the acceptance by~~ the U. S ~~. Food and Drug Administration (FDA) of our resubmission of the Biologics License Application (BLA) for ROCTAVIAN, and approvals of VOXZOGO in Australia for patients with achondroplasia ages two and older and in Japan for children with achondroplasia of all ages. We also continued progress in our earlier stage clinical programs, BMN 255 for the treatment of hyperoxaluria in chronic liver disease and BMN 331, a gene therapy product~~

~~candidate for Hereditary Angioedema (HAE)~~ . Please see the disclosures below in ~~this Part I, Item 1 of~~ this Annual Report on Form 10- K for further discussion of these recent developments. Commercial Products ~~A summary of our commercial products is provided below:~~ Commercial ~~ProductsIndication2022~~ **ProductsIndication2023** Net Product ~~RevenuesProducts marketed by BioMarin~~ **Revenues (in millions of U. S. Dollars) Enzyme Products** : VIMIZIM (elosulfase alpha) **Mucopolysaccharidosis (** MPS ~~(1~~) IVA $ ~~663~~ **701** . ~~8~~ **0** NAGLAZYME (galsulfase) MPS VI $ ~~443~~ **420** . ~~8~~ **3** PALYNZIQ (pegvaliase- pqpz) **Phenylketonuria** (**PKU) $ 303. 9 BRINEURA (cerliponase alfa) Neuronal ceroid lipofuscinosis type** 2 **(CLN2**) ~~PKU~~ $ ~~255~~ **161** . ~~0~~ **9 ALDURAZYME (laronidase) MPS I $ 131. 2 Other Products: VOXZOGO (vosoritide) Achondroplasia $ 469. 9** KUVAN (sapropterin dihydrochloride) PKU $ ~~227~~ **180** . **8** ~~6 VOXZOGO (vosoritide) Achondroplasia (3) $ 169. 1 BRINEURA (cerliponase alfa) CLN2 (4) $ 154. 3~~ ROCTAVIAN (valoctocogene roxaparvovec) ~~(5)~~ Severe Hemophilia A $ ~~— Products not marketed by BioMarin: ALDURAZYME (laronidase) (6) MPS I $ 128. 4 (1) Mucopolysaccharidosis (2) For the treatment of adult patients with phenylketonuria (PKU) (~~3 ~~) For the treatment of achondroplasia in children aged five years and older for the U~~. ~~S., aged two years and older for the EU and for various age ranges for other markets. For more information, see " VOXZOGO " below. (4) Neuronal ceroid lipofuscinosis type 2 (~~5 ~~) The European Commission (EC) conditionally approved ROCTAVIAN in the third quarter of 2022, but no sales occurred in 2022. For more information, see " ROCTAVIAN " below. (6) Marketed by Sanofi~~ 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 certain complex carbohydrates known as glycosaminoglycans (GAGs), 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. VIMIZIM is approved for marketing in the U. S., the EU and other international markets. 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 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 is a PEGylated recombinant phenylalanine (Phe) ammonia lyase enzyme, which is delivered through subcutaneous injection to reduce blood Phe concentrations. PALYNZIQ is our second approved treatment for PKU ~~.~~ PKU is caused by a deficiency of activity of an enzyme, ~~phenylalanine hydroxylase (~~ 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.** . PALYNZIQ is approved for marketing in the U. S. for adult patients with PKU who have uncontrolled blood Phe concentrations greater than 600 micromol / L on existing management. PALYNZIQ is also approved for marketing in the EU ~~and ,~~ Australia **, and Brazil** for patients ages 16 and older who have inadequate blood Phe control (blood Phe concentrations greater than 600 micromol / L) despite prior management with available treatment options. In the U. S., PALYNZIQ is only available 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. ~~)~~ ,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 Sanofi.Under our collaboration agreement with Sanofi,we are responsible for manufacturing ALDURAZYME and supplying it to Sanofi.We receive payments ranging from 39.5 % to 50 % on worldwide net ALDURAZYME sales by Sanofi depending on sales volume.Sanofi and BioMarin 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 Sanofi and BioMarin 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 Sanofi and us.ALDURAZYME is approved for marketing in the U.S.,the EU and other international markets. **Clinical Development Programs A summary** ~~VOXZOGO is a once daily injection analog~~ of **our clinical development** 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..... adequate control of blood Phe levels. KUVAN is approved for marketing 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. Generic versions of KUVAN are available in several countries around the world, including multiple generic versions in the U. S. We are also aware that manufacturers are challenging our patent portfolio related to KUVAN in several jurisdictions, and several generic versions of KUVAN have been approved either centrally by the ~~EMA~~ **EC** or on a country- by- country basis throughout the EU. 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 generic versions of KUVAN in the

U. S. and ~~international markets. VOXZOGO is a once daily injection analog of C- type Natriuretic Peptide (CNP) for the treatment of achondroplasia, the most common form of disproportionate short stature in humans. In patients with achondroplasia, endochondral bone growth, an essential process by which bone tissue is created, is negatively regulated due to a gain of function mutation in fibroblast growth factor receptor 3 gene (FGFR3). VOXZOGO acts as a positive regulator of the signaling pathway downstream of FGFR3 to promote endochondral bone growth. VOXZOGO is approved for marketing in the EU, Australia and Brazil for patients with achondroplasia ages two and older with open growth plates and in Japan for children with achondroplasia of all ages with open growth plates. The FDA granted accelerated approval for the use of VOXZOGO in the U. S. for patients with achondroplasia ages five and older with open growth plates. The FDA issued us a Rare Pediatric Disease Priority Review Voucher (PRV) in connection with VOXZOGO' s accelerated approval, which confers priority review to a subsequent drug application that would not otherwise qualify for priority review. The PRV program is designed to encourage development of new drugs and biologics for the treatment of rare pediatric diseases. In the first quarter of 2022, we sold the PRV we obtained in connection with VOXZOGO' s accelerated approval for a gross lump sum payment of $ 110. 0 million. We continue to research VOXZOGO' s safety and effectiveness in children with achondroplasia. On February 23, 2022, we announced results from our Phase 2 randomized, double- blind, placebo- controlled clinical trial of VOXZOGO in infants and young children up to five years of age with achondroplasia, and on June 13, 2022, we announced additional details from the analysis. Results at 52 weeks trended in favor of VOXZOGO compared to placebo on height (adjusted for age and gender) and annualized growth velocity, consistent with improvements previously observed after one year of treatment in children over five years of age and without significantly impacting upper- to- lower body segment ratio. The safety profile was generally consistent with older children from the Phase 3 study and product label population. Serious adverse events (SAEs) were higher in the placebo group (18 %) compared to children treated with VOXZOGO (7 %). All SAEs, including a fatal respiratory arrest (reported as a sudden infant death syndrome in a treated infant with pre- existing respiratory morbidity), were deemed by the study investigators to be unrelated to treatment. The most common adverse events were mild and self- limiting injection site reactions. As part of our efforts to expand access to VOXZOGO for younger children, on January 3, 2023, we announced that we submitted, and the EMA subsequently validated, our Type II Variation application to extend the indication for VOXZOGO in the EU to treat children with achondroplasia under the age of 2. We also announced that we submitted a supplemental New Drug Application (NDA) to the FDA to treat children with achondroplasia under the age of 5. Additionally, on August 3, 2022, we announced our interventional Phase 2 study with VOXZOGO for the treatment of infants under the age of two who are at risk for foramen magnum compression completed enrollment. The study is investigating the safety of VOXZOGO in infants at risk of requiring surgery to alleviate compression at the foramen magnum, the opening in the base of the skull through which the spinal cord passes. Moreover, we are evaluating VOXZOGO as a potential treatment for children with other genetic short stature conditions beyond achondroplasia. A 52- week investigator- initiated study sponsored by Children' s National Hospital in Washington, D. C. to investigate VOXZOGO in children with selected genetic forms of short stature is ongoing and expected to complete in 2023. Preliminary 6- month results from 12 subjects demonstrated a positive response in all subgroups with interindividual variability. BRINEURA is a recombinant human tripeptidyl peptidase 1 (TPP1) for the treatment of patients with CLN2, a form of Batten disease. CLN2 is an incurable, rapidly progressive disease that typically 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. BRINEURA is the first treatment approved to slow the progression of loss of ambulation in children with CLN2 disease and was one of the first therapies to go through an accelerated review procedure in the EU. 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 – Regulation of Product Marketing and Promotion – Combination Products " in this Annual Report on Form 10- K for additional information on combination products. BRINEURA is approved for marketing in the U. S. (for ages three and older) and in the EU (for all ages from birth) and in other~~ international markets. ROCTAVIAN is an adeno associated virus (AAV5) vector gene therapy 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. **ROCTAVIAN was conditionally approved by the EC in August 2022 and approved by the FDA in the U. S. in June 2023.** Our European launch of ROCTAVIAN is underway following ROCTAVIAN' S conditional approval for marketing in the EU ~~in August 2022~~ for the treatment of severe hemophilia A in adult patients without a history of factor VIII inhibitors and without detectable antibodies to AAV5. We plan to provide the **European Medicines Agency (** EMA **)** further clinical data **in an effort** to convert our conditional approval to a standard marketing authorization. Please see " Government Regulation – Adaptive Pathways " in this Annual Report on Form 10- K for additional information on conditional marketing authorizations. ~~Moreover, we completed outcomes- based agreements (OBAs) for ROCTAVIAN with third- party payers in Germany, which make us subject to potential repayments if a patient does not respond to therapy or the therapeutic effect of the drug falls below specified thresholds.~~ We **have and** continue to collaborate with ~~other~~ payers **around the world** to secure **reimbursement** ~~additional OBAs~~ for ROCTAVIAN ~~,~~ **on terms** which are intended to assist payers with realizing the value and sharing the risk of a one- time treatment. **For example** ~~On October 12, 2022~~ , we ~~announced that~~ **have agreed with** the **German National Association** ~~FDA accepted for review our resubmission~~ of ~~the BLA~~ **Statutory Health Insurance Funds an outcome- based prospective cohort model** for ROCTAVIAN **which will allow future reimbursement to be increased** ~~for~~ **or decreased based on real** ~~the treatment of adults with severe hemophilia A. The BLA resubmission incorporates our responses to all deficiencies identified in the FDA' s August 2020 Complete Response Letter to our original BLA submission. The Prescription Drug User Fee Act (PDUFA) target action date for the resubmitted BLA is March 31, 2023. Typically, BLA resubmissions are followed by a six~~ **world** ~~month review procedure. However, three additional months of review may be necessary in connection with our recent submission to the FDA of~~ data **collected** from ~~our three~~ **the German** ~~- year analysis of the global Phase 3 study of ROCTAVIAN, as discussed below. Additionally, the FDA completed a Pre- License Inspection of the ROCTAVIAN manufacturing facility in early December 2022. We have provided responses to the FDA' s comments and observations received at the close of the inspection, and we believe all are addressable. On May 31, 2022, we announced an update to our previously reported results of an open- label Phase 1 / 2 study of ROCTAVIAN for the treatment of adults with severe hemophilia~~ **Haemophilia Registry** ~~A. The six- year update for the 6e13 vg / kg and five- year update for the 4e13 vg / kg cohorts showed~~

~~a sustained treatment benefit of ROCTAVIAN. All participants, except one in the 4e13 vg / kg cohort as discussed below, had remained off~~ - **of patients** ~~prophylactic factor VIII treatment~~ - **treated** ~~since receiving their single dose of ROCTAVIAN. Six months prior to the data cut, one participant in the 4e13 vg / kg cohort temporarily resumed prophylactic factor VIII treatment for one month, after which he was bleed free through the last follow up. In addition, the mean annualized bleed rates (ABR) for the most recent year were less than one in both cohorts and below pre- treatment baseline levels. On January 8, 2023, we announced topline results from our three- year analysis of the global Phase 3 study of ROCTAVIAN for the treatment of adults with severe hemophilia A. All 132 study participants received a single dose of ROCTAVIAN and had a minimum of 36 months of follow- up. For a pre- specified group of 112 participants (two of whom discontinued from the study prior to reaching three years of follow- up) in a non- interventional prospective baseline observational study after dosing~~ with ROCTAVIAN ~~(the Rollover Population), in year three the mean ABR was reduced by 80 % from baseline, with a mean ABR for treated bleeds of 1. 0 (median 0. 0). For the Rollover Population, in year three the mean annualized factor VIII infusion rate was reduced by 94 % from baseline, with a mean annualized infusion rate of 8. 4 (median 0. 0). As of the three- year data cut, 92 % of the Rollover Population participants remained off factor VIII prophylactic therapy. At the end of the three year post- infusion with ROCTAVIAN, the population of 132 participants had a mean factor VIII activity level of 18. 8 (median 8. 4) IU / dL, as measured by the chromogenic substrate (CS) assay. In the 17 participants (one of whom discontinued from the study prior to reaching four years of follow- up) who had been dosed at least four years prior to the data cut, mean factor VIII activity was 15. 2 (median 7. 4) IU / dL by the CS assay at the end of year three. The mean ABR for treated bleeds in year four for this subpopulation was 0. 8 (median 0. 0) and the mean annualized infusion rate was 11. 1 (median 0. 0). In addition to the ongoing Phase 1 / 2 and Phase 3 studies of ROCTAVIAN described above, we have multiple other clinical studies of ROCTAVIAN underway. We are conducting an ongoing Phase 3, single arm, open- label study to evaluate the efficacy and safety of ROCTAVIAN at a dose of 6e13 vg / kg with prophylactic corticosteroids in people with severe hemophilia A~~ . We are also ~~conducting~~ **continuing our development efforts on ROCTAVIAN expansion opportunities. Please see " Risk Factors " included in Part I, Item 1A of this Annual Report on Form 10- K for a discussion of the risks related to ROCTAVIAN in the U. S. and international markets. Research and Development Programs We have multiple clinical and preclinical product candidates in various stages of development that are intended to address the root causes of genetic conditions with a significant unmet medical need. Generally, our development programs have well- understood biology and provide** an ~~ongoing Phase 1 / 2 Study with the 6e13 vg / kg dose of ROCTAVIAN in people with~~ **opportunity to be first- to- market or offer a substantial benefit over existing treatment options. In 2023, we conducted clinical trials on** ~~severe~~ **several** ~~hemophilia A with~~ **product candidates for the treatment of various diseases and progressed** pre- **clinical** ~~existing AAV5 antibodies and a Phase 1 / 2 Study with the 6e13 vg / kg dose of ROCTAVIAN in people with severe hemophilia A with active~~ **activities , including studies intended to support Investigational New Drug (IND) application or Clinical Trial Application (CTA) submissions. During the first quarter of 2024,** ~~or~~ **our management began** ~~prior factor VIII inhibitors. Overall, ROCTAVIAN continues to have~~ a **strategic portfolio review of** ~~favorable safety profile and has been generally well tolerated by participants across~~ all **research** ~~doses in the Phase 1 / 2~~ and Phase 3 studies. No participants developed..... inhibited growth, delayed and regressed mental development (**R & D** ~~in the severe form of the disease~~) , enlarged liver and spleen, joint..... Programs A summary of our clinical development programs ~~is provided below: Clinical Development ProgramsTargetIndicationStageROCTAVIANSevere Hemophilia AFDA regulatory review BMN 255HyperoxaluriaClinical Phase 1 / 2BMN 331Hereditary Angioedema (HAE) Clinical Phase 1 / 2 BMN 255 is a small- molecule therapy that is designed~~ to **determine** ~~treat hyperoxaluria in chronic liver disease. We concluded the multiple- ascending dose phase of the first- in- human study with BMN 255. In January 2023, we shared early data that demonstrated a rapid and potent increase in plasma glycolate following treatment with BMN 255,~~ which ~~is predicted to~~ **R & D assets** have ~~a profound reduction in oxalate excretion in patients. We plan to initiate and fully enroll an expanded study in patients with chronic liver disease and hyperoxaluria in 2023. We believe~~ the **highest** ~~availability of a potent~~ **potential** ~~, orally bioavailable, small molecule like BMN 255 may be able to significantly reduce disease and treatment burden in a~~ patient **impact** ~~population with significant unmet need. BMN 331 is a gene therapy product candidate for HAE. Dosing continues in the Phase 1 / 2 HAERMONY study to evaluate BMN 331, an~~ **and highest potential value creation** ~~investigational AAV5- mediated gene therapy~~ for **stockholders** ~~people living with HAE, including dose escalation to the 6e13vg / kg dose, which our non- clinical studies project to provide therapeutic levels of C1- Inhibitor. In January 2023, we shared that the first participant treated with the 6e13vg / kg dose of BMN 331 demonstrated C1- Inhibitor levels that were approaching the normal range. A second participant is scheduled for dosing at the 6e13vg / kg dose level in the near term~~ . We manufacture the active pharmaceutical ingredients (API) for ALDURAZYME, NAGLAZYME, PALYNZIQ ~~and~~ **,** VOXZOGO **, and ROCTAVIAN** in our production facilities located in Novato, California. **Our commercial- scale gene therapy manufacturing facility, located in Novato, California, also supports our clinical development activities. This facility has the potential to produce multiple gene therapy products to meet global commercial demand, depending on dose and production mix.** We manufacture the API for BRINEURA and VIMIZIM in our manufacturing facility in Shanbally, Cork, Ireland. ~~These~~ **Our Novato and Shanbally** facilities have been inspected and have demonstrated compliance with current Good Manufacturing ~~Practices~~ - **Practice** (~~cGMPs~~ - **cGMP**) to the satisfaction of the FDA, the EC and health agencies in other countries **. We also have installed aseptic filling and drug product packaging capabilities at the Shanbally site. Regulatory inspections of this new drug product filling facility are planned and / or anticipated over the coming months** . We contract with third parties to manufacture KUVAN API. ~~All~~ **Additionally, most of** our **drug** product manufacturing (which includes vials, syringes, tablets, and powder) **is performed externally by contract manufacturers. The volume mix will change as drug product filing operations initiate** and ~~most~~ **expand in the Shanbally site.** ~~packaging~~ **Packaging** operations are ~~performed by~~ **effectively split between installed capacity at the Shanbally site and several** contract manufacturers. We expect to continue to contract with outside service providers for certain manufacturing services, including drug substance, drug product, 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~~ - **sale** . Third- party manufacturers' facilities are subject to periodic inspections to confirm compliance with applicable law and must be cGMP 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. ~~In July 2017, we commissioned our commercial- scale gene therapy manufacturing facility, located in Novato, California, where we conduct cGMP production of ROCTAVIAN to support commercial sales in Europe, anticipated commercial demand in other markets and clinical development activities. The facility has been inspected and has demonstrated compliance with cGMPs to the satisfaction of the EC. This~~

~~facility also supports cGMP production of BMN 331 to support clinical development activities. This facility has the potential to produce multiple gene therapy products to meet global commercial demand, depending on dose and production mix. The facility holds a GMP certificate and its production processes have been 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 **to produce** ~~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. **Please see the risk factor, " 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. " described in " Risk Factors " in Part I, Item 1A of this Annual Report on Form 10- K.** 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 all our products, other than ALDURAZYME. 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. Sanofi 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 ~~2023~~ **2024** , the size of our sales force will be appropriate to effectively reach our target customers in markets where our products are directly marketed. The launch of any future products, if approved, will likely require expansion of our commercial organization, including our sales force, in the U. S. and international markets. 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 Customers for our products (other than ALDURAZYME) include a limited number of specialty pharmacies and end- users, such as hospitals and non- U. S. government agencies. We also sell our products (other than ALDURAZYME) to our authorized distributors and to certain larger pharmaceutical wholesalers globally, which act as intermediaries between us and end- users and generally do not stock significant quantities of our products. However, in certain countries, governments place large periodic orders for NAGLAZYME and VIMIZIM. The timing of these orders can be inconsistent and can create significant quarter to quarter variation in our revenue. PALYNZIQ is currently distributed in the U. S. pursuant to the REMS program through a limited number of certified specialty pharmacies. During ~~2022~~ **2023** , ~~37~~ **36** % of our net product revenue was generated by three customers. Sanofi is our sole customer for ALDURAZYME and is responsible for **distributing,** 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 larger competitors may have advantages over us due to greater financial or scientific resources, lower labor and other costs, or higher headcount and more robust organizational structures, while smaller competitors may have advantages over us due to lower overhead costs, being more nimble, or being able to focus on a narrower set of indications or development programs. Our competitors have considerable experience in drug manufacturing, preclinical and clinical research and development, 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. Other than ROCTAVIAN and KUVAN, as described below, our products have no direct approved competition currently on the market in the U. S. or the EU; 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. 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., JCR Pharmaceuticals Co., Ltd (acquired by ArmaGen, Inc.)., Orchard Therapeutics Plc and RegenxBio Inc. and earlier stage product candidates, including product candidates from Denali Therapeutics Inc. and Immusoft Corporation. NAGLAZYME, for the treatment of MPS VI, has potential competition from clinical stage product candidates from Inventiva S. A. and Paradigm Biopharmaceuticals Limited and other potential candidates in earlier stages. VIMIZIM, for the treatment of MPS IVA, has potential competition from preclinical product candidates from Esteve Pharmaceuticals, S. A., and RegenxBio Inc. and other potential candidates in earlier stages. BRINEURA, for the treatment of CLN2, has potential competition from preclinical product candidates from Lexeo Therapeutics, Inc., RegenxBio Inc. and the Roche Group. **PALYNZIQ and** KUVAN ~~and PALYNZIQ~~ There are currently no other approved, non- generic drugs on the market in the U. S. or the EU for the treatment of PKU. However, generic versions of KUVAN are available in several countries around the world, including multiple generic versions in the U. S. We are also aware that manufacturers are challenging our patent portfolio related to KUVAN in several jurisdictions, and several generic versions of KUVAN have been approved either centrally by the EMA or on a country- by- country basis throughout the EU. 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 generic versions of KUVAN in the U. S. and international markets. **PALYNZIQ and** KUVAN ~~and PALYNZIQ~~ also have potential competition from clinical stage product candidates from ~~Homology Medicines, Inc.,~~ Jnana Therapeutics Inc., Nestle Health Science, S. A., **Sanofi, S. A.,** PTC Therapeutics, Inc. **Moderna**

Therapeutics Inc., Agios Pharmaceuticals Inc., SOM Innovation Biotech, S. A., and Synlogic, Inc. and earlier stage product candidates, including product candidates from ~~Codexis, Inc,~~ Generation Bio Co., ~~LogicBio Therapeutics, Inc.,~~ Moderna Therapeutics, Inc., ~~Sangamo~~ **Poseida** Therapeutics, Inc. ~~and SOM Innovation Biotech~~ , ~~S~~ **Tessera Therapeutics, Inc** . ~~A~~ **, and Evox Therapeutics Limited** . We and other companies are also developing gene therapy product candidates for PKU. VOXZOGO, for the treatment of achondroplasia, could have competition from clinical stage products under development by Ascendis Pharma A / S, Pfizer, Inc., QED Therapeutics, Inc. (a subsidiary of BridgeBio Pharma, Inc.), Ribomic Inc. and Sanofi and preclinical product candidates from other companies, including Astellas Pharma Inc. **, Tyra Biosciences, Inc., Abbisko Therapeutics Co Ltd, SiSaf Ltd, Peptron Inc., and Immunoforge, Co. Ltd.** ROCTAVIAN, a gene therapy ~~product candidate~~ for **the treatment of adults with** severe hemophilia A, has potential competition from marketed recombinant factor VIII replacement therapies, **including products marketed by Sanofi S. A., Takeda Pharmaceutical Company Limited, Bayer AG, Novo Nordisk A / S, CSL Behring, and Pfizer, Inc.,** a novel bispecific antibody marketed by the Roche Group, and clinical stage programs, including gene therapy product candidates under development by ASC Therapeutics, Inc., ~~Bayer AG,~~ Pfizer, Inc., **and** the Roche Group ~~and Sangamo Therapeutics, Inc~~ . In addition, Novo Nordisk A / S, Pfizer, Inc., the Roche Group and Sanofi are developing novel non- factor replacement product candidates in the clinic for the treatment of hemophilia A. **Substantially** ~~BMN 255, a small~~ -- **all - molecule of our clinical and preclinical** product ~~candidate~~ **candidates have** ~~for hyperoxaluria in chronic liver disease, has~~ potential competition from **several** ~~marketed products from Alnylam Pharmaceuticals, Inc., clinical stage product candidates from BridgeBio Pharma, Inc., Chinook Therapeutics, Inc. and Dicerna Pharmaceuticals, Inc. (a subsidiary of Novo Nordisk A / S.) and preclinical product candidates from other~~ companies, **which in some cases** ~~including Amarna Therapeutics and Intellia Therapeutics~~ , **have development programs in later** ~~Inc. BMN 331, a gene therapy product candidate for HAE, has potential competition from marketed products from BioCryst Pharmaceuticals, Inc., CSL Behring GmbH and Takeda Pharmaceutical Company Limited, clinical stage~~ **stages than our own** ~~product candidates from Astria Therapeutics, Inc., CSL Behring GmbH, Intellia Therapeutics, Inc., Ionis Pharmaceuticals, Inc. and Pharvaris N. V. and preclinical product candidates from other companies, including Orchard Therapeutics, Inc. and Spark Therapeutics, Inc. (a subsidiary of the Roche Group)~~ . Patents, Proprietary Rights and Regulatory Exclusivity Our success depends on an intellectual property portfolio that supports our future revenue streams and also ~~erects~~ **creates** 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. U. S. patents, as well as most foreign patents, are generally effective for 20 years from the date the earliest application was filed. U. S. patents that were issued on applications filed before June 8, 1995, may be effective until 17 years from the issue date, if that is later than the 20- year date. In some cases, the patent term may be extended to recapture a portion of the term lost during regulatory review of the claimed therapeutic or, in the case of the U. S., because of U. S. Patent and Trademark Office (USPTO) delays in prosecuting the application. In the U. S., under the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly known as the Hatch- Waxman Act), a patent that covers a drug approved by the FDA may be eligible for patent term extension (for up to five years, but not beyond a total of 14 years from the date of product approval) as compensation for patent term lost during the FDA regulatory review process. The duration and extension of the term of foreign patents varies in accordance with local law. In the EU, Supplementary Protection Certificates **(** ~~, or~~ SPCs ~~,~~**)** are available to extend a patent term up to five years to compensate for patent protection lost during regulatory review. Although all EU Member States must provide SPCs, SPCs must be applied for and granted on a country- by- country basis. Limited exceptions apply to the protection conferred by the SPC. The table below lists our ~~outstanding~~ **active** patents and patent applications of primary importance for our products other than ALDURAZYME **and NAGLAZYME** by territory, general subject matter (including composition, methods of treatment and approved use, methods of production and purification, pharmaceutical compositions and clinical formulations) and latest expiry date. With respect to ALDURAZYME **and NAGLAZYME** , the last of our patents expired in November 2020 **and November 2023, respectively** . One or more patents with the same or earlier expiry dates may fall under the same general subject matter and are not listed separately in the table below. We continue to pursue additional patents and patent term extensions in the U. S. and other territories covering various aspects of our products that may, if issued, extend patent exclusivity beyond the expiration dates listed in the table below. ProductTerritoryPatent No (s). General Subject MatterPatent ExpirationBRINEURAU. S. 8, 029, 781Method of treatmentMarch 7, 2023 (1) 9, 044, 473Method of treatment by administration into the cerebrospinal fluidFebruary 18, 203210, 279, 015Formulation; kitMay 5, 2036EU1673104Pharmaceutical compositionAugust 30, **2024EP3294345FormulationMay** ~~202416793229. 2 (2) FormulationMay~~ 5, ~~2036KUVANEU3138566; 3977999 (2) Use for treating with once daily dosing regimenNovember 17, 20242545939; Use for treating once daily after a mealApril 11, 20283461503; 4029519 (2) Use for treating after a mealApril 11, 2028NAGLAZYMEU. S. 7, 713, 709Antibody assaysJuly 20, 2028EU1565209; 2327414Compositions; pharmaceutical compositions; use to treat an enzyme deficiencyNovember 7, 2023PALYNZIQU~~ **2036PALYNZIQU** . S. 7, 534, 595Composition; method of **treatingMay** ~~treatingAugust 16, 2027 / May~~ 24, 2032 (~~3~~ **2**) 10, 221, 408PurificationFebruary 3, 20319, 557, 340Antibody detection assayJuly 30, 202911, 505, 790RegimenFebruary 3, 2031EU2152868Composition; pharmaceutical compositionMay 23, 2028 / May 23, 2033 (~~4~~ **3**) 2531209; 3025728Formulation; purificationFebruary ~~03~~ **3** , 2031ROCTAVIANUS9, 504, 762; 10, 463, 718; 11, 406, 690Compositions, Methods of Treatment, ProductionSeptember 10, 2034 (~~5~~ **4**) 10, 512, **675; 11, 690,** ~~675Formulation~~ **898Formulation** , Clinical Methods of **TreatmentApril 10, 2037 December 19, 2038EU3044231Compositions, Methods of** TreatmentSeptember **10** ~~23, 2036EU3044231Compositions, Methods of TreatmentSeptember 30~~ , 2034 (~~6~~ **5**) VIMIZIMU. S. 8, 128, 925Compositions; methods of treatmentApril 10, 20308, 765, 437Purification; formulation; methods of treatmentJanuary 10, 2032EU2245145Composition; use for treatingApril 30, 2029 (~~7~~ **6**) 2595650Purification; composition; use for treating; formulationJuly 22, 2031VOXZOGOU. S. 8, 198, 242Compositions, Methods of Treatment June 11, 2030 (~~8~~ **7**) 9, 907, 834FormulationAugust 1, 203610, 646, 550Clinical methods of treatmentAugust 1, 2036EU2432489Compositions, Methods of TreatmentMay 20, 2030 (~~9~~ **8**) (1) ~~Under a~~ **Date of expiry includes** patent term extension (PTE) **.** ~~that has been granted~~ (2) ~~Patent application~~ **Date of expiry includes the granted PTE.** (3) We ~~filed~~ **applied** for **SPCs** ~~a PTE~~ for this patent, and ~~if granted,~~ **we have to date received SPC to extend** the patent expiration ~~will extend~~ to May ~~24~~ **23** , ~~2032~~ **2033 in certain European countries, including Austria, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland France, Greece, Hungary, Ireland, Iceland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Spain, Slovakia, Slovenia, Sweden, and United Kingdom** . (4) We ~~applied for SPCs for this patent, and we have to date received SPC to extend the patent expiration to May 23, 2033 in certain European countries, including Austria, Cyprus, Czech Republic, Denmark, Estonia, Finland France, Greece, Hungary, Ireland, Iceland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Portugal, Spain, Slovenia and Sweden. (5) We~~ filed for a PTE for these patents, and if granted, **we expect** the patents' expirations

will extend to ~~September 10~~ **June 29** , ~~2039~~ **2037 for the 9, 504, 762 patent and November 21, 2036 for the 11, 406, 690 patent. (5) We applied for SPCs for this patent and we have to date received SPC to extend the patent expiration to August 25, 2037 in certain European countries, including Austria, Cyprus, Denmark, Estonia, Finland, Hungary, Italy, Lithuania, Luxembourg, Latvia, Malta, Netherlands, and Portugal** . (6) We applied for SPCs for this patent, and we have to date received SPC to extend the patent expiration to ~~September 10~~ **April 30** , ~~2037~~ **2029** in certain European countries, including Austria, Belgium, Bulgaria, ~~Cyprus~~ **Cypress , Croatia, Czech Republic, Denmark, Estonia, Finland, France** , Germany, ~~Denmark~~ **Greece** , ~~Estonia~~ **Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia** , Spain, ~~Finland~~ **Sweden** , ~~France,~~ **Switzerland and the** United Kingdom ~~, Croatia, Hungary, Ireland, Iceland, Italy, Lithuania, Luxembourg, Latvia, Malta, Netherlands, Norway, Poland, Portugal, Romania, Sweden and Slovakia~~ . (7) We ~~applied~~ **filed** for ~~SPCs~~ **a PTE** for this patent, and **if granted,** we **expect** ~~have to date received SPC to extend~~ the patent expiration **will extend** to ~~April 30~~ **May 20** , **2035** ~~2029 in certain European countries, including Austria, Bulgaria, Cypress, Czech Republic, Denmark, Estonia, Finland, France, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland and the United Kingdom~~ . (8) We ~~filed~~ **applied** for **SPCs** ~~a PTE~~ for this patent ~~, and if granted, the patent expiration will extend to May 20, 2035. (9) We applied for SPCs for this patent in Hungary, Germany, Poland, Netherlands, Norway, Denmark, Czech Republic, Italy, France, Spain, Greece, Belgium, Finland, Sweden, Ireland, Croatia, Austria and the United Kingdom,~~ and have been granted SPCs so far in **Greece, Estonia, Hungary, Sweden, France,** Italy ~~and~~ **,** Austria **, Japan, and Australia,** extending the patent expiration to May ~~30~~ **20** , 2035. In addition to patent protection, certain of our products are entitled to regulatory exclusivity in the U. S. and the EU through the dates set forth below: Commercial ProductsUnited StatesOrphanDrugExclusivityExpiration (1) UnitedStatesBiologicExclusivityExpiration (2) EuropeanUnionOrphan DrugExclusivityExpiration (1)

~~BRINEURA202420292027PALYNZIQ202520302029ROCTAVIANPendingPending2032VIMIZIMExpired20262024VOXZOGO2028Not~~

BRINEURA202420292027PALYNZIQ202520302029ROCTAVIAN203020352032VIMIZIMExpired20262024VOXZOGO2028Not Applicable2031 (1) See " Government Regulation — Other Regulation — Orphan Drug Designation " in this Annual Report on Form 10- K for further discussion. (2) See " Government Regulation — Other Regulation — Exclusivity for Biologics in the U. S. " in this Annual Report on Form 10- K for further discussion. With respect to our clinical product candidates, we believe we have the necessary intellectual property rights to allow 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. Regulation by governmental authorities in the U. S., European countries 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 non- U. S. regulation. Our products require approval from the FDA, the EC (on the basis of the scientific opinions issued by the EMA) and corresponding agencies in other countries before they can be marketed. Failure to comply with applicable U. S. and foreign 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 **Biologics License Applications (** BLAs **)** , warning or untitled letters **, investigations** , product recalls, product seizures, total or partial suspension or withdrawal of marketing, production or distribution authorizations, injunctions, fines, civil penalties, and criminal prosecution. Approval Process in the U. S. and EU Satisfaction of FDA and EU 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. 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 in the U. S. or a CTA in the EU), 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. On January 31, 2022, Regulation EU No 536 / 2014 (CTR) became fully applicable in the EU. The CTR established a centralized application procedure where one of the National Competent Authorities (NCA) of the Member States where the trial will take place takes the lead in reviewing certain aspects of the application, while the other NCAs have a lesser involvement than they had under the previous regime established by Directive 2001 / 20 / EC (CTD). The CTD indeed introduced the first set of harmonized rules on clinical trials in the EU but resulted in a patchwork of different national regimes. The CTR was adopted with a view to introducing a more uniform set of the rules across the EU for the authorization of clinical trials. Such authorization still involves the national regulatory authorities and Ethics Committees of each of the EU Member States where the trial is to be conducted. However, the relevant procedures have now been streamlined with a view to facilitating a swifter and more seamless authorization and deployment of multi- center trials occurring in more than one EU Member State. More specifically, the CTR allows sponsors to rely on one single submission for CTAs regardless of the number of Member States where the trial takes place and based on a single harmonized application. Furthermore, under the CTR, deadlines for regulatory approvals are shortened with a view to accelerating the authorization process. The CTR also established an EU Portal which will act as a single- entry point for submission of data and information relating to clinical trials. Until January 30, 2025, the CTD will continue to apply in parallel to the CTR for a transitional period. From January 31, 2025 all trials will have to comply with the CTR. 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 EU and national regulations and requirements, including good laboratory practices (GLP). The results of preclinical testing, along with other information, including information about product chemistry, manufacturing and controls and a proposed clinical trial protocol are reviewed by 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, and appropriate reviews have been satisfactorily completed by the applicable Institutional Review Boards (IRBs) or Ethics Committees, 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. 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 that are deployed to support NDAs, BLAs or Marketing Authorization Applications (MAAs) for marketing approval are typically conducted in three sequential phases, but the phases may overlap or be combined. Typically, we undertake a three- phase human clinical testing program as follows: • 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- 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 applicable regulatory agency. Approval of the application by the applicable regulatory agency is required before marketing of the product may begin. In the European Economic Area (i. e., the EU as well as Iceland, Liechtenstein and Norway) (the EEA), there are two types of marketing authorizations (MA), namely: (i) the " Union " MA, which is issued by the EC through the so- called " centralized procedure ", based on the positive opinion of the EMA' s Committee for Medicinal Products for Human Use (CHMP), and results in a single marketing authorization that is valid across the EEA; and (ii) " National MAs, " which are issued by the competent NCAs and only cover their respective territory. The centralized procedure is mandatory for certain types of products such as: (i) medicinal products derived from certain biotechnology processes, (ii) designated orphan medicinal products, (iii) medicinal products containing a new active substance indicated for the treatment of certain diseases such as HIV / AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune diseases and other auto- immune dysfunctions, viral diseases; and (iv) Advanced Therapy Medicinal Products (ATMPs) (such as gene therapy, somatic cell therapy or tissue- engineered medicines). 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. Similarly, in the EU, the submission of an MAA is subject to the payment of fees, a waiver of which may be obtained only under limited circumstances. The FDA and the EMA initially review the applications for a threshold determination that it is sufficiently complete to permit substantive review. 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 **for new molecular entities** is typically ~~an additional~~ ten months **from the date the FDA files the application** 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~~ **from the date the FDA files the application** . 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 and the NDA / BLA has been resubmitted, 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 EU, 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 must 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 European authorities may typically inspect one or more clinical sites and / or the sponsor to assure compliance with GCP regulations and may equally inspect the facility or the facilities at which the drug is manufactured to ensure compliance with cGMPs regulations. Neither the FDA nor the EC 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. Fast Track Designation and Accelerated Approval 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. Under

the fast track program and the FDA' s accelerated approval regulations, the FDA may approve a drug for a serious or life- threatening illness that provides meaningful therapeutic benefit to patients over existing treatments based upon a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. In clinical trials, a surrogate endpoint is a measurement of laboratory or clinical signs of a disease or condition that substitutes for a direct measurement of how a patient feels, functions, or survives. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. A drug candidate approved on this basis is subject to rigorous post- marketing compliance requirements, including the completion of a Phase 4 or post- approval clinical trial to confirm the effect on the clinical endpoint. Failure to conduct a required post- approval study or confirm a clinical benefit through a post- marketing study will allow the FDA to withdraw the drug from the market on an expedited basis. All promotional materials for drug candidates approved under accelerated regulations are subject to prior review by the FDA. The Food and Drug Omnibus Reform Act (FDORA) **added** ~~was recently enacted, which included~~ provisions related to the accelerated approval pathway. Pursuant to FDORA, the FDA is authorized to require a post- approval study to be underway prior to approval or within a specified time period following approval. FDORA also requires the FDA to specify conditions of any required post- approval study, which may include milestones such as a target date of study completion and requires sponsors to submit progress reports for required post- approval studies and any conditions required by the FDA not later than 180 days following approval and not less frequently than every 180 days thereafter until completion or termination of the study. FDORA enables the FDA to initiate ~~criminal prosecutions~~ **enforcement action** for the failure to conduct with due diligence a required post- approval study, including a failure to meet any required conditions specified by the FDA or to submit timely reports. 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. The EMA has an adaptive pathways approach which allows for early and progressive patient access to a medicine in cases of high medical need. To achieve this goal, several approaches are envisaged including for example identifying small populations with severe disease where a medicine' s benefit- risk balance could be favorable or making more use of real- world data where appropriate to support clinical trial data. The adaptive pathways concept applies primarily to treatments in areas of high medical need where it is difficult to collect data via traditional routes and where large clinical trials would unnecessarily expose patients who are unlikely to benefit from the medicine. The approach builds on regulatory processes already in place within the existing EU legal framework. These include: scientific advice; compassionate use; the conditional MA; patient registries and other pharmacovigilance tools that allow collection of real- life data and development of a risk- management plan for each medicine. A conditional MA may be granted prior to the submission of comprehensive clinical data if the benefit of the immediate availability on the market of the product is deemed to outweigh the risk inherent in the fact that additional data are still required. In emergency situations, a MA for such medicinal products may be granted also where comprehensive pre- clinical or pharmaceutical data have not been provided. Under this procedure a MA can be granted as soon as sufficient data becomes available to demonstrate that the drug' s benefits outweigh its risks, with safeguards and controls in place post- authorization. This procedure can also be combined with a rolling review of data during the development of a promising medicine, to further expedite its evaluation. Conditional MAs are typically subject to obligations that are reviewed annually. These include the obligation to complete ongoing studies, or to conduct new studies, with a view to confirming that the risk- benefit balance is favorable. Conditional MAs are valid for one year and are renewable. PRIME Program The EMA launched its PRIME regulatory program 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. **Product Marketing and Promotion** A marketing approval authorizes commercial marketing of the drug with specific prescribing information for specific indications **Similar rules apply outside of** ~~. The FDA and European authorities closely regulate~~ the **U.S.For example,products approved in the EU may be subject to** post- **authorization requirements such as the obligation** ~~approval marketing and promotion of commercial products,including standards and regulations for direct-~~ to **perform post** ~~- consumer advertising~~ **authorization efficacy studies** (**PAES) or post- authorization safety studies (PASS) imposed as conditions to the MA,or other Risk Minimization Measures (RMMs),such as educational programs or controlled access programs,** which ~~is prohibited in the~~ **may sometimes vary from one** EU **Member State to another** ~~for prescription products such as our products),off- label promotion,industry- sponsored scientific and educational activities and promotional activities involving the Internet.For further detail,please see" Post- Approval Regulatory Requirements" below -~~ Regulation of Manufacturing Standards The FDA as well as other regulatory agencies around the world,regulate and inspect the equipment,facilities,laboratories and processes used in the manufacturing and testing of products prior to granting approval to market products.If after receiving approval from the FDA and other agencies such as the EC we make a material change in manufacturing equipment,location or process,additional regulatory review and approval may be required.We also must adhere to cGMP regulations and product- specific regulations enforced by the FDA and other regulatory agencies through their facilities inspection program.The FDA and other regulatory agencies around the world conduct regular,periodic visits to reinspect our equipment,facilities,laboratories and processes following an initial approval.Combination products are defined by the FDA as products composed of two or more regulated components (e.g.,a biologic and / or drug and a device).Biologics / drugs and devices each have their own regulatory requirements,and combination products may have additional requirements.For example,in the EU,if a device intended to administer a medicinal product is sold together with such medicinal product in such a way that they form a single integral product which is intended exclusively for use in the given combination and which is not reusable,that single integral product is regulated as a medicinal product.In addition,the relevant general safety and performance requirements established for medical devices by EU medical devices legislation apply to the device component of such combination products.A number of our products qualify as combination products and are regulated under the applicable framework,and we expect that a number of our pipeline product candidates will be evaluated for regulatory approval under such framework as well. ~~If use of~~ **Post- Approval Regulatory Requirements Following approval,the FDA** ~~an~~ **and** ~~in vitro diagnostic~~ **the regulatory authorities around the world will impose certain post- approval requirements related to a product.For instance,the FDA and European authorities closely regulate the post- approval**

marketing and promotion of approved products,including standards and regulations for direct- to- consumer advertising (which is **prohibited in** ~~essential to safe and effective use of a drug or biologic product,then~~ **the EU** ~~the FDA generally will require approval or clearance of the diagnostic,known as a companion diagnostic,at the same time that the FDA approves the therapeutic product.The review of these in vitro companion diagnostics in conjunction with the review of a drug or biologic involves coordination of review by the FDA' s Center~~ for ~~Drug Evaluation and Research~~ **prescription products such as** ~~or~~ **our** ~~Center for Biologics Evaluation~~ **products),off- label promotion,industry- sponsored scientific** and ~~Research~~ **educational activities** and ~~by~~ **promotional activities involving** the **Internet.** ~~FDA' s Center for Devices and~~ . As a condition of NDA or BLA approval, the FDA may require a REMS, to help ensure that the benefits of the drug outweigh the potential risks. A 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 **. Similar rules apply outside of the U. S. For example, products approved in the EU may be subject to post- authorization requirements such as the obligation to perform post- authorization efficacy studies (PAES) or post- authorization safety studies (PASS) imposed as conditions to the MA, or other Risk Minimization Measures (RMMs), such as educational programs or controlled access programs, which may sometimes vary from one EU Member State to another** . Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing. Similar rules apply outside of the U..... and promotional activities involving the Internet. Moreover, if a company obtains original approval for a product via an accelerated approval pathway, the company will be typically 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 marketing approval for a product. ~~Approved~~ **Commercial** 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 EC, 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 the EC / EMA may also require post- marketing testing, known as Phase 4 testing, a risk evaluation and mitigation strategy, 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, the EMA / NCAs, during which the inspectors audit manufacturing facilities to assess 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. Similarly, in the EU, stringent rules have been introduced to fight medicine falsifications and to ensure that the trade in medicines is subject to rigorous controls. Measures required to ensure that include: a unique identifier and an anti- tampering device on the outer packaging of drugs, stringent rules on import of active pharmaceutical ingredients and record- keeping requirements for wholesale distributors. Approval Regulation Outside of the U. S. and the EU For marketing outside the U. S. and the EU, we are subject to non- U. S. 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 preclinical or clinical testing. The amount of time required to obtain necessary approvals may be longer or shorter than that required for FDA or EC 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. The Biologics Price Competition and Innovation Act of 2009 (BPCIA), which was enacted as part of 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), created an abbreviated approval pathway for biological products that are demonstrated to be " biosimilar " **to** or " interchangeable " with an FDA- licensed reference biological product. ~~Biosimilarity~~ **Biosimilars** ~~sufficient to reference~~ **are licensed based on FDA' s findings of safety, purity, and potency for** a prior FDA- licensed product ~~requires that~~ **called a reference product.** ~~there~~ **There must** be no differences in conditions of use, route of administration, dosage form, and strength **to rely on a given reference product** , and **there can be** 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 **comparative** clinical study, absent a waiver from the **FDA** ~~Secretary of the U~~ . **A biosimilar also may** ~~S. Department of Health and Human Services. In order to~~ meet the higher hurdle of interchangeability **such that it can be substituted for a reference product without the intervention of the prescribing health care provider. For licensure as an interchangeable biosimilar** , a sponsor must demonstrate that the biosimilar product can be expected to produce the same clinical result as the reference product **in any given patient** , and for a product that is administered more than once **to an individual** , that the risk of **switching in terms of safety or diminished efficacy of alternating or** 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, and the first interchangeable product was approved in 2021. 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 **data** exclusivity from the time of first licensure of the reference product ~~and~~ **during which** no **biosimilar referencing such biologic can be licensed by FDA, and no such biosimilar** application ~~for a biosimilar~~ **relying on the reference product** can be submitted for four years from the date of **first** 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~~ **is eligible for** exclusivity **precluding marketing** ~~against a finding~~ of ~~interchangeability~~ **interchangeable biosimilars referencing** ~~for other biologics for~~ the same **reference product** ~~condition of use~~ for the lesser of (i) one year after first commercial marketing of the first interchangeable biosimilar **to be approved** , (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~~ **the interchangeable applicant has been sued under the BPCIA and any related** patent ~~lawsuit~~ **litigation** is ongoing within the 42- month period. Data Exclusivity and Market Exclusivity in the EU The EU provides opportunities for market and data exclusivity for all products containing a New Active Substance, or NAS (such as a chemical, biological or radiopharmaceutical substance not previously authorized as a medicinal product in the EU), which have been granted an MA. These products receive eight years of data exclusivity and an additional two years of market exclusivity. The data exclusivity period prevents generic or biosimilar applicants from relying on the pre- clinical and clinical trial data contained in the dossier of the reference product when applying for a generic or biosimilar MA in the EU during a period of eight years from the date on which the reference product was first authorized in the EU. The market exclusivity period prevents a successful generic or biosimilar applicant from commercializing its product in the EU until ten years have elapsed from the initial MA of the reference product in the EU. The overall ten- year market exclusivity period can be extended to a maximum of eleven years if, during the first eight years of those ten years, the MA holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Orphan drug designation is granted by the FDA and the EC 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. **or as a condition that affects more than 200, 000 individuals in the U. S. and for which there is no reasonable expectation that the costs of development of said drug will be recovered from sales 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 derived from the orphan status, 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 criteria, 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 and, in the EU, it must be maintained until the time of the granting of the MA. Orphan designation is indeed lost in the EU if it is established that the product no longer meets the orphan criteria at the time a MA is granted for such product. 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~~ **condition** , 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 (PIP) 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. **A competitor may also demonstrate that its proposed product is " clinically superior " to a product with orphan drug exclusivity, allowing for approval and market entry of the same drug for the same condition during the first product' s orphan drug exclusivity period.** In the EU, a MA may be granted to a similar medicinal product with the same orphan indication during the regulatory exclusivity period with the consent of the MA holder for the original orphan medicinal product or if the MA holder of the original orphan medicinal product is unable to supply sufficient quantities. A MA may also be granted to a similar medicinal product with the same orphan indication if the second applicant can establish that its 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. Healthcare Reform The U. S. federal and state governments continue to propose and pass legislation designed to regulate the healthcare industry, including legislation that seeks to directly or indirectly regulate pharmaceutical drug pricing. For more information, see Item 1A. Risk Factors " Government healthcare reform could increase our costs and adversely affect our revenue and results of operations. " **In addition, in the EU, EMA, the EC and other comparable regulatory authorities continue to propose and pass legislation and issue additional guidelines that may affect the applicable legislative framework. In particular, the EU pharmaceutical legislation is currently the subject of a review process, in the context of the Pharmaceutical Strategy for Europe initiative, launched by the EC in November 2020. The EC' s proposal for a revision of several legislative instruments related to medicinal products (potentially reducing the duration of regulatory exclusivity, revising the eligibility for expedited pathways, etc.) was published on April 26, 2023. The proposed revisions remain to be agreed and adopted by the European Parliament and European Council. The proposals may be substantially revised before adoption. The revisions may, however, have a significant impact on our activities in the long term.** Other 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 Centers for Medicare & Medicaid Services (CMS) information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), physician assistants, certain types of advanced practice nurses 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. 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 while other states prohibit various other marketing- related activities. Other states require submission or disclosure of certain pricing information. 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 **and** ~~. 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. Sanctions under these federal and state laws may include significant penalties, including administrative and criminal sanctions, 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. 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 non- U. S. 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 U. K., that restrict improper payments to public and private parties. Many countries have laws prohibiting these types of payments within the respective country. In the EU, for example, harmonized rules prohibit gifts, pecuniary advantages or benefits in kind to Health Care Professionals (HCPs) unless they are inexpensive and relevant to the practice of medicine or pharmacy. Similarly, strict rules apply to hospitality at sales promotion events. Based on these rules, a body of industry guidelines and sometimes national laws in force in individual EU Member States has been introduced to fight improper payments or other transfers of value to HCPs, and in general inducements that may have a broadly promotional character. Historically, pharmaceutical companies have been the target of FCPA and other anti- corruption and similar investigations, as well as of wide media attention, sometimes resulting in significant penalties, image and other costs for such companies. 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 pricing and / or 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 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 Pricing and Reimbursement Programs for Marketed Drugs in the U. S. Medicaid, the 340B Drug Pricing Program, and Medicare Federal law requires that a pharmaceutical manufacturer, as a condition of having its products receive federal reimbursement under Medicaid and Medicare Part B, must pay rebates to state Medicaid programs for all units of its covered outpatient drugs dispensed to Medicaid beneficiaries and paid for by a state Medicaid program under either a fee- for- service arrangement or through a managed care organization. This federal requirement is effectuated through a Medicaid drug rebate agreement between the manufacturer and the Secretary of Health and Human Services. CMS administers the Medicaid drug rebate agreements, which provide, among other things, that the drug manufacturer will pay rebates to each

state Medicaid agency on a quarterly basis and report certain price information on a monthly and quarterly basis. The rebates are based on prices reported to CMS by manufacturers for their covered outpatient drugs. For non- innovator products, generally generic drugs marketed under abbreviated new drug applications (referred to as 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. To date, the rebate amount for a drug has been capped at 100 % of the AMP; however, effective January 1, 2024, this cap **was** ~~will be~~ eliminated, which means that a manufacturer could pay a rebate amount on a unit of the drug that is greater than the average price the manufacturer receives for the drug. 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 **and biological products** 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. 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. **There is ongoing litigation that may restrict the number of third- party contract pharmacies that can dispense drugs that manufacturers sell to 340B covered entities and who qualifies as patients of these 340B covered entities. The outcome of this litigation may change the scope of the 340B program in coming years.** 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 **. Under the Inflation Reduction Act (IRA), manufacturers are also required to provide quarterly rebates for certain single- source drugs and biologics (including biosimilars) covered under Medicare Part B with prices that increase faster than the rate of inflation. This requirement started on January 1, 2023, for drugs approved on or before December 1, 2020, and begins six quarters after a drug is first marketed for all other drugs** . 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 enrollees once had a gap in their coverage (between the initial coverage limit and the point at which catastrophic coverage begins) where Medicare did not cover their prescription drug costs, known as the coverage gap. However, beginning in 2019, Medicare Part D enrollees paid 25 % of brand drug costs after they reached the initial coverage limit- the same percentage they were responsible for before they reached that limit- thereby closing the coverage gap from the enrollee' s point of view. Most of the cost of closing the coverage gap is being borne by innovator companies and the government through subsidies. Each manufacturer of drugs approved under NDAs or BLAs is required to enter into a Medicare Part D coverage gap discount agreement and provide a 70 % discount on those drugs dispensed to Medicare Part D enrollees in the coverage gap, in order for its drugs to be reimbursed by Medicare Part D. Beginning in 2025, the ~~Inflation Reduction Act (~~IRA ~~)~~ eliminates the coverage gap under Medicare Part D by significantly lowering the enrollee maximum out- of- pocket cost and requiring manufacturers to subsidize, through a newly established manufacturer discount program, 10 % of Part D enrollees' prescription costs for brand drugs **above a deductible and** below the out- of- pocket maximum, and 20 % once the out- of- pocket maximum has been reached. Although these discounts represent a lower percentage of enrollees' costs than the current discounts required below the out- of- pocket maximum (that is, in the coverage gap phase of Part D coverage), the new manufacturer contribution required above the out- of- pocket maximum could be considerable for very high- cost patients and the total contributions by manufacturers to a Part D enrollee' s drug expenses may exceed those currently provided. The IRA ~~will~~ also **requires manufacturers to provide annual Medicare Part D rebates for single- source drugs and biological products with prices that increase faster than the rate of inflation. The IRA also** ~~allow~~ **allows** the U. S. Department of Health and Human Services (HHS) to **directly** negotiate the selling price of ~~certain~~ **a statutorily specified number of** drugs and biologics **each year** that CMS reimburses under Medicare Part B and Part D **.** ~~, although only~~ **Only** high- expenditure single- source drugs that have been approved for at least 7 years (11 years for biologics) can **qualify** ~~be selected by CMS~~ for negotiation, with the negotiated price taking effect two years after the selection year. ~~The~~ **Negotiations for Medicare Part D products begin in 2024 with the** negotiated ~~prices~~ **price taking effect in 2026, and negotiations for Medicare Part B products begin in 2026 with the negotiated price taking effect in 2028. In August 2023, HHS announced the ten Medicare Part D drugs and biologics that it selected for negotiations, and by October 1, 2023, each manufacturer of the selected drugs signed a manufacturer agreement to participate in the negotiations. HHS will announce the negotiated maximum fair price by September 1, 2024, and this price cap** , which **cannot exceed** ~~will first become effective in 2026, will be capped at~~ a statutory ceiling price **, will come into effect on** ~~- Beginning in October 2022 for Medicare Part D and~~ January **1,** ~~2023~~ **2026 . A drug** ~~for -~~ **or** ~~Medicare Part B,~~ **biological product that has an orphan drug designation for only one rare disease or condition will be excluded from** the IRA ~~will also penalize~~ **' s price negotiations requirements, but loses that exclusion if it has designations for more than one rare disease or condition, or if is approved for an indication that is not within that single designated rare disease or condition, unless such additional designation or such disqualifying approvals are withdrawn by the time CMS evaluates the** drug **for selection for negotiation** ~~manufacturers that increase prices of Medicare Part D and Part B drugs at a rate greater than the rate of inflation~~ . U. S. Federal Contracting and Pricing Requirements Manufacturers are also required to make their covered drugs, which are generally drugs approved under NDAs or BLAs, available to authorized users of the Federal Supply Schedule (FSS) of the General Services Administration. The law also requires manufacturers to offer deeply discounted FSS contract pricing for purchases of their covered drugs by the Department of Veterans Affairs, the Department of Defense, the Coast Guard, and the Public

Health Service (including the Indian Health Service) in order for federal funding to be available for reimbursement or purchase of the manufacturer' s drugs under certain federal programs. FSS pricing to those four federal agencies for covered drugs must be no more than the Federal Ceiling Price (FCP), which is at least 24 % below the Non- Federal Average Manufacturer Price (Non- FAMP) for the prior year. The Non- FAMP is the average price for covered drugs sold to wholesalers or other middlemen, net of any price reductions. The accuracy of a manufacturer' s reported Non- FAMPs, FCPs, or FSS contract prices may be audited by the government. Among the remedies available to the government for inaccuracies is recoupment of any overcharges to the four specified federal agencies based on those inaccuracies. If a manufacturer were found to have knowingly reported false prices, in addition to other penalties available to the government, the law provides for 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. 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. In the EU there is an increasing trend requiring public disclosure of development data, in particular clinical trial data. These data were traditionally regarded as Confidential Commercial Information (CCI); however, under policies adopted in the EU, clinical study data submitted to the EMA in MAAs, including preclinical data, and patient level data, may be subject to public disclosure. This is confirmed in the CTR, the new EU legislation on clinical trials, according to which clinical trial applications and all the related documentation are uploaded and stored in the Clinical Trials Information System (CTIS) which is managed by the EMA. Confirming the transparency principle, the CTR provides that the information stored in such system is publicly accessible unless confidentiality is justified on the basis of a limited set of exceptions. These exceptions, which are to be interpreted narrowly in the EU, include the protection of CCI, in particular through taking into account the status of the MA for the applicable product; however, CCI is overridden in those cases where the authorities conclude that there is an overriding public interest in disclosure. Case law of the Court of Justice of the EU has also confirmed the absence of a general presumption of confidentiality over documents containing clinical and preclinical data provided to the EMA in support of a MAA. Pediatric Indications In the U. S., under the Pediatric Research Equity Act of 2007 (PREA), **most** 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 statute or regulation, PREA does not apply to any drug for an indication for which orphan drug designation has been granted **; the orphan drug exemption, however, does not apply where the product is a molecularly- targeted oncology drug** . 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 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 PIP with the EMA and must conduct pediatric clinical trials in accordance with that PIP, unless a deferral or waiver is granted by the EMA on request by the applicant (e. g., because the relevant disease or condition occurs only in adults). The PIP requirement also applies when a MA holder intends to add a new indication, pharmaceutical form or route of administration for a medicinal product that has already been authorized. 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. Once all the studies and measures agreed have been conducted in accordance with the PIP, products 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 granted subject to specific conditions. These conditions include that the applicant demonstrates having complied with all the measures contained in the PIP, that the summary of product characteristics, and if appropriate the package leaflet, reflects the results of studies conducted in compliance with such PIP, and that the product is authorized in all Member States. The rewards for conducting studies in the pediatric population can be granted irrespective of the fact that the information generated in compliance with the agreed PIP fails to lead to the authorization of a pediatric indication. Privacy and Security Legislation In the ordinary course of our business, we may process personal or sensitive data. Accordingly, we are, or may become, subject to numerous data privacy and security obligations, including federal, state, local, and foreign laws, regulations, guidance, and industry standards related to data privacy, security, and protection. Such obligations may include, without limitation, the Federal Trade Commission Act, the California Consumer Privacy Act of 2018 (CCPA), the Canadian Personal Information Protection and Electronic Documents Act, the **EU** ~~European Union~~ ' s General Data Protection Regulation 2016 / 679 (EU GDPR), the EU GDPR as it forms part of United Kingdom (UK) law by virtue of section 3 of the European Union (Withdrawal) Act 2018 (UK GDPR). The legislative and regulatory environments regarding privacy and data protection are continually evolving and developing, in response to increasing global attention. In the U. S., for example, we are subject to the CCPA along with the California Privacy Rights Act of 2020 (CPRA). The CCPA imposes obligations on covered businesses to provide specific disclosures related to a business' s collecting, using, and disclosing personal data and to respond to certain requests from California residents related to their personal data (for example, requests to know of the business' s personal data processing activities, to delete the individual' s personal data, and to opt out of certain personal data disclosures). Also, the CCPA provides for civil penalties and a private right of action for data breaches which may include an award of statutory damages. In addition, the CPRA, effective January 1, 2023, expanded the CCPA. The CPRA, among other things, gives California residents the ability to limit use of certain sensitive personal data, establish restrictions on personal data retention, expands the types of data breaches that are subject to the CCPA' s private right of action, and establishes a new California Privacy Protection Agency to implement and enforce the new law. Other jurisdictions where we operate have enacted or proposed similar legislation and / or regulations. Several states within the United States have enacted or proposed data privacy laws. Additionally, we are, or may become, subject to various U. S. federal and state consumer protection laws which require us to

publish statements that accurately and fairly describe how we handle personal data and choices individuals may have about the way we handle their personal data. We are also subject to the EU' s General Data Protection Regulation GDPR, which requires that personal data is only collected for specified, explicit and legal purposes as set out in the GDPR or local laws, and the data may then only be processed in a manner consistent with those purposes. The personal data collected and processed must be adequate, relevant and not excessive in relation to the purposes for which it is collected and processed, it must be held securely, not transferred outside of the EEA (unless certain steps are taken to ensure an adequate level of protection), and must not be retained for longer than necessary for the purposes for which it was collected. The GDPR also requires companies processing personal data to implement adequate technical measures in order to ensure the most appropriate level of security which may vary depending on different factors such as the categories of processed personal data, the state of the art, the costs of implementation and the nature, scope, context and purposes of processing as well as the risk of varying likelihood and severity for the rights and freedoms of natural persons. In addition, the GDPR requires companies processing personal data to take certain organizational steps to ensure that they have adequate records, policies, security, training and governance frameworks in place to ensure the protection of data subject rights, including as required to respond to complaints and requests from data subjects. For example, the GDPR requires us to make more detailed disclosures to data subjects, requires disclosure of the legal basis on which we can process personal data, provides for conditions under which a valid consent for processing can be obtained, requires the appointment of a data protection officer where sensitive personal data (i. e., health data) is processed on a large scale, imposes mandatory data breach notification throughout the EEA and imposes additional obligations when contracting with service providers or partners. In addition, to the extent a company processes, controls or otherwise uses " special category " of personal data (including patients' health or medical information, genetic information and biometric information), more stringent rules apply, further limiting the circumstances and the manner in which a company is legally permitted to process that data. ~~Failure to comply with these laws could result in significant penalties, including, under GDPR, fines of up to 20 million Euro or 4 % of the total worldwide annual turnover of the preceding financial year, whichever is higher. The CCPA and EU GDPR are examples of the increasingly stringent and evolving regulatory frameworks related to personal data processing that may increase compliance obligations and exposure for any noncompliance.~~ Human Capital As of December 31, ~~2022~~ **2023** , we had 3, **401** ~~082 full- time~~ employees worldwide, of whom 1, ~~343~~ **509** were in operations, ~~736~~ **807** were in research and development, ~~495~~ **535** were in sales and marketing and ~~508~~ **550** were in administration. Of the 3, **401** ~~082 full- time~~ employees as of December 31, ~~2022~~ **2023** , 2, ~~066~~ **282** employees were in the U. S. and Canada, and 1, ~~016~~ **119** employees were in **outside of North America** ~~other non- U. S. countries~~ , including ~~818~~ **902** in Europe and the Middle East, ~~129~~ **141** in Latin America and ~~69~~ **76** in Asia Pacific. We also leverage temporary workers to fill short- term positions for our business and manufacturing needs. A significant portion of our employee base in the U. S. and Ireland works onsite supporting manufacturing and laboratory ~~operations. As restrictions from the COVID- 19 pandemic have eased, a significant portion of our global workforce who worked remotely during the pandemic has made a return to their respective office locations on a hybrid basis, with a small number of employees continuing to fully work remotely. On October 6, 2022, we announced a plan to simplify our organization, which included a planned reduction in headcount of approximately 120 employees (representing approximately 4 % of the Company' s global workforce), most of whom were from the Company' s U. S.~~ operations. Diversity, Equity and Inclusion At BioMarin, prejudice, racism and intolerance are unacceptable. We are committed to diversity, equity and inclusion (DEI) across all aspects of our organization, including hiring, promotion and development practices. At the direction of BioMarin' s senior leadership team, our human resources department has implemented policies and programs to foster DEI at all levels of the organization. In addition, the Corporate Governance and Nominating and Compensation Committees of our Board of Directors regularly receive reports on our DEI policies and programs and offer valuable insights and recommendations to management in addition to providing appropriate oversight. As of December 31, ~~2022~~ **2023** , racial and ethnic minorities represented ~~47~~ **49** % of our employees in the U. S. Globally, ~~50~~ **51** % of our workforce were women and ~~47~~ **52** % of our positions at director- level and above were held by women. We are committed to continuing our ongoing efforts to ensure diversity in all positions, including leadership. ~~We remain steadfast in our commitment to fostering a community that reflects equality~~ **Equality** ~~and~~ **,** inclusiveness and ~~working towards making~~ **belonging are central to** BioMarin **' s culture, and we work to make our company** a place where every employee feels heard, respected and valued. **We** ~~This commitment is a cultural value, and we~~ believe **encouraging and** incorporating **ideas** ~~and encouraging different perspectives~~ from employees ~~of varied~~ **with different** backgrounds ~~and experiences~~ helps us better serve our patients, achieve our business goals and objectives and provide employees with a fulfilling work experience. Since 2020, BioMarin' s DEI Employee Advisory ~~Committee~~ **Committees** ~~has~~ **have** helped to define our DEI roadmap and ensure that perspectives from employees of different age, gender, sexual orientation, race, ethnicity, tenure, level and location are considered in how we build the most inclusive environment. We also continue to support ~~and increase the number of~~ our employee resource groups that build community for employees from underrepresented ~~groups~~ **populations** . **Our** ~~In addition, our~~ foundational DEI training is **a pillar of our DEI strategy and is** required for all employees ~~,~~ ~~with a 100 % global participation rate in 2022~~ , and we offer opportunities for advanced DEI training **for all employees** as well **. In addition, we provide mentorship and leadership development programs, including programs designed specifically for underrepresented employees** . We are honored to be recognized as a company of choice. In ~~2022~~ **2023** ~~,~~ we were recognized for the ~~second~~ **third** year in a row as a Best Place to Work for lesbian, gay, bisexual, transgender and queer (LGBTQ) equality by the Human Rights Campaign, scoring 100 % on their Corporate Equality Index, one of the foremost benchmarking surveys and reports in the U. S. measuring corporate policies and practices related to LGBTQ workplace equality ~~. In JUST Capital' s America' s Most JUST Companies 2023 rankings, our overall rank was eight out of 41 in our industry, and our " Workers " rank, which is intended to measure how a company invests in its employees, was 29 out of 951 companies across all industries and 4 out of 41 pharmaceutical and biotechnology companies~~ . Compensation, Benefits and Well- being We offer competitive compensation and benefits in order to attract and retain excellent employees and support their overall well- being. Our total rewards compensation package includes market- competitive salary, the potential to earn bonuses or sales commissions, equity, healthcare benefits, retirement savings plans, paid time off and family leave, wellness programs **such as subsidized access to fitness centers and onsite fitness facilities** , free flu vaccinations and an Employee Assistance Program and other mental health services. We believe employees should be paid for the value of their work, regardless of race, ethnicity, gender or other protected characteristics. To this end, we benchmark and tie compensation to market data as well as to an employee' s experience, function, and performance. We regularly review our workforce compensation practices and strive for equity. Specifically, we partner with independent, third- party experts to conduct a regular and detailed pay equity assessment to determine whether gender and race / ethnicity have a significant impact on pay levels across the organization. This pay equity analysis is conducted on an employee' s total compensation, including base pay, bonus and equity. If we identify any pay gap across the organization, we typically make adjustments to mitigate such gaps. Our managers also receive training in how to recognize and prevent discrimination in hiring, performance management

and compensation decisions. Professional Growth and Development We help our employees develop the skills and capabilities to support BioMarin' s growth and innovation. We continually invest in our employees' career growth and provide them with a wide range of development opportunities, including face- to- face, virtual and self- directed learning, mentoring, mobile coaching and external development. We offer our employees career- specific training and resources and support development opportunities through company sponsored programs in addition to our tuition reimbursement program. We also provide our high- potential employees with a variety of leadership coaching and management programs. Patient and Community Connections We are striving to support our local communities around the world by developing programs that inspire and enrich both our patient populations and the areas where we live and work. We actively engage with underrepresented populations through a variety of outreach and programs. We collaborate with Biotech Partners, a non- profit organization in the San Francisco Bay Area focused on helping students who are underrepresented in the biotechnology field to gain experience through classroom instruction and paid internships. We also partner with Health Career Connection, a national non- profit that prepares the next generation of diverse, transformational health, equity and racial justice leaders by providing promising undergraduate college students from underrepresented backgrounds and under- resourced communities with paid internship programs, health equity scholars programs and alumni professional development initiatives. In addition, we award annual scholarships to students living with rare disease through our Rare Scholars program. Other Information We were incorporated in Delaware in October 1996. Our principal executive offices are located at 770 Lindaro Street, San Rafael, California 94901 and our telephone number is (415) 506- 6700. Our annual reports on Form 10- K, quarterly reports on Form 10- Q, proxy statements, current reports on Form 8- K and amendments to those reports filed or furnished pursuant to Section 13 (a) or 15 (d) of the Securities Exchange Act of 1934, as amended (the Exchange Act) are available free of charge at www. bmrn. com as soon as reasonably practicable after electronically filing such reports with the Security and Exchange Commission (the SEC). Such reports and other information may be accessed through the SEC' s website at www. sec. gov. Information contained in our website is not part of this or any other report that we file with or furnish to the SEC. Item 1A. Risk Factors An investment in our securities involves a high degree of risk. We operate in a dynamic and rapidly changing industry that involves numerous risks and uncertainties. The risks and uncertainties described below are not the only ones we face. Other risks and uncertainties, including those that we do not currently consider material, may impair our business. If any of the risks discussed below actually occur, our business, financial condition, operating results or cash flows could be materially adversely affected. This could cause the value of our securities to decline, and you may lose all or part of your investment. Business and Operational Risks The course of treatment for patients using our products is expensive. For all our products except ROCTAVIAN, 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 revenues and gross margin 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. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future **based on new legislation, the availability of alternative therapies and their pricing, coverage and reimbursement decisions by third- party payers, or other factors** . 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 European Union (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 pricing and / or 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 margin may be adversely affected ~~vectors for gene therapy and to seek the CTGTAC' s insight into strategies to evaluate and mitigate risks in the context of AAV vector- based product design and quality,preclinical studies,and clinical trials.ROCTAVIAN and BMN 331 are AAV vector- based product candidates.Further,the FDA continues to develop and publish new guidance and policies,such as the publication of four draft or final gene therapy- specific guidance documents in 2022.These guidance documents and other recent policy statements demonstrate that the FDA' s regulatory requirements for gene therapies are likely to continue to evolve based upon factors such as the intended disease or class of diseases,product type or mechanism of action,as well as broader considerations such as the kinds of evidence that will be required for gene therapy products to take advantage of expedited development programs.Delay or failure to obtain,or unexpected costs in obtaining,the regulatory approval necessary to bring our gene therapy product candidates to market could have a negative effect on our business and financial condition~~ .In addition to the risks set forth in this Risk Factors section associated with commercializing more traditional pharmaceutical drugs,there are additional,unique commercial risks associated with gene therapy products like ROCTAVIAN.Due to the relative novelty of gene therapy and the potential to provide extended duration therapeutic treatment with a one- time administration,we face uncertainty with respect to the pricing,coverage and reimbursement

of these products.In order to recover our research and development costs and commercialize one- time treatments on a profitable basis,the cost of a single administration of ROCTAVIAN is substantial,and it is likely other gene therapy products would also require relatively high prices.Therefore,coverage and reimbursement by governments and other third- party payers is essential for the vast majority of patients to be able to afford ROCTAVIAN or other gene therapy products that we may commercialize in the future.Accordingly,sales of our gene therapy products will depend substantially 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 our gene therapy products.With respect to ROCTAVIAN specifically,we have entered into,and plan to enter into additional,outcomes- based agreements for the product with third- party payers to assist with realizing the value and sharing the risk of a one- time treatment,which make us subject to potential repayments if a patient does not respond to therapy or the therapeutic effect of the drug falls below specified thresholds.Although we will record reserves for potential refunds under the outcomes-based agreements for ROCTAVIAN in the same period as sales,our revenues and financial results could be adversely affected if our assumptions underlying our refund reserves differ from actual experience or otherwise underestimate refund obligations.Additionally,the **novelty and** increased complexity of reimbursement with outcomes- based arrangements heightens the risk that our price reporting may be inaccurate or delayed,which may result in fines and liability.We also face uncertainty as to whether gene therapy will gain the acceptance of the public or the medical community.The commercial success of ROCTAVIAN or any other gene therapy product candidate that may be approved in the future will depend,in part,on the acceptance of physicians,patients and third- party payers of gene therapy products in general,and our product in particular,as medically necessary,cost- effective and safe.In particular,our success will depend upon physicians prescribing our product in lieu of existing treatments they are already familiar with and for which greater clinical data may be available.Moreover,physicians and patients may delay acceptance of one of our gene therapy treatments until the product has been on the market for a certain amount of time. **Although administration of a gene therapy product like ROCTAVIAN is intended to correct an inborn genetic defect for at least several years,there is a risk that the therapeutic effect will not be durable and production of the desired protein or ribonucleic acid will decrease more quickly or cease entirely earlier than expected.If the therapeutic effect decreases significantly or ceases entirely,it is uncertain whether redosing is possible or would be effective.Furthermore,because gene therapy 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.Additionally,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.** 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 successful commercialization of,and demand for,ROCTAVIAN or future gene therapy products ~~.~~. All of our products target diseases with relatively small patient populations. Our two newest products, VOXZOGO and ROCTAVIAN, address potentially larger patient populations than most of our other products; however, their market sizes are considerably smaller than many drugs marketed by other pharmaceutical and biotechnology companies. As a result, our per- patient prices must be relatively high in order to recover our development and manufacturing costs and achieve and maintain 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 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. 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 **for seven years, along with other regulatory exclusivities that could block approval**) or commercialize their products before we do. With respect to ROCTAVIAN ~~, which has been conditionally approved in the EU and may be approved in the U. S. and other markets in the future~~ , we face a highly developed and competitive market for hemophilia A treatments. As we commercialize ROCTAVIAN, we may face intense competition from large pharmaceutical companies with extensive resources and established relationships in the hemophilia A community. If we do not compete successfully, our revenues 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. Even if our product candidates are approved, if doctors elect a course of treatment which does not include our products, this decision would reduce demand for our products and adversely affect revenues. For example, if gene therapy becomes widely used as a treatment of genetic diseases, the use of enzyme replacement therapy, such as ALDURAZYME, NAGLAZYME, and VIMIZIM in MPS diseases, could be greatly reduced. Changes in treatment method can be caused by the introduction of other companies' products or the development of new technologies or surgical procedures which may not directly compete with ours, but which have the effect of changing how doctors decide to treat a disease. Our future growth and development depend in part on our ability to successfully develop new products from our ~~research and~~ development activities. The development of biopharmaceutical products is very expensive and time intensive and involves a great degree of risk. The outcomes of research and development programs, especially for innovative biopharmaceuticals **like gene therapy products** , are inherently uncertain and may not result in the commercialization of any products. Our competitors compete with us to attract organizations for acquisitions, joint ventures, licensing arrangements or other collaborations. To date, several of our former and current product programs have been acquired through acquisitions and several of our former and current product programs have been developed through licensing or collaborative arrangements, such as ALDURAZYME, KUVAN and NAGLAZYME. These collaborations include licensing proprietary technology from, and other relationships with, academic research institutions. Our future success will depend, in part, on our ability to identify additional opportunities and to successfully enter into partnering or acquisition agreements for those opportunities. If our competitors successfully enter into partnering arrangements or license agreements with academic research institutions, we will then be precluded from pursuing those specific opportunities. Because each of these opportunities is unique, we may not be able to find a substitute. Several pharmaceutical and biotechnology companies have already established themselves in the field of genetic diseases. These companies have already begun many drug development programs, some of which ~~may~~ target diseases that we are also targeting **or may target in the future** , and have already entered into partnering and licensing arrangements with academic research institutions, reducing the pool of available opportunities. Universities and public and private research institutions also compete with us. While these organizations primarily have educational or basic research objectives, they may develop proprietary technology and acquire patents that

we may need for the development of our product candidates. We will attempt to license this proprietary technology, if available. These licenses may not be available to us on acceptable terms, if at all. If we are unable to compete successfully with respect to acquisitions, joint venture and other collaboration opportunities, we may be limited in our ability to develop new products and to continue to expand our product pipeline. Generic versions of KUVAN are available in several countries around the world, including multiple generic versions in the U. S **. and the EU** . This generic competition has adversely affected and will continue to adversely affect our revenues from KUVAN, and we cannot accurately predict the rate of decline of KUVAN revenues in these countries. We are also aware that manufacturers are challenging our patent portfolio related to KUVAN in several jurisdictions, and several generic versions of KUVAN have been approved either centrally by the European **Commission** ~~Medicines Agency~~ (~~EMA~~ **EC**) or on a country- by- country basis throughout the EU. If these patent challenges are successful, or if a manufacturer chooses to offer a generic version of KUVAN, notwithstanding our existing patents, our revenues from KUVAN may decline faster than expected. For planning purposes, we estimate the timing of the accomplishment of various scientific, clinical, regulatory and other product development goals, which we sometimes refer to as milestones. These milestones may include the commencement or completion of scientific studies and clinical trials and the submission of regulatory filings. From time to time, we publicly announce the expected timing of some of these milestones. All of these milestones are based on a variety of assumptions. The actual timing of these milestones can vary dramatically compared to our estimates or the milestones may never be achieved, in many cases for reasons beyond our control. For example, in 2021 and early 2022, we announced that we planned to resubmit our Biologics License Application (BLA) for ROCTAVIAN to the Food and Drug Administration (FDA) in the first half of 2022; however, we did not file the BLA until the third quarter of 2022 due to the additional time we needed to include supplemental information and analyses of data requested by the FDA. If we do not meet development milestones as publicly announced, the commercialization of our products may be delayed or never occur and the credibility of our management may be adversely affected and, as a result, our stock price may decline. We have in the past and may in the future enter into licensing arrangements, and we may not realize the benefits of such licensing arrangements. We have in the past and may in the future enter into licensing arrangements with third parties. It is possible that we may not achieve financial or strategic benefits that justify a specific license, or we may otherwise not realize the benefits of such licensing arrangement. Further, licensing arrangements impose various diligence, milestone and royalty payment and other obligations on us. If we fail to comply with our obligations under any current or future licenses, our licensors may have the right to terminate these license agreements, which could harm our business prospects, financial condition and results of operations. Additionally, counterparties to our license agreements have in the past alleged and may in the future allege that we have breached a license agreement, which can result in litigation or other disputes that can divert management' s attention away from our business and require us to expend resources, as well as potentially having to negotiate new or reinstated licenses with less favorable terms. Any such situation could adversely affect our business, financial condition, and results of operations. **Activist investor actions threatened or commenced against us have and could in the future cause us to incur substantial costs, divert management' s attention and resources, cause uncertainty about the strategic direction of our business and adversely affect our business, financial position and results of operations. We have been, and may in the future be, subject to activities initiated by activist investors. In December 2023, we entered into a Cooperation Agreement with Elliott Investment Management L. P., Elliott Associates, L. P. and Elliott International, L. P. (collectively, " Elliott "). We may not be successful in engaging constructively with one or more investors in the future despite our efforts to maintain constructive and ongoing communications with all investors, including Elliott. Resulting actions taken by activist investors from time to time have and could in the future conflict with our strategic direction, divert the attention of our Board of Directors, management, and employees, be costly and time- consuming, and disrupt the momentum in our business and operations, as well as our ability to execute our strategic plan. These types of actions may also create perceived uncertainties as to the future direction of our business or strategy, which may be exploited by our competitors and may make it more difficult to attract and retain qualified personnel, and may impact our relationships with investors, vendors, customers and other third parties. These types of actions could also impact the market price and the volatility of our common stock. In addition, we may choose to initiate, or may become subject to, litigation as a result of activist investor actions, which would serve as a further distraction to our Board of Directors, senior management and employees and could require us to incur significant additional costs.** We must obtain regulatory approval to market and sell our product candidates. For example, in the U. S., we must obtain FDA approval for each product candidate that we intend to commercialize, and in the EU, we must obtain approval from the ~~European Commission (~~ EC ~~)~~, based on the opinion of the Committee for Medicinal Products for Human Use (CHMP) of the **European Medicines Agency (** EMA **)** . The FDA and EC approval processes are typically lengthy and expensive, and approval is never certain. To obtain regulatory approval, we must first show that our product candidates are safe and effective for target indications through preclinical studies and clinical trials. Preclinical studies and clinical development are long, expensive and uncertain processes. Completion of clinical trials may take several years, and failure may occur at any stage of development. The length of time required varies substantially according to the type, complexity, novelty and intended use of a product candidate. Interim results of a preclinical test or clinical trial do not necessarily predict final results, and acceptable results in early clinical trials may not be repeated in later clinical trials. 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 authority will mean that other authorities will also approve the same product candidate. ~~For example, the EC' s conditional approval of ROCTAVIAN in August 2022 does not guarantee that the FDA will approve the same drug.~~ Similarly, in the EU, a positive CHMP opinion for approval of a product candidate does not guarantee that the EC will approve ~~a drug~~ **the product candidate** . Moreover, regulatory authorities may approve a product candidate for fewer or more limited indications than requested. In addition, regulatory authorities may not approve the labeling claims that are necessary or desirable for the successful commercialization of our product candidates. We have had fewer interactions with regulatory authorities outside the U. S. and the EU as compared to our interactions with the FDA **, the EC** and **the** 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 EC approval. Moreover, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries. Approval by the FDA or EC does not ensure approval by regulatory authorities in other countries, and approval by one or more non- U. S. regulatory authorities does not ensure approval by regulatory authorities in other non- U. S. countries or by the FDA or EC. However, a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory process in others. The non- U. S. regulatory approval process may include all of the risks associated with obtaining FDA or EC approval. We may not obtain non- U. S. 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. We also rely on independent third- party **Contract Research Organizations (** CROs **)** to file some of our non-

U. S. marketing applications, and while we keep a close oversight on the activities we delegate to CROs, 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. Although the FDA **, the EC** and the EMA have programs to facilitate expedited development and accelerated approval processes, the timelines agreed under legislative goals or mandated by regulations are subject to the possibility of substantial delays. Accordingly, even if any of our applications receives a designation to facilitate expedited development and accelerated approval processes, these designations may not result in faster review or approval for our product candidates compared to product candidates considered for approval under conventional procedures and, in any event, do not assure ultimate approval of our product candidates by regulatory authorities. In addition, the FDA **, the EC** , the EMA and other comparable international regulatory authorities have substantial discretion over the approval process for pharmaceutical products. These regulatory ~~agencies~~ **authorities** may not agree that we have demonstrated the requisite level of product safety and efficacy to ~~grant~~ **warrant** approval and may require, and in the past have required, additional data. If we fail to obtain regulatory approval for our product candidates, we will be unable to market and sell those product candidates, which would have a negative effect on our business and financial condition. Regulatory ~~agencies~~ **authorities** 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~~ **product** ~~candidate~~ **candidates** or lead to significant post- approval studies, limitations or restrictions. For example, on August 18, 2020, the FDA issued a Complete Response Letter (CRL) to our BLA for ROCTAVIAN for the treatment of adults with severe hemophilia A. In the CRL, the FDA introduced a new request for two- year follow- up safety and efficacy data on all study participants from our ongoing Phase 3 study of ROCTAVIAN. In January 2022, we announced results from the requested two- year data analysis from our Phase 3 study. In the third quarter of 2022, we resubmitted our BLA, and the FDA subsequently accepted our submission with ~~a~~ **an original** Prescription Drug User Fee Act (PDUFA) target action date of March 31, 2023. ~~Typically~~ **In early 2023** , **we supplemented our** BLA ~~resubmissions are followed~~ by ~~a six~~ **submitting our three** - ~~month review procedure. However~~ **year analysis of the global Phase 3 study of ROCTAVIAN** , ~~we anticipate~~ **which the FDA deemed to be a Major Amendment to our BLA due to the substantial amount of additional data, and extended the PDUFA target action date by** three ~~additional~~ months **. The FDA approved ROCTAVIAN for the treatment** of **adults with severe hemophilia A on June 29, 2023. Further, on April 26, 2023, the EC adopted a proposal for a new Directive and Regulation to** ~~review~~ **revise the existing pharmaceutical legislation. If adopted in the form proposed, the recent EC proposals to revise the existing EU laws governing authorization of medicinal products** may ~~be necessary based on the~~ **result in a decrease in** data ~~read- out we announced on January 8, 2023~~ **and market exclusivity for our product candidates in the EU** . In addition, some of our product candidates are intended to be used in combination with a medical device, such as an injector or other delivery system ~~or companion diagnostic~~ . ~~Such~~ **Some of these** products **intended to be used with a medical device** may be regulated as " combination products " in the U. S. and the EU, which are generally defined as products consisting of components from two or more regulatory categories (e. g., drug / device, device / biologic, drug / biologic). In the U. S., 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. In the EU, ~~if~~ **medical devices and medicinal products are regulated separately, through different legislative instruments. The related applicable requirements will vary depending on the type of drug- device combination product. If, for example,** a device intended to administer a medicinal product is sold together with such medicinal product in such a way that they form a single integral product which is intended exclusively for use in the given combination and which is not reusable, that single integral product is regulated as a medicinal product. In addition, the relevant general safety and performance requirements **(GSPRs)** established for medical devices by EU medical devices legislation apply to the device component of such combination products. **In addition, some of our products require use with an in vitro companion diagnostic. For example, ROCTAVIAN is approved with a companion diagnostic test intended to detect pre- existing anti- AAV5 antibodies, which may render the gene therapy less effective or ineffective. Our other products and product candidates may also require use with an in vitro companion diagnostic if the FDA determines that the companion diagnostic is essential for safe and effective use of the product candidate. The FDA generally will require approval or clearance of the diagnostic, known as a companion diagnostic, at the same time that the FDA approves the therapeutic product. Most companion diagnostics require approval of a premarket approval application. In the EU, companion diagnostics are deemed to be in vitro diagnostic medical devices and must conform with the applicable GSPRs. To demonstrate compliance with the GSPRs, companion diagnostics must undergo a conformity assessment by a Notified Body. If the related medicinal product has been, or is in the process of being, authorized through the centralized procedure for the authorization of medicinal products, the Notified Body will, before it can issue a CE Certificate of Conformity, be required to seek a scientific opinion from the EMA on the suitability of the companion diagnostic for use in relation to the medicinal product concerned. For medicinal products that have been or are in the process of authorization through any other route provided in EU legislation, the Notified Body must seek the opinion of the national competent authority of an EU Member State.** Our product candidates intended for use with separately regulated devices **, such as companion diagnostics** , 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 **, or certifications** . Where approval of the drug or biologic product and device is sought under a single application **, such as a drug with an injector or delivery system** , the increased complexity of the review process may delay approval. The FDA **and EU** review ~~process~~ **processes** and **related** criteria are **complex** ~~not well- established areas~~ , which could also lead to delays in the approval process. In addition, because these 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. **Furthermore, despite our recent success obtaining regulatory approval for ROCTAVIAN in the U. S. and conditional approval in the EU, we may experience regulatory challenges for other gene therapy product candidates 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, the FDA and EC have only approved a relatively small number of vector- based gene therapy products thus far. 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 future gene therapy product candidates in any jurisdiction. Regulatory requirements governing gene and cell therapy products are still evolving and may continue to change in the future. Further, the FDA continues to develop and publish new guidance and policies, generally, by releasing one or more gene therapy- specific guidance documents each year. These guidance documents and other recent policy statements demonstrate that regulatory requirements for gene therapies are likely to continue to evolve based upon factors such as the intended disease or class of diseases, product type or mechanism of action, broader considerations such as the kinds of evidence that will be required for gene therapy products to take advantage of expedited development programs, and the experiences obtained by FDA when applying their legal and regulatory authorities to an evolving field, like gene therapy products. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring our gene therapy product candidates to market could have a negative effect on our business and financial condition. From time to time during the development and regulatory approval process for our products and product candidates, we engage in discussions with the FDA **, the EC** , the EMA and other 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~~ **authorities** 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. Moreover, sometimes different regulatory ~~agencies~~ **authorities** 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, the **EC, the** EMA and other comparable international 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 EC** , the EMA and other comparable international regulatory authorities, and if we fail to comply with regulatory requirements or if we experience unanticipated problems with our products, we may be subject to penalties, we will be unable to generate revenues 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. **Our products** ~~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 **except ROCTAVIAN** , ~~PALYNZIQ~~ **which** has received regulatory approval to be commercially marketed in the U. S. ~~, the EU,~~ and ~~Australia. VOXZOGO has received regulatory approval to be commercially marketed in the U. S., the EU, and Brazil. ROCTAVIAN has received~~ conditional 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 **EC, the** EMA and / or other comparable international and national regulatory authorities. These requirements include submissions of safety and other post- marketing information and reports, registration and listing requirements, current ~~good~~ **Good** ~~manufacturing~~ **Manufacturing** ~~practices~~ **Practices** (cGMP) requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, import and export requirements and record keeping. 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: 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. **In addition, in the EU, the marketing authorization for BRINEURA was granted under " exceptional circumstances ". As a result, the risk- benefit balance of BRINEURA is reviewed annually and the marketing authorization may be withdrawn if the risk- benefit ratio is no longer favorable. The conditional marketing authorization for ROCTAVIAN is, moreover, valid for one year and must be reviewed annually until all related conditions have been fulfilled to permit transfer to a full authorization. Failure to continue to show favorable risk- benefit balance for BRINEURA or satisfy the conditions related to ROCTAVIAN' s conditional marketing authorization could result in the withdrawal of the marketing approvals for these products.** 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 **and Summary of Product Characteristics** . In particular, a product may not be promoted for uses that are not approved by the FDA or the EC as reflected in the product' s approved labeling. Although the FDA and other comparable international and national regulatory authorities do not regulate a physician' s choice of drug treatment made in the physician' s independent medical judgment, they do restrict promotional communications from companies or their sales force with respect to off- label uses of products for which marketing clearance has not been issued. The FDA and other national competent authorities or international regulatory ~~agencies~~ **authorities** 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 are not able to promote any products we develop for indications or uses for which they are not approved. Additionally, in the EU, it is prohibited to promote prescription drugs to the general public and we are therefore limited to promote our products exclusively to healthcare professionals. **Public prosecutors, industry associations, healthcare professionals and other members of the public closely scrutinize advertising and promotion of any product in the EU.** Moreover, if original FDA approval for one of our product candidates is granted via the accelerated approval pathway, we will 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 with due diligence could result in the withdrawal of the FDA' s marketing approval for a product candidate. For example, VOXZOGO is approved in the U. S. under accelerated approval based on an improvement in annualized growth velocity. Continued

approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory studies. To fulfill this post- marketing requirement, we intend to use our ongoing open- label extension studies compared to available natural history. In addition, the FDA and the EC often require post- marketing testing and surveillance to monitor the effects of products. The FDA, the ~~EMA~~ **EC** and other comparable international regulatory ~~agencies~~ **authorities** 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: • **the issuance of safety alerts, press releases or other communications containing warnings about related products; • modifications to promotional materials or corrective information to healthcare professionals; •** restrictions on our ability to conduct clinical trials, including full or partial clinical holds on ongoing or planned trials; • **suspensions or** restrictions on **our operations, including** product manufacturing processes; • restrictions on the marketing of a product; • restrictions on product distribution; • requirements to conduct post- marketing clinical trials; • untitled or warning letters or other adverse publicity; • withdrawal of the products from the market **• suspended or withdrawn regulatory approvals** ; • refusal **or delays** 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~~ **EC** or any other comparable international regulatory authorities withdraws its approval of a product, we will be unable to generate revenues 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. 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 **the intended indication and 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. From time to time, we have and may in the future publish or report preliminary, initial or interim data from our clinical trials. Preliminary, initial or interim data from our clinical trials may not be indicative of the final results of the trial and are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and / or more patient data become available. In this regard, such data may show initial evidence of clinical benefit, but as patients continue to be followed and more patient data become available, there is a risk that any therapeutic effects will not be durable in patients and / or will decrease over time or cease entirely. Preliminary, initial or interim data also remain subject to audit and verification procedures that may result in the final data being materially different from such preliminary, initial or interim data. As a result, preliminary, initial or interim data should be considered carefully and with caution until the final data are available. 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. 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 preclinical 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. 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 been under scrutiny for many years 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. For example, in the EU, governments influence the price of medicinal products through their pricing and reimbursement rules and control of national healthcare systems that fund a large part of the cost of those products to consumers. EU Member States are free to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed to by the government. An EU Member State may approve a specific price for the medicinal product, or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market, including volume- based arrangements, caps and reference pricing mechanisms. Other EU Member States allow companies to fix their own prices for medicines but monitor and control company profits. The downward pressure on healthcare costs in general, particularly prescription medicines, has become very intense. Pharmaceutical products may face competition from lower- priced products in foreign countries that have placed price controls on pharmaceutical products and may also compete with imported foreign products. Furthermore, there is no assurance that a product will be considered medically reasonable and necessary for a specific indication or cost- effective by third- party payers. There is also no assurance that an adequate level of reimbursement will be established even if coverage is available or that the third- party payers' reimbursement policies will not adversely affect our business. 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 revenues 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., there have been and continue to be a number of legislative initiatives to contain healthcare costs. In the U. S., there have been several recent congressional inquiries, proposed and enacted federal and state legislation and executive action 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. Any reduction in reimbursement from Medicare and other government programs may result in a similar reduction in payments from private payers. Recently, **several** healthcare reform initiatives culminated in the enactment of the Inflation Reduction Act (IRA) in August 2022, which ~~will~~ **allows** , among other things, ~~allow~~ U. S. Department of Health and Human Services (HHS) to negotiate the selling price of ~~certain~~ **a statutorily specified number of** drugs and biologics **each year** that the CMS reimburses under Medicare Part B and Part D **.** ~~, although only~~ **Only** high- expenditure single- source drugs that have been approved for at least 7 years (11 years for biologics) can be selected by CMS for negotiation. The IRA permits the Secretary of HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. **HHS has and will continue to issue and update guidance as these programs are implemented.** Manufacturers that fail to comply with the IRA may be subject to various penalties, including civil monetary penalties **. The IRA' s provisions are taking effect progressively starting in 2023, although they may be subject to legal challenges. Thus, while it is unclear how the IRA will be implemented, it will likely have a significant impact on the pharmaceutical industry** . Prior to the IRA, the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010 (collectively, 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 executive, judicial and congressional challenges to certain aspects of the PPACA. Although the PPACA has generally been upheld thus far, it is unclear how continued challenges to the law may 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. In addition, individual states in the U. S. have also increasingly ~~passed legislation~~ **enacted laws** and implemented regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, price disclosure and reporting requirements, 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 Member States, 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 **commercial** 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 Member States and other non- U. S. 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. If the price of one of our products decreases substantially in a reference price country, it could impact the price for that product in other countries. Consequently, a downward trend in prices of our products in some countries could contribute to similar downward trends elsewhere, which would have a material adverse effect on our revenues and results of operations. Moreover, ~~in order to obtain reimbursement for our products in~~ some **EU Member States** ~~countries, we may be required~~ - **require** ~~to conduct clinical trials~~ **the completion of additional studies** that compare the cost- effectiveness of ~~our~~ **a particular medicinal** ~~products~~ - **product candidate** to ~~other~~ **currently** available therapies **. This Health Technology Assessment (HTA) process, which is currently governed by the national laws of the individual EU Member States, is the procedure according to which the assessment of the public health impact, therapeutic impact and the economic and societal impact of use of a given medicinal product in the national healthcare systems of the individual country is conducted. The outcome of HTA regarding specific medicinal products will often influence the pricing and reimbursement status granted to these medicinal products by the competent authorities of individual EU Member States. In 2022, the EC adopted the HTA regulation, which is intended to boost cooperation among EU Member States in evaluating new medicinal products. The HTA regulation will apply starting in 2025 and may result in increased downward pricing pressure in the EU** . We anticipate that the IRA, PPACA and 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. 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. 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. **or as a condition that affects more than 200, 000 individuals in the U. S. and for which there is no reasonable expectation that the costs of development of said drug will be recovered from sales in the U. S.** In the EU, pursuant to **the Regulation (EC) No. 141 / 2000 (** the Orphan Regulation **), as implemented by Regulation (EC) No. 847 / 2000** , orphan drug designation is available if a sponsor can establish that: (1) the medicine is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting no more than five in 10, 000 people in the EU at the time the application is made, or, (2) that it is intended for the diagnosis, prevention or treatment of a life- threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives derived from the orphan status, it is unlikely that the marketing of the medicine in the EU would generate sufficient return to justify the necessary investment. In both cases, 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 medicine will be of significant benefit to those affected by that condition. In the U. S., 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~~ **designated** 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 **for the approved therapeutic indication** (extendable to twelve years for orphan drugs that have complied with an agreed Pediatric Investigation Plan (PIP) pursuant to Regulation 1901 / 2006), during which **the EMA cannot accept another marketing authorization application or accept an application to extend existing authorizations for** similar ~~medicines~~ **medicinal products** for the same indication ~~cannot~~ **and no related marketing authorization (MA) can** be ~~placed on the market, is~~ granted. MAs may also be granted to a similar medicinal product with the same orphan indication if: (i) the applicant can establish that the second medicinal product, although similar to the orphan medicinal product already authorized is safer, more effective or otherwise clinically superior to the orphan medicinal product already authorized; (ii) the MA holder for the first orphan medicinal product grants its consent; or (iii) if the MA holder of the orphan medicinal product is unable to supply sufficient quantities **. MAs may also be granted for the same therapeutic indication in relation to products that are not similar** . 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 **and resulting regulatory exclusivity** 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 and / or the Orphan Regulation, as applicable, to maintain a competitive position. If we do not obtain orphan drug **designation and related regulatory** exclusivity for our products that do not have broad patent protection **or if a competing product is determined to be" clinically superior" to any of our products that has secured orphan drug exclusivity** , our competitors may then sell the same drug to treat the same condition and our revenues will be reduced. Even though we have obtained orphan drug designation for certain of our product candidates and even if we obtain orphan drug designation for our future product candidates, due to the uncertainties associated with developing biopharmaceutical products, we may not be the first to obtain marketing approval for any particular orphan indication, which means that we may not obtain orphan drug **regulatory** 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 certain biologics and gene therapies, there may be some uncertainty regarding how similarity between product candidates designed to treat the same rare disease or condition may affect such product candidates' orphan drug **regulatory** exclusivities. For biologics and gene therapies, the FDA' s determination of whether a drug is the same drug or a different drug will be based on the principal molecular structural features of the products. For gene therapy products, the FDA has stated in guidance that it generally intends to consider certain key features such as transgenes and vectors used in gene therapy products to be principal molecular structural features **. The FDA has not yet proffered additional information on orphan drug sameness for gene therapy or similar products** . 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 **, ROCTAVIAN** and VIMIZIM products are regulated by the FDA as biologics under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act (the PHS Act). Biologics require the submission of a BLA and ~~approval~~ **licensure** 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~~ **licensure** of biological products that are demonstrated to be " biosimilar " **to** or " interchangeable " with an FDA- ~~approved~~ **licensed** biological product. A similar abridged MA process is available to biosimilar products in the EU. In particular, applicants for MAs of biosimilars are required to demonstrate through comprehensive comparability studies with the reference biological medicine that: a) their biological medicine is highly similar to the reference medicine, notwithstanding natural variability inherent to all biological medicines; and b) there are no clinically meaningful differences between the biosimilar and the reference medicine in terms of safety, quality and efficacy. In the U. S., 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 **in any given patient** , and for a product that is administered more than once, that the risk of switching **in terms of safety or diminished efficacy of alternating or 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 **data** exclusivity for reference

products **but such data exclusivity only blocks licensure of biosimilars relying on the product as a reference product; it will not prevent the licensure of the same product for the same or different indications that does not seek to rely on reference product data** . In the EU, 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 applications may be submitted and the reference product' s data may be referenced but** 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 as a result of Marketing Authorization Applications (MAAs) in the EU, as well as our product candidates that may be approved in the future, could be reference products for biosimilar marketing applications. Changes in funding for the FDA, the EMA, other comparable ~~international~~ regulatory authorities and other government agencies or government shutdowns could hinder the ability of such **authorities and** agencies to hire and retain key leadership and other personnel or otherwise prevent those **authorities and** agencies from performing normal functions on which the operation of our business may rely, which could negatively impact our business. Changes in funding levels of **regulatory authorities and** government agencies can affect their ability to hire and retain key personnel and carry out their normal functions that support our business. For example, the ability of the FDA or the EMA to timely review and approve INDs or MAAs for our product candidates may be hindered by a lack of resources and qualified personnel. In addition, funding of other **regulatory authorities and** government agencies on which our operations rely, including those that fund research and development activities, is subject to the political budget process, which is inherently fluid and unpredictable. Government shutdowns could also impact the ability of **regulatory authorities and** government agencies to function normally and support our operations. For example, the U. S. federal government has shut down repeatedly since 1980, including for a period of 35 days beginning on December 22, 2018. During a shutdown, certain regulatory **authorities and** agencies, such as the FDA, have had to furlough key personnel and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. In addition to the risks set forth..... the ultimate outcome of the trials. 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~~ **most** ~~year~~ **years** since our inception **and** ~~, with the~~ **there** ~~exceptions of 2008, 2010, 2020 and 2022~~ **is no guarantee that we will achieve or maintain profitability in the future** . 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 or~~ are unable to sustain profitability and positive cash flows on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce our operations. If we fail to obtain the capital necessary to fund our operations, our financial results and financial condition will be adversely affected and we will have to delay or terminate some or all of our product development programs. As of December 31, ~~2022~~ **2023** , we had cash, cash equivalents and investments totaling $ 1. ~~6~~ **7** billion and debt obligations of $ 1. 1 billion (undiscounted), which consisted of our 0. 599 % senior subordinated convertible notes due in 2024 (the 2024 Notes) and our 1. 25 % senior subordinated convertible notes due in 2027 (the 2027 Notes). The 2024 Notes and the 2027 Notes (collectively, the Notes), if not converted, will be required to be repaid in cash at maturity in August 2024 and May 2027, 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. We may require additional financing to fund the repayment of the 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; • 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; • Sanofi' s 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 equity and / or equity- linked securities will result in additional dilution to our stockholders. Furthermore, additional financing may not be available in amounts or on terms satisfactory to us or at all. This could result in the delay, reduction or termination of our research, which could harm our business. We have incurred substantial indebtedness that may decrease our business flexibility, access to capital, and / or increase our borrowing costs, which may adversely affect our operations and financial results. As of December 31, ~~2022~~ **2023** , we had $ 1. 1 billion (undiscounted) principal amount of indebtedness, including $ 495. 0 million (undiscounted) principal amount of indebtedness under the 2024 Notes and $ 600. 0 million (undiscounted) principal amount of indebtedness under the 2027 Notes ~~. In October 2018, we entered into an unsecured credit agreement (the 2018 Credit Agreement) 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 (the 2018 Credit Facility). In May 2021, we amended the 2018 Credit Facility to, among other things, extend the maturity date of the 2018 Credit Facility from October 19, 2021 to May 28, 2024~~ . 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 the Notes.~~ If we default under any series of the Notes, such series of Notes could become immediately due and payable and it could lead to defaults under the other series of 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 2024 Notes and 2027 Notes, which, if not converted, will be required to be repaid in cash at maturity in August 2024 and May 2027, respectively. While we could seek to obtain additional third- party financing to pay for any amounts due in cash upon maturity of the Notes, we cannot be sure that such third- party financing will be available on commercially reasonable terms, if at all. **Prior** ~~In addition, we also may borrow up~~ to **commercialization** ~~$ 200. 0 million in revolving loans under the 2018 Credit Facility, which would be required to be repaid in cash at maturity on May 28, 2024. Before we can begin commercial manufacture~~ of our products, regulatory authorities must approve marketing applications that identify authorized 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 compliance with cGMP requirements** . In addition, our pharmaceutical manufacturing facilities are continuously subject to scheduled and unannounced **regulatory** ~~inspection~~ **inspections** by the FDA, and other comparable EU and other national and international regulatory authorities, before and after product approval, to monitor and ensure compliance with cGMP and other regulations. Our manufacturing ~~facility~~ **facilities** in the U. S. **are licensed** ~~has received a good manufacturing practice certificate from the EMA~~ for the manufacture ~~and distribution~~ of **PALYNZIQ,** ROCTAVIAN ~~in the EU~~, ~~been approved by the FDA and the EC for the manufacture of PALYNZIQ, and been approved by the FDA, the EC, and health agencies in other countries for the manufacture of~~ ALDURAZYME, BRINEURA, NAGLAZYME, VIMIZIM **,** and VOXZOGO. Our manufacturing facility in Shanbally, Cork, Ireland **is licensed** ~~has been approved by the FDA, the EC, and health agencies in other countries~~ for the manufacture of VIMIZIM and BRINEURA **and packaging operations for VOXZOGO and PALYNZIQ** . 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 **, national** 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 **, national** 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. Due to the complexity of manufacturing our product candidates and products, we may not be able to manufacture sufficient quantities. Our inability to produce enough of our product candidate at acceptable costs may result in the delay or termination of development programs. With respect to our commercial portfolio, we may not be able to manufacture our products successfully with a commercially viable process or at a scale large enough to support their respective commercial markets or at acceptable margins. **For example, demand for VOXZOGO in certain markets has outpaced our projections in recent quarters, and we have and could continue to face challenges meeting demand, requiring us to postpone planned entry into additional markets until VOXZOGO inventory levels increase or delay certain VOXZOGO development activities. As a result of such inventory constraints, we have and could continue to lose potential VOXZOGO revenues that may never be recouped and our VOXZOGO development program could be adversely impacted.** 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 **.Our** ~~processes,including other healthy genes~~ **gene** ~~,and we may not learn the nature and magnitude of these side effects until long after clinical trials have been completed.Moreover,gene~~ therapy ~~products~~ **product and product candidates** are **based on** relatively novel ~~and~~ **technology,which presents additional manufacturing risks in relation to our other,more traditional drug development programs.Gene therapy products are** complex 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 gene therapy 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 **gene therapy** clinical studies in a timely manner,if at all,or commercializing our gene therapy products on a profitable basis,if at all . 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 have been within our expectations, which are based on industry norms. If the failure rate increased substantially, we could experience increased costs, lost revenue, damage to customer relations, time and expense investigating the cause and, depending upon the cause, similar losses with respect to other lots or products. If problems are not discovered before the product is released to the market, recall and product liability costs may also be incurred. In order to produce product within our time and cost parameters, we must continue to produce product within our expected success rate and yield expectations. Because of the complexity of our manufacturing processes, it may be difficult or impossible for us to determine the cause of any particular lot failure and we must effectively take corrective action in response to any failure in a timely manner. We currently rely on third parties for portions of the manufacture of each of our products. 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 **, supranational, national,** 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. 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, including inflation. 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. If our Manufacturing, Marketing and Sales Agreement with Sanofi were terminated, we could be prevented from continuing to commercialize ALDURAZYME or our ability to successfully commercialize ALDURAZYME would be delayed or diminished. Either party may terminate the Manufacturing, Marketing and Sales Agreement (the MMS Agreement) between Sanofi and us related to ALDURAZYME for specified reasons, including if the other party is in material breach of the MMS Agreement, has experienced a change of control, as such term is defined in the MMS Agreement, or has declared bankruptcy and also is in breach of the MMS Agreement. Although we are not currently in breach of the MMS Agreement, there is a risk that either party could breach the MMS Agreement in the future. Either party may also terminate the MMS Agreement upon one- year prior written notice for any reason. If the MMS Agreement is terminated for breach, the breaching party will transfer its interest in the BioMarin / Genzyme LLC to the non- breaching party, and the non- breaching party will pay a specified buyout amount for the breaching party' s interest in ALDURAZYME and in the BioMarin / Genzyme LLC. If we are the breaching party, we would lose our rights to ALDURAZYME and the related intellectual property and regulatory approvals. If the MMS Agreement is terminated without cause, the non- terminating party would have the option, exercisable for one year, to buy out the terminating party' s interest in ALDURAZYME and in the BioMarin / Genzyme LLC at a specified buyout amount. If such option is not exercised, all rights to ALDURAZYME will be sold and the BioMarin / Genzyme LLC will be dissolved. In the event of termination of the buyout option without exercise by the non- terminating party as described above, all right and title to ALDURAZYME is to be sold to the highest bidder, with the proceeds to be split between Sanofi and us in accordance with our percentage interest in the BioMarin / Genzyme LLC. If the MMS Agreement is terminated by either party because the other party declared bankruptcy, the terminating party would be obligated to buy out the other party and would obtain all rights to ALDURAZYME exclusively. If the MMS Agreement is terminated by a party because the other party experienced a change of control, the terminating party shall notify the other party, the offeree, of its intent to buy out the offeree' s interest in ALDURAZYME and the BioMarin / Genzyme LLC for a stated amount set by the terminating party at its discretion. The offeree must then either accept this offer or agree to buy the terminating party' s interest in ALDURAZYME and the BioMarin / Genzyme LLC on those same terms. The party who buys out the other party would then have exclusive worldwide rights to ALDURAZYME. The Amended and Restated Collaboration Agreement between us and Sanofi will automatically terminate upon the effective date of the termination of the MMS Agreement and may not be terminated independently from the MMS Agreement. If we were obligated or given the option to buy out Sanofi' s interest in ALDURAZYME and the BioMarin / Genzyme LLC, and thereby gain exclusive rights to ALDURAZYME, we may not have sufficient funds to do so and we may not be able to obtain the financing to do so. If we fail to buy out Sanofi' s interest, we may be held in breach of the agreement and may lose any claim to the rights to ALDURAZYME and the related intellectual property and regulatory approvals. We would then effectively be prohibited from developing and commercializing ALDURAZYME. If this happened, not only would our product revenues decrease, but our share price would also decline. A significant portion of the sales of our products are generated from countries other than the U. S., and we expect international markets will continue to be important for the sales of any products approved in the future. We have operations in Canada and in several European, Middle Eastern, Asian, and Latin American countries. We expect that we will continue to expand our international operations in the future. International operations inherently subject us to a number of risks and uncertainties, including: • the increased complexity and costs inherent in managing international operations; • diverse regulatory and compliance requirements, and changes in those requirements that could restrict our ability to manufacture, market and sell our products; • ~~political~~ **geopolitical** and economic instability, such as the instability caused by Russia' s invasion of Ukraine; • 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 non- U. S. 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. For example, Russia' s invasion of Ukraine and the related impacts to Ukraine' s infrastructure and healthcare system has significantly impacted our ability to provide our therapies to patients in Ukraine. Sanctions issued by the U. S. and other countries against Russia and Belarus in response to the attack on Ukraine and related counter- sanctions issued by Russia have made it very difficult for us to operate in Russia and may have a material adverse impact on our ability to sell our products and / or collect receivables from customers in Russia and Belarus. 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 revenues and profitability. We make a significant portion of our initial international sales of newly launched products through early access, special access or " named patient sales " programs in markets where we are not required to obtain regulatory approval **before establishing these programs** . For example, a significant portion of our international sales of VOXZOGO since the product' s launch have been made through such programs. The specifics of the programs vary from country to country. Generally, special approval must be obtained to initiate such programs, and in some cases, special approval must be obtained for each patient. The approval normally requires an application **to national competent authorities in which the product is intended to be supplied** or a lawsuit accompanied by evidence of medical need. These programs are not well defined in some countries and are subject to changes in requirements, funding levels, unmet medical need and classification of the disease treated by our product. 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 measures to limit purchases of our products, including initially denying coverage for purchasers, delaying orders, requiring additional in- country testing 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 or official reimbursement 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, obtain and maintain a full product approval or official reimbursement, 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. A significant and growing portion of our revenues and earnings, as well as our substantial international ~~net~~ assets **and liabilities** , are exposed to changes in foreign exchange rates. As we operate in multiple foreign currencies, including the Euro, the Brazilian Real, the ~~Canadian Dollar~~ **Russian Ruble** , the Colombian Peso, the Argentine Peso and several other currencies, changes in those currencies relative to the U. S. Dollar (USD) will impact our revenues and expenses. If the USD were to weaken against another currency, assuming all other variables remained constant, our revenues would increase, having a positive impact on earnings, and our overall expenses would increase, having a negative impact on earnings. Conversely, if the USD were to strengthen against another currency (as was the case for many currencies in 2022), assuming all other variables remained constant, our revenues would decrease, having a negative impact on earnings, and our overall expenses would decrease, having a positive impact on earnings. In addition, because our financial statements are reported in USD, changes in currency exchange rates between the USD and other currencies have had, and will continue to have, an impact on our results of operations. Therefore, significant changes in foreign exchange rates can impact our results and our financial guidance. We implement currency hedges intended to reduce our exposure to changes in certain foreign currency exchange rates. However, our hedging strategies may not be successful, and any of our unhedged foreign exchange exposures will continue to be subject to market fluctuations. These risks could cause a material adverse effect on our business, financial position and results of operations and could cause the market value of our common stock to decline. U. S. export control and economic sanctions may adversely affect our business, financial condition and operating results. Moreover, compliance with such regulatory requirements may increase our costs and negatively impact our ability to sell our products and collect cash from customers. 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 hinder our 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. For example, sanctions issued by the U. S. and other jurisdictions against Russia and Belarus in response to the invasion of Ukraine have made it very difficult for us to operate in Russia and may have a material adverse impact on our ability to sell our products and / or collect receivables from customers in Russia and Belarus. Moreover, if we fail to comply with these laws and regulations, we could be subject to substantial civil or criminal penalties, including the possible loss of export or import privileges and fines. 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, the general license will be renewed in the future or we will remain in compliance with the general license. 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. Moreover, U. S. export control and economic sanctions may make operating in certain countries more difficult and expensive. For example, we may be unable to find distributors or financial institutions willing to facilitate the sale of our products and collection of cash from such sales in a cost- effective manner, if at all. 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 U. S. 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 non- U. S. government 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 non- U. S. government officials for purposes of applicable anti- corruption laws. Although we have adopted policies and procedures designed to ensure that we, our employees and third- party agents will comply with such laws, there can be no assurance that such policies or procedures will work effectively at all times or protect us against liability under these or other laws for actions taken by our employees, partners and other third parties with respect to our business. If we are not in compliance with anti- corruption laws and other laws governing the conduct of business with government entities and / or officials (including local laws), we may be subject to criminal and civil penalties and other remedial measures, which could harm our business, financial condition, results of operations, cash flows and prospects. Investigations of any actual or alleged violations of such laws or policies related to us could harm our business, financial condition, results of operations, cash flows and prospects. Moreover, there has been enhanced scrutiny of company- sponsored patient assistance programs, including insurance premium and co- pay assistance programs and donations to third- party independent charities that provide such assistance. There has also been enhanced scrutiny by governments on reimbursement support offerings, clinical education programs and promotional speaker programs. If we, our third- party agents or donation recipients are deemed to have failed to comply with laws, regulations or government guidance in any of these areas, we could be subject to criminal or civil sanctions. Any similar violations by our competitors could also negatively impact our industry reputation and increase scrutiny over our business and our products. 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. Where appropriate, we seek patent protection for certain aspects of our technology. Patent protection may not be available for some of the products we are developing. If we must spend significant time and money protecting or enforcing our patents, designing around patents held by others or licensing, potentially for large fees, patents or other proprietary rights held by others, our business and financial prospects may be harmed. The patent positions of biopharmaceutical products are complex and uncertain. The scope and extent of patent protection for some of our products and product candidates are particularly uncertain because key information on some of our product candidates has existed in the public domain for many years. The composition and genetic sequences of animal and / or human versions of ALDURAZYME, NAGLAZYME and many of our product candidates have been published and are believed to be in the public domain. The chemical structure of 6R- BH4 (the active ingredient in KUVAN) has also been published. Publication of this information may prevent us from obtaining or enforcing patents relating to our products and product candidates, including without limitation composition- of- matter patents, which are generally believed to offer the strongest patent protection. We own or have licensed patents and patent applications related to our products. However, these patents and patent applications do not ensure the protection of our intellectual property for a number of reasons, including without limitation the following: • With respect to pending patent applications, unless and until actually issued, the protective value of these applications is impossible to determine. We do not know whether our patent applications will result in issued patents. • Patents have limited duration and expire. • Enforcing patents is expensive and may absorb significant time of our management. Management would spend less time and resources on developing products, which could increase our operating expenses and delay product programs **.** • Receipt of a patent may not provide much, if any, practical protection. For example, if we receive a patent with a narrow scope, then it will be easier for competitors to design products that do not infringe on our patent. • The Leahy- Smith America Invents Act of 2011, which reformed certain patent laws in the U. S., may create additional uncertainty. Among the significant changes are switching from a " first- to- invent " system to a " first- to- file " system, and the implementation of new procedures that permit competitors to challenge our patents in the U. S. Patent and Trademark Office after grant. It is also unclear whether our trade secrets are adequately protected. Our current and former employees, consultants or contractors may unintentionally or willfully disclose trade secrets to competitors. Enforcing a claim that someone else illegally obtained and is using our trade secrets, as with patent litigation, is expensive and time consuming, requires significant resources and has an unpredictable outcome. In addition, courts outside of the U. S. are sometimes less willing to protect trade secrets. Furthermore, our competitors may independently develop equivalent knowledge, methods and know- how, in which case we would not be able to enforce our trade secret rights against such competitors. In the EU, materials we submit to the EMA in connection with our clinical trials that were traditionally regarded as confidential, proprietary information, such as study protocols, information regarding manufacturing methods and controls, and intermediate data analyses, are now subject to public disclosure. Moreover, clinical trial data submitted to the EMA in our MAAs are also available to the public. We are only permitted to redact from public disclosures commercially confidential information, a standard which is construed narrowly and subject to the interpretation and final decision of the EU regulatory authorities. EU regulations have resulted and will continue to result in the EMA' s public disclosure of certain of our proprietary information related to recently completed and future clinical trials and MAA submissions. The move toward public disclosure of such development information could adversely affect our business in many ways, including, for example, resulting in the disclosure of our confidential methodologies for development of our products, preventing us from obtaining intellectual property right protection for innovations, requiring us to allocate significant resources to prevent other companies from violating our intellectual property rights, adding even more complexity to processing health data from clinical trials consistent with applicable data privacy regulations, increasing scrutiny of our product candidates and products, and enabling competitors to use our clinical trial information and data to gain approvals for their own products. Competitors may interfere with our patent process in a variety of ways. Competitors may claim that they invented the claimed invention prior to us or that they filed their application for a patent on a claimed invention before we did. Competitors may also claim that we are infringing on their patents and therefore we cannot practice our technology. Competitors may also contest our patents by showing the patent examiner or a court that the invention was not original, was not novel or was obvious, for example. In litigation, a competitor could claim that our issued patents are not valid or are unenforceable for a number of reasons. If a court agrees, we would not be able to enforce that patent. Moreover, **follow- on manufacturers, including** generic **and biosimilar** manufacturers **,** may use litigation and regulatory means to obtain approval for generic **, biosimilar, or other follow- on** versions of our products notwithstanding our filed patents or patent applications. If we are unable to protect our intellectual property, third parties could develop competing products, which could adversely affect our revenues and financial results generally. Similar to us, competitors continually seek intellectual property protection for their technology. Several of our **products** ~~development programs~~ , such as ROCTAVIAN **, and development programs** ,

focus on therapeutic areas that have been the subject of extensive research and development by third parties for many years. Due to the amount of intellectual property in our field of technology, we cannot be certain that we do not infringe intellectual property rights of competitors or that we will not infringe intellectual property rights of competitors granted or created in the future. For example, if a patent holder believes our product infringes its patent, the patent holder may sue us even if we have received patent protection for our technology. If someone else claims we infringe their intellectual property, we would face a number of issues, including the following: • Defending a lawsuit takes significant executive resources and can be very expensive. • If a court decides that our product infringes a competitor' s intellectual property, we may have to pay substantial damages. • With respect to patents, in addition to requiring us to pay substantial damages, a court may prohibit us from making, selling, offering to sell, importing or using our product unless the patent holder licenses the patent to us. The patent holder is not required to grant us a license. If a license is available, it may not be available on commercially reasonable terms. For example, we may have to pay substantial royalties or grant cross licenses to our patents and patent applications. • We may need to redesign our product so it does not infringe the intellectual property rights of others. • Redesigning our product so it does not infringe the intellectual property rights of competitors may not be possible or could require substantial funds and time. We may also support and collaborate in research conducted by government organizations, hospitals, universities or other educational institutions. These research partners may be unwilling to grant us any exclusive rights to technology or products derived from these collaborations. **For example, under the Bayh- Dole Act which only applies to patents for inventions generated from federally funded research, the U. S. Department of Commerce may allow the government to use " march- in " rights for prescription drug patents as a means to control prices.** If we do not obtain required licenses or rights, we could encounter delays in our product development efforts while we attempt to design around other patents or may be prohibited from making, using, importing, offering to sell or selling products requiring these licenses or rights. There is also a risk that disputes may arise as to the rights to technology or products developed in collaboration with other parties. If we are not able to resolve such disputes and obtain the licenses or rights we need, we may not be able to develop or market our products. Risks Related to Ownership of Our Securities Our stock price has been and may in the future be volatile, and an investment in our stock could suffer a decline in value. Our stock price has been and may in the future be volatile. Our valuation and stock price may have no meaningful relationship to current or historical earnings, asset values, book value or many other criteria based on conventional measures of stock value. The market price of our common stock ~~will~~ **have, and in the future could,** fluctuate due to factors including: • product sales and profitability of our products; • manufacturing, supply or distribution of our product candidates and products ~~;~~ • progress of our product candidates through the regulatory process and our ability to successfully commercialize any such products that receive regulatory approval; • results of clinical trials, announcements of technological innovations or new products by us or our competitors; • generic competition to KUVAN tablets and powder described above in this Risk Factors section or potential generic competition from future competitors; • government regulatory action affecting our product candidates, our products or our competitors' product candidates and products in both the U. S. and non- U. S. countries; • developments or disputes concerning patent or proprietary rights; • general market conditions and fluctuations for the emerging growth and pharmaceutical market sectors; • economic conditions in the U. S. or abroad; • negative publicity about us or the pharmaceutical industry; • changes in the structure of healthcare payment systems; • cybersecurity incidents experienced by us or others in our industry; • broad market fluctuations in the U. S., the EU or in other parts of the world; • actual or anticipated fluctuations in our operating results, including due to timing of large periodic orders for our products by governments in certain countries; • changes in company assessments or financial estimates by securities analysts; • **certain actions by activist investors that may be threatened or commenced against us; •** acquisitions of products, businesses, or other assets; and • sales of our shares of stock by us, our significant stockholders, or members of our management or Board of Directors. Furthermore, the stock markets have recently experienced extreme price and volume fluctuations that have affected and continue to affect the market prices of equity securities of many companies. In some cases, these fluctuations have been unrelated or disproportionate to the operating performance of those companies. In the past, companies that have experienced volatility in the market price of their stock have been subject to securities class action litigation. For example, in September 2020, after a substantial drop in our stock price that followed an announcement providing a regulatory update regarding ROCTAVIAN, we and certain of our officers were sued in a putative class action lawsuit alleging violations of the federal securities laws for allegedly making materially false or misleading statements. In addition, in October 2021, after a drop in our stock price that followed an announcement providing a regulatory update regarding BMN 307, we and certain of our current and former officers were sued in a putative class action lawsuit alleging violations of the federal securities laws for allegedly making materially false or misleading statements. We may be the target of additional litigation of this type in the future as well. Securities litigation against us could result in substantial costs and divert our management' s time and attention from other business concerns, which could harm our business. In addition, our stock price can be materially adversely affected by factors beyond our control, such as disruptions in global financial markets or negative trends in the biotechnology sector of the economy, even if our business is operating well. Conversion of the Notes will dilute the ownership interest of existing stockholders, including holders who had previously converted their Notes, or may otherwise depress the price of our common stock. The conversion of some or all of the Notes will dilute the ownership interests of existing stockholders. Any sales in the public market of the common stock issuable upon such conversion could adversely affect prevailing market prices of our common stock. In addition, the existence of the Notes may encourage short selling by market participants because the conversion of the Notes could be used to satisfy short positions, or anticipated conversion of the Notes into shares of our common stock could depress the price of our common stock. The fundamental change repurchase feature of the Notes may delay or prevent an otherwise beneficial attempt to take us over. The terms of the Notes require us to offer to repurchase the Notes in the event of a fundamental change (as defined in each indenture governing the Notes). A takeover of us would trigger options by the respective holders of the applicable Notes to require us to repurchase such Notes. This may have the effect of delaying or preventing a takeover of us that would otherwise be beneficial to our stockholders or investors in the Notes. Anti- takeover provisions in our charter documents and under Delaware law may make an acquisition of us, which may be beneficial to our stockholders, more difficult. We are incorporated in Delaware. Certain anti- takeover provisions of Delaware law and our charter documents as currently in effect may make a change in control of us more difficult, even if a change in control would be beneficial to the stockholders. Our anti- takeover provisions include provisions in our restated certificate of incorporation and amended and restated bylaws providing that stockholders' meetings may only be called by our Chairman, the lead independent director or the majority of our Board of Directors and that the stockholders may not take action by written consent and requiring that stockholders that desire to nominate any person for election to our Board of Directors or to make any proposal with respect to business to be conducted at a meeting of our stockholders be submitted in appropriate form to our Secretary within a specified period of time in advance of any such meeting. Additionally, our Board of Directors has the authority to issue shares of preferred stock and to determine the terms of those shares of stock without any further action by our stockholders. The rights of

holders of our common stock are subject to the rights of the holders of any preferred stock that may be issued. The issuance of preferred stock could make it more difficult for a third party to acquire a majority of our outstanding voting stock. Delaware law also prohibits corporations from engaging in a business combination with any holders of 15 % or more of their capital stock until the holder has held the stock for three years unless, among other possibilities, our Board of Directors approves the transaction. Our Board of Directors may use these provisions to prevent changes in the management and control of us. Also, under applicable Delaware law, our Board of Directors may adopt additional anti- takeover measures in the future. Our amended and restated bylaws designate the Court of Chancery of the State of Delaware and the federal district courts of the U. S. as the exclusive forums for the adjudication of certain disputes, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers, or employees. Our amended and restated bylaws provide that the Court of Chancery of the State of Delaware is the sole and exclusive forum for the following types of actions or proceedings under Delaware statutory or common law: • any derivative claim or cause of action brought on our behalf; • any claim or cause of action for breach of a fiduciary duty owed by any **current or former** director, officer or other employee of BioMarin to us or our stockholders; • any claim or cause of action against us or any of our **current or former** directors, officers or other employees arising pursuant to any provision of the General Corporation Law of the State of Delaware, our restated certificate of incorporation or our amended and restated bylaws; any claim or cause of action seeking to interpret, apply, enforce or determine the validity of our restated certificate of incorporation or our amended and restated bylaws; • any claim or cause of action as to which the General Corporation Law of the State of Delaware confers jurisdiction to the Court of Chancery of the State of Delaware; and • any claim or cause of action against us or any of our **current or former** directors, officers or other employees that is governed by the internal affairs doctrine. This exclusive-forum provision would not apply to suits brought to enforce a duty or liability created by the Securities Act of 1933, as amended, the Exchange Act or any other claim for which the U. S. federal courts have exclusive jurisdiction. In addition, our amended and restated bylaws provide that the federal district courts of the U. S. of America will be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act. While the Delaware courts have determined that such choice of forum provisions are facially valid, a stockholder may nevertheless seek to bring a claim in a venue other than those designated in the exclusive forum provisions. In such instance, we would expect to vigorously assert the validity and enforceability of the exclusive forum provisions of our amended and restated bylaws. This may require significant additional costs associated with resolving such action in other jurisdictions and there can be no assurance that the provisions will be enforced by a court in those other jurisdictions. These exclusive forum provisions may limit a stockholder' s ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers, or other employees, which may discourage lawsuits against us and our directors, officers, and other employees. If a court were to find either of our exclusive forum provisions to be inapplicable or unenforceable in an action, we may incur further significant additional costs associated with resolving the dispute in other jurisdictions, all of which could seriously harm our business. Our amended and restated bylaws further provide that any person or entity that acquires any interest in shares of our capital stock will be deemed to have notice of and consented to the provisions of such provisions. General Risk Factors We depend upon our key personnel and our ability to attract and retain qualified employees. Our future growth and success will depend in large part on our continued ability to attract, retain, manage and motivate our employees. The loss of the services of a significant portion of our workforce or any member of our senior management or the inability to hire or retain qualified personnel could adversely affect our ability to execute our business plan and harm our operating results. Because of the specialized nature of our business, we rely heavily on our ability to attract and retain qualified scientific, technical and managerial personnel. In particular, the loss of one or more of our senior executive officers could be detrimental to us if we do not have an adequate succession plan or if we cannot recruit suitable replacements in a timely manner. While our senior executive officers are parties to employment agreements with us, these agreements do not guarantee that they will remain employed with us in the future. In addition, in many cases, these agreements do not restrict our senior executive officers' ability to compete with us after their employment is terminated. **In November 2023, we announced the retirement of Jean- Jacques Bienaimé, our then- current President and Chief Executive Officer, and the appointment of Alexander Hardy as President and Chief Executive Officer, each effective December 1, 2023. If Mr. Hardy' s succession as President and Chief Executive Officer is not managed successfully, including his ability to lead a team that can effectively implement our strategic plans, it could disrupt our business and affect our financial condition and operating results. Additionally, on January 11, 2024, we announced that Jeffrey Ajer would step down as our Executive Vice President and Chief Commercial Officer effective July 1, 2024. The recent changes in our management team could cause retention and morale concerns among current employees, as well as operational risks.** The competition for qualified personnel in the pharmaceutical field is intense, and there is a limited pool of qualified potential employees to recruit. **Recently, like many** ~~This competition was exacerbated during the~~ **other** ~~COVID- 19 pandemic~~ **employers in the U. S.** , ~~and~~ we ~~have recently~~ experienced increased employee turnover ~~like many other employers in the U~~ . ~~S. during the " great resignation. "~~ Due to the intense competition for talent, we may be unable to continue to attract and retain qualified personnel necessary for the development of our business or to recruit suitable replacement personnel. **Additionally, we cannot be sure that the compensation costs of doing so will not adversely affect our operating results, and we may not be able to hire and train employees quickly enough to meet our needs.** If we ~~are unsuccessful in~~ **fail to retain employees and effectively manage** our ~~recruitment~~ **hiring needs, our efficiency, ability to meet forecasts, employee morale, productivity, and the success of our strategic plans could suffer, which may have** ~~and~~ **an** ~~retention efforts,~~ **adverse effect on** our business ~~may be harmed~~ **, financial condition, and operating results** . Our success depends on our ability to manage our growth. Our two newest products, VOXZOGO and ROCTAVIAN, address potentially larger patient populations than most of our other products, and product candidates that we are currently developing or may license or acquire in the future may be intended for similarly larger patient populations than we have historically targeted. In order to continue development of such product candidates and marketing of products with larger markets, we will need to continue expanding our operations. To manage expansion effectively, we need to continue to develop and improve our research and development capabilities, manufacturing and quality capacities, sales and marketing capabilities, financial and administrative systems and standard processes for global operations. **For example, strong demand for VOXZOGO in certain markets has outpaced our projections in recent quarters, and we expect to face challenges meeting our current estimates of VOXZOGO demand through the first half of 2024.** Our staff, financial resources, systems, procedures or controls may be inadequate to support our operations and may increase our exposure to regulatory, competitive, and corruption risks and our management may be unable to manage successfully current or future market opportunities or our relationships with customers and other third parties. New tax laws or regulations that are enacted or existing tax laws and regulations that are interpreted, modified or applied adversely to us or our customers may have a material adverse effect on our business and financial condition. New tax laws or regulations could be enacted at any time, and existing tax laws or regulations could be interpreted, modified or applied in a manner that is adverse to us or our customers, which could adversely affect our

business and financial condition. For example, the Tax Cuts and Jobs Act, the Coronavirus Aid, Relief, and Economic Security Act and the Inflation Reduction Act enacted many significant changes to the U. S. tax laws. Future guidance from the Internal Revenue Service and other tax authorities with respect to such legislation may affect us, and certain aspects of such legislation could be repealed or modified in future legislation **. Among other changes, the Tax Cuts and Jobs Act amended the Code to require that, for tax years beginning after December 31, 2021, certain research and experimental expenditures be capitalized and amortized over five years if incurred in the United States or fifteen years if incurred in foreign jurisdictions for tax years beginning after December 31, 2021. Although the U. S. Congress has considered legislation that would defer, modify, or repeal the capitalization and amortization requirement, there is no assurance that such changes will be made. If the requirement is not deferred, repealed or otherwise modified, it may increase our cash tax** . In addition, it is uncertain if and to what extent various states will conform to federal tax laws. Any future tax legislation could increase our U. S. tax expense and could have a material adverse impact on our business and financial condition. Moreover, changes in the tax laws of jurisdictions in which we conduct business could arise, including as a result of the base erosion and profit shifting (BEPS) project that is being led by the Organization for Economic Co- operation and Development (OECD), and other initiatives led by the OECD or the EC. For example, the OECD, which represents a coalition of member countries including the U. S. and other countries in which we have operations, is working on proposals, commonly referred to as " BEPS 2. 0 ", which, if **and to the extent** implemented, would make important changes to the international tax system. These proposals are based on two " pillars ", Pillar One focuses on the allocation of taxing rights in respect of certain profits of multinational enterprises with annual global revenue above 20 billion euros and profitability above 10 % to the jurisdictions within which they carry on business (based on the thresholds, we currently expect to be outside the scope of the Pillar One proposals **, but could fall within their scope in the future**) and Pillar Two imposes a minimum effective tax rate of 15 % on certain multinational enterprises that have consolidated revenues of at least 750 million euros in at least two out of the last four years (based on the thresholds, we currently expect that we ~~could~~ **are likely to** fall within the scope of the Pillar Two proposals). **A** ~~The EU has adopted a Council Directive requiring aspects of the Pillar Two proposal to be transposed into the national laws of EU Member States by December 31, 2023, and a~~ number of ~~other~~ countries in which we conduct business **have enacted with effect from January 1, 2024, or** are ~~also planning to~~ **in the process of** ~~enact~~ **enacting** ~~such~~ **, core elements of Pillar Two** rules. The **OECD has issued administrative guidance providing transition and safe harbor rules around the** implementation of ~~such~~ **Pillar Two. We are monitoring developments and evaluating the impacts these new** rules **will have on our** ~~may increase the amount of~~ tax **rate** ~~we have to pay~~ , **including eligibility to qualify** ~~increase tax uncertainty and may adversely affect our provision~~ for **these safe harbor rules** ~~income taxes, results of operations and cash flows~~ . It is not uncommon for taxing authorities in different countries to have conflicting views, for instance, with respect to, among other things, the manner in which the arm' s length standard is applied for transfer pricing purposes, or with respect to the valuation of intellectual property. If tax authorities successfully challenge our transfer prices as not reflecting arm' s length transactions, they could require us to adjust our transfer prices and thereby reallocate our income to reflect these revised transfer prices, resulting in a higher tax liability. In addition, if a country from which income is reallocated does not agree with the reallocation, both that country and the other country to which the income was allocated could tax the same income, potentially resulting in double taxation. If tax authorities were to allocate income to a higher tax jurisdiction, subject our income to double taxation or assess interest and penalties, it would increase our consolidated tax liability, which could adversely affect our business, financial condition, results of operations and cash flows. 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, reputation, 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. **We recently received a subpoena from the U. S. Department of Justice requesting that we produce certain documents regarding our sponsored testing programs relating to VIMIZIM and NAGLAZYME. We have produced documents in response to the subpoena and are cooperating fully, but there is no assurance that such sponsored testing programs, or our other operations or programs, will not be found to violate such laws.** Federal and state false claims laws, including the civil False Claims Act and the Civil Monetary Penalties Law, 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, among other things, 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~~ **federal and state** healthcare ~~reform~~ legislation ~~has~~ **have** 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 non- U. S. 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 U. S. **, state privacy laws and regulations impose restrictive requirements regulating the use and disclosure of health information and other sensitive personal information that is not subject to HIPAA. For example** , California enacted the California Consumer Privacy Act (CCPA), which took effect on January 1, 2020. The CCPA gives California consumers expanded rights to access and delete their personal information, opt out of certain personal information sales, 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 was expanded substantially on January 1, 2023 when the California Privacy Rights Act of 2020 (CPRA) took effect and amended the CCPA. Following the CPRA amendments, the CCPA, among other things, ~~give~~ **gives** consumers the ability to limit use of information deemed to be sensitive, increase the maximum penalties for violations concerning consumers under age 16, expands an individual' s private right of action and establishes the California Privacy Protection Agency to implement and enforce the new law and impose administrative fines. ~~In addition to California, other~~ **Other** U. S. states have recently adopted consumer data protection and privacy laws, and more U. S. states may do so in the future. This creates the potential for a patchwork of overlapping but different state laws and 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, financial condition, and results of operations. Many other states are considering proposed comprehensive data privacy legislation and all 50 states have passed some form of legislation relating to privacy or cybersecurity. Aspects of the CCPA, CPRA and similar laws in other states and their interpretation and enforcement remain uncertain. The potential effects of these laws are far- reaching and may require us to modify our data processing practices and policies and to incur substantial costs and expenses in an effort to comply. Complying with these or other similar laws, regulations, amendments to or re- interpretations of existing laws and regulations, and contractual or other obligations relating to privacy, data protection, data transfers, data localization, or information security may require us to make changes to our services to enable us or our customers to meet new legal requirements, incur substantial operational costs, modify our data practices and policies, and restrict our business operations. Any actual or perceived failure by us to comply with these laws, regulations, or other obligations may lead to significant fines, penalties, regulatory investigations, lawsuits, significant costs for remediation, damage to our reputation, or other liabilities. The European Regulation 2016 / 679, known as the General Data Protection Regulation (GDPR), as well as EEA Member State legislations supplementing such regulation, apply to the processing of personal data of individuals located in the EEA, including health- related information, by companies located in the EEA, or in certain circumstances, by companies located outside of the EEA. These laws impose strict obligations on the ability to collect, record, store, disclose, use and transmit personal data, including health- related information. These include several requirements relating to (i) obtaining, in some situations, the informed 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). Switzerland has adopted similar restrictions. The GDPR and other European data protection laws generally restrict the transfer of personal information from Europe, including the EEA and Switzerland, to the U. S. and most other countries unless the ~~parties to~~ **U. S. companies participate in** the ~~transfer~~ **EU- U. S. Data Privacy Framework in accordance with the EC' s adequacy decision adopted on July 10, 2023, or** have implemented specific safeguards to protect the transferred personal information **. U. S. companies can join the EU- U. S. Data Privacy Framework by committing to comply with a detailed set of privacy obligations and U. S. companies that do not fall under the EU- U. S. Data Privacy Framework must implement certain specific safeguards** . One of the primary safeguards allowing U. S. companies to import personal information from the EEA has been the EC' s Standard Contractual Clauses (SCCs). However, the Court of Justice of the EU (CJEU) issued a decision that called into question whether the SCCs can lawfully be used for transfers of personal information from Europe to the United States or most other countries. ~~At present, there are few, if any, viable alternatives to the SCCs, on which we have relied for personal information transfers from Europe to the United States and other " third countries. "~~ After the mentioned CJEU judgment, new sets of SCCs were published on June 4, 2021. Most importantly, the use of SCCs does not any longer automatically ensure compliance with the GDPR. Instead, companies remain required to conduct a data transfer impact assessment for each transfer, which adds a compliance burden. Potential pecuniary fines for noncompliance with the GDPR 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 has increased our compliance costs. The EU regulations that make certain materials we submit to the EMA in connection with our clinical trials subject to public disclosure have increased the risk that we may unintentionally disclose personal information protected under the GDPR and thereby incur associated penalties and suffer reputational damage. In addition to the U. S. and European countries, other countries in which we operate have also enacted data privacy laws or may do so in the future. For example, Brazil' s General Data Protection Law (LGPD), which is modeled on the GDPR, took effect **in** ~~on August 16,~~ 2020. Substantial new laws and regulations affecting compliance have also been adopted in the U. S. and certain non- U. S. 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 (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), other health care professionals (such as physicians assistants and nurse practitioners), and teaching hospitals, as well as investment and ownership interests held by such physicians and their immediate family members during the preceding calendar year. 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, marketing expenditures, and drug pricing. Likewise, in many non- U. S. countries there is an increasing focus on the relationship between drug companies and healthcare practitioners. Recently enacted non- U. S. legislation creates reporting obligations on payments, gifts and benefits made to these professionals. **Outside the U. S., interactions between pharmaceutical companies and health care professionals are also governed by strict laws, such as national anti- bribery laws of European countries, national sunshine rules, regulations, industry self- regulation codes of conduct and physicians' codes of professional conduct.** 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~~ **authorities** 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 significant criminal, civil or administrative sanctions, including damages, fines, disgorgement, imprisonment, contractual damages, reputational harm **, public reprimands** , 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. If product liability lawsuits are successfully brought against us, we may incur substantial liabilities. We are exposed to the potential product liability risks inherent in the testing, manufacturing and marketing of human pharmaceuticals. We currently maintain insurance against product liability lawsuits for the commercial sale of our products and for the clinical trials of our product candidates. Pharmaceutical companies must balance the cost of insurance with the level of coverage based on estimates of potential liability. Historically, the potential liability associated with product liability lawsuits for pharmaceutical products has been unpredictable. Although we believe that our current insurance is a reasonable estimate of our potential liability and represents a commercially reasonable balancing of the level of coverage as compared to the cost of the insurance, we may be subject to claims in connection with our clinical trials and commercial use of our products and product candidates for which our insurance coverage may not be adequate and we may be unable to avoid significant liability if any product liability lawsuit is brought against us. If we are the subject of a successful product liability claim that exceeds the limits of any insurance coverage we obtain, we may incur substantial charges that would adversely affect our earnings and require the commitment of capital resources that might otherwise be available for the development and commercialization of our product programs. **In the EU, new rules on liability of defective products were proposed on September 28, 2022. If adopted, these rules will make it easier for patients to claim damages for defective products, for example by alleviating their burden of proof.** We rely significantly on information technology systems and any failure, inadequacy, interruption or security lapse of that technology, including any cybersecurity incidents, could harm our ability to operate our business effectively and have a material adverse effect on our business, reputation, financial condition, and results of operations. We rely significantly on our information technology systems **, including enterprise resource planning (ERP), production management, and other information systems,** to effectively manage and maintain our operations, inventory and internal reports, to manufacture and ship products to customers and to timely invoice them. Any failure, inadequacy or interruption of that infrastructure or security lapse (whether intentional or inadvertent) of that technology, including cybersecurity incidents or attacks, could harm our ability to operate our business effectively. **We are currently preparing to implement a new global ERP system, which will replace existing operating and financial systems. The preparation and implementation of a new ERP system has, and will continue to, require significant investment of capital and human resources.** Our **results of operations could be adversely affected if we experience delays or cost overruns during the implementation process, or if the ERP system or associated process changes do not give rise to the benefits that we expect. Potential failure or flaws in the new ERP system may pose risks to our** ability to **operate successfully and efficiently and failure to implement the appropriate internal controls with respect to the new ERP system may result in the system producing inaccurate or unreliable information. Any disruptions, delays or deficiencies in the design or implementation of the new ERP system or related internal controls, or in the performance of legacy information technology systems, could result in potentially much higher costs than we had incurred and adversely affect our ability to effectively fulfill contractual obligations, file related government reports in a timely manner, operate and** manage ~~and maintain~~ **our business** ~~our~~ **or otherwise affect our controls environment. Any of these consequences could have an adverse effect on our results of** operations ~~, inventory~~ and **financial condition** ~~internal reports, to manufacture and ship our products to customers and timely invoice them depends significantly on our enterprise resource planning, production management and other information systems~~ . ~~Our~~ **In addition, our** technology systems, including our cloud technologies, continue to increase in multitude and complexity, making them potentially vulnerable to breakdown, cyberattack and other disruptions. Potential problems and interruptions associated with the implementation of new or upgraded technology systems or with maintenance or adequate support of existing systems could disrupt or reduce the efficiency of our operations and expose us to greater risk of security breaches. Cybersecurity incidents resulting in the failure of our enterprise resource planning system, production management or other systems to operate effectively or to integrate with other systems, or a breach in security or other unauthorized access or unavailability of these systems or those of any third parties in our supply chain or on whom we otherwise depend, have occurred in the past and may affect our ability in the future to manage and maintain our operations, inventory and internal reports, and result in delays in product fulfillment and reduced efficiency of our operations. As part of our business, we collect, store, and transmit large amounts of confidential information, proprietary data, intellectual property, and personal data. The information and data processed and stored in our technology systems, and those of our research collaborators, CROs, contract manufacturers, suppliers, distributors, or other third parties on whom we depend to operate our business, may be vulnerable to loss, damage, denial- of- service, unauthorized access or misappropriation. Data security ~~breaches~~ **incidents** may be the result of unauthorized or unintended activity (or lack of activity) by our employees, contractors, or others with authorized access to our network or malware, hacking, business email compromise, phishing, ransomware or other cyberattacks directed by third parties. While we have implemented measures to protect our information and data stored in our technology systems and those of the third parties that we rely on, our efforts may not be successful. We have experienced and may continue to experience cybersecurity incidents, although to our knowledge we have not experienced any material incident or interruption to date. If such a significant event were to occur, it could result in a material disruption of our development programs and commercial operations, including due to a loss, corruption or unauthorized disclosure of our trade secrets, personal data or other proprietary or sensitive information. Further, these cybersecurity incidents can lead to the public disclosure of personal information (including sensitive personal information) of our employees, clinical trial patients and others and result in demands for ransom or other forms of blackmail. Such attacks, including phishing attacks and attempts to misappropriate or compromise confidential or proprietary information or sabotage enterprise IT systems, are of ever- increasing levels of sophistication and are made by groups and individuals with a wide range of motives (including industrial espionage) and expertise, including by organized criminal groups, “ hacktivists ”, nation states and others. Moreover, the costs to us to investigate and mitigate cybersecurity incidents could be significant. For example, the loss of clinical trial data could result in delays in our product development or regulatory approval efforts and significantly increase our costs to recover or reproduce the data. Any security breach that results in the unauthorized access, use or disclosure of personal data may require us to notify individuals, governmental authorities, credit reporting agencies, or other parties pursuant to privacy and security laws and regulations or other obligations. Such a security compromise could harm our reputation, erode

confidence in our information security measures, and lead to regulatory scrutiny. To the extent that any disruption or security breach resulted in a loss of, or damage to, our data or systems, or inappropriate disclosure of confidential, proprietary or personal information, we could be exposed to a risk of loss, enforcement measures, penalties, fines, indemnification claims, litigation and potential civil or criminal liability, which could materially adversely affect our business, financial condition and results of operations. Not all our contracts contain limitations of liability, and even where they do, there can be no assurance that limitations of liability in our contracts are sufficient to protect us from liabilities, damages, or claims related to our data privacy and security obligations. We cannot be sure that our insurance coverage will be adequate or sufficient to protect us from or to mitigate liabilities arising out of our privacy and security practices, that such coverage will continue to be available on commercially reasonable terms or at all, or that such coverage will pay future claims. **Further, the SEC has adopted new rules that require us to provide greater disclosures around proactive security protections that we employ and reactive issues (e. g., security incidents). Any such disclosures, including those under state data breach notification laws, can be costly, and the disclosures we make to comply with, or the failure to comply with, such requirements could lead to adverse consequences.** If a natural disaster, terrorist or criminal activity or other unforeseen event caused significant damage to our facilities or those of our third- party manufacturers and suppliers or significantly disrupted our operations or those of our third- party manufacturers and suppliers, we may be unable to meet demand for our products and lose potential revenue, have reduced margins, or be forced to terminate a program. The occurrence of an earthquake or other catastrophic disaster could cause damage to our facility and equipment, or that of our third- party manufacturers or single- source suppliers, which could materially impair the ability for us or our third- party manufacturers to manufacture our products and product candidates. Our Galli Drive facility, located in Novato, California, is currently our only manufacturing facility for ALDURAZYME, NAGLAZYME, VOXZOGO and PALYNZIQ and is one of two manufacturing facilities for BRINEURA and VIMIZIM. Our gene therapy manufacturing facility is also located in Novato, California, and it is currently our only manufacturing facility to support **ongoing** ROCTAVIAN clinical development activities ~~,~~ **and** commercial demand for ROCTAVIAN ~~in the EU, and anticipated commercial demand for ROCTAVIAN to the extent it receives approval by the FDA or other regulatory authorities~~ . These facilities are located in the San Francisco Bay Area near known earthquake fault zones and are vulnerable to significant damage from earthquakes. We, the third- party manufacturers with whom we contract and our single- source suppliers of raw materials, which include many of our critical raw materials, are also vulnerable to damage from other types of disasters, including fires, explosions, floods, and similar events. If any disaster were to occur, or any terrorist or criminal activity caused significant damage to our facilities or the facilities of our third- party manufacturers and suppliers, our ability to manufacture our products, or to have our products manufactured, could be seriously, or potentially completely, impaired, and our commercialization efforts and revenues could be seriously impaired. Moreover, other unforeseen events, such as power outages, could significantly disrupt our operations or those of our third- party manufacturers and suppliers, which could result in **damage to our facilities and** significant delays in the manufacture of our products and adversely impact our commercial operations and revenues ~~. Pacific Gas and Electric Company, the electric utility in the San Francisco Bay Area where many of our facilities are located, commenced widespread blackouts during the fall of 2019 to avoid and contain wildfires sparked during strong wind events by downed power lines or equipment failures. While we have not experienced damage to our facilities or material disruption to our operations as a result of these power outages, ongoing blackouts, particularly if prolonged or frequent, could impact our business going forward~~ . The insurance that we carry, the inventory that we maintain and our risk mitigation plans may not be adequate to cover our losses resulting from disasters or other business interruptions. Our business is affected by macroeconomic conditions. Various macroeconomic factors could adversely affect our business and the results of our operations and financial condition, including changes in inflation, interest rates, **or** foreign currency exchange rates, natural disasters, ~~lasting~~ **geopolitical instability resulting from war, terrorism and other violence, such as the instability caused by Russia' s invasion of Ukraine,** effects of **potential** ~~the COVID- 19 pandemic or other~~ global public health threats and overall economic conditions and uncertainties, including those resulting from the current and future conditions in the global financial markets and volatility and disruptions in the equity and debt markets. For instance, COVID- 19 previously adversely affected our ability to source materials and supplies. ~~If inflation~~ **Inflation** (such as that recently observed in the U. S. and elsewhere) **has** ~~or other factors were to significantly increase~~ **increased** our business costs **and could become more significant in the future** , **and** it may not be feasible to pass price increases on to our customers due to the process by which healthcare providers are reimbursed for our products by the government. Interest rates, the liquidity of the credit markets and the volatility of the capital markets could also affect the value of our investments and our ability to liquidate our investments in order to fund our operations. We purchase or enter into a variety of financial instruments and transactions, including investments in commercial paper, the extension of credit to corporations, institutions and governments and hedging contracts. If any of the issuers or counterparties to these instruments were to default on their obligations, it could materially reduce the value of the transaction and adversely affect our cash flows. We sell our products in countries that face economic volatility and weakness. Although we have historically collected receivables from customers in those countries, sustained weakness or further deterioration of the local economies and currencies may cause customers in those countries to be unable to pay for our products. Additionally, if one or more of these countries were unable to purchase our products, our revenues would be adversely affected. Interest rates and the ability to access credit markets could also adversely affect the ability of our customers / distributors to purchase, pay for and effectively distribute our products, which could limit our ability to obtain sufficient materials and supplies necessary for production of our therapies. Similarly, these macroeconomic factors could affect the ability of our contract manufacturers, sole- source or single- source suppliers to remain in business or otherwise manufacture or supply product. Failure by any of them to remain a going concern could affect our ability to manufacture products. Additionally, ~~the lasting~~ effects of ~~the COVID- 19 pandemic could continue to adversely affect our business, results of our operations, and financial condition. The COVID- 19 pandemic impacted our global revenue sources and overall business operations by, for example, presenting challenges to our ability to find adequate resources to staff clinical trials, impacting patients' ability to participate in trials, affecting our ability to source materials and supplies for trials and otherwise delaying trials, and the pandemic could continue to adversely impact our financial results and our business generally in 2023. Ongoing and future effects of the COVID- 19 pandemic (or~~ any ~~future~~ pandemic or other global public health threat ~~)~~ on all aspects of our business and operations and the duration of such effects are highly uncertain and difficult to predict. ~~Moreover~~ **For instance** , **a global** ~~while the long- term economic impact and the duration of the COVID- 19~~ pandemic **could** ~~may be difficult to predict, the pandemic has resulted in, and may continue to~~ result in ~~,~~ significant disruption of global financial markets, which could reduce our ability to access capital and could negatively affect our liquidity and the liquidity and stability of markets for our common stock and Notes. In addition, a recession, further market correction or depression resulting from **a future** ~~the COVID- 19 pandemic or other~~ global public health threat could materially adversely affect our business and the value of our common stock and Notes. To the extent macroeconomic conditions continue to adversely affect our business and financial results, they may also have the effect of heightening many of the other risks

described in this Risk Factors section, such as those relating to our conducting a significant amount of our sales and operations outside of the U. S., exposure to changes in foreign exchange rates, our need to generate sufficient cash flows to service our indebtedness and finance our operations and the volatility of our stock price.