PTC THERAPEUTICS, INC.
Form 10-K
March 16, 2017
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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

(MarkOne)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended: December 31, 2016

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

Commission file number: 001-35969

PTC THERAPEUTICS, INC.
(Exact Name of Registrant as Specified in its Charter)

Delaware	04-3416587
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
100 Corporate Court South Plainfield, New Jersey (Address of Principal Executive Offices)	07080 (Zip Code)

(908) 222-7000
(Registrant's telephone number, including area code)
Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Name of each exchange on which registered
Common Stock, $0.001 par value	NASDAQ Global Select Market

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes No
Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes No
Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes No
Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

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

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

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

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

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on the NASDAQ Global Select Market on June 30, 2016, the last business day of the registrant’s most recently completed second fiscal quarter, was $230,565,407. For purposes of this calculation, shares of Common Stock held by directors and officers have been treated as shares held by affiliates.

As of February 24, 2017, the registrant had 34,556,440 shares of Common Stock, $0.001 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Part III of this Annual Report incorporates by reference information from the definitive Proxy Statement for the registrant’s 2017 Annual Meeting of Shareholders which is expected to be filed with the Securities and Exchange Commission not later than 120 days after the registrant’s fiscal year ended December 31, 2016.

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FORWARD-LOOKING STATEMENTS

This Annual Report on Form10-K contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this Annual Report on Form 10-K, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “might,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “sh similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this Annual Report on Form 10-K include, among other things, statements about:

- statements related to our expectations with respect to the closing of our planned acquisition of all rights to Emflaza™ (deflazacort) from Marathon Phamaceuticals, LLC, including with respect to matters of timing, the anticipated financial impact and potential benefits to us, and related integration matters;
- our ability to resolve the matters set forth in the Refuse to File letter we received from the United States Food and Drug Administration, or FDA, in connection with our New Drug Application, or NDA, for Translarna™ (ataluren) for the treatment of nonsense mutation Duchenne muscular dystrophy, or nmDMD, including whether filing our NDA over protest with the FDA will result in a timely or successful review of our NDA, and whether we will be required to perform additional clinical and non-clinical trials or analyses at significant cost;
- our ability to enroll, fund, and complete Study 041, a multicenter, randomized, double-blind, 18-month, placebo-controlled clinical trial of Translarna for the treatment of nmDMD followed by an 18-month open label extension, according to the protocol agreed with the European Medicines Agency, or EMA and by the trial’s deadline;
- our ability to maintain our marketing authorization of Translarna for the treatment of nmDMD in the European Economic Area, or EEA (which is subject to the specific obligation to conduct and submit the results of Study 041 to the EMA and is also subject to annual review and renewal by the European Commission following reassessment of the benefit-risk balance of the authorization by the EMA);
- the timing and scope of our continued commercialization of Translarna as a treatment for nmDMD, including our ability to successfully negotiate adequate pricing and reimbursement processes on a timely basis, or at all, in the countries in which we have or may obtain regulatory approval;
- our ability to obtain additional and maintain existing reimbursed named patient and cohort early access programs for Translarna for the treatment of nmDMD on adequate terms, or at all;
- our estimates regarding the potential market opportunity for Translarna, including the size of eligible patient populations and our ability to identify such patients;
- our estimates regarding expenses, future revenues, third party discounts and rebates, capital requirements and needs for additional financing, including our ability to maintain the level of our expenses consistent with our internal budgets and forecasts and to secure additional funds on favorable terms or at all;
- the timing and conduct of our ongoing, planned and potential future clinical trials and studies of Translarna for the treatment of nmDMD, mucopolysaccharidosis type I, or MPS I, aniridia, and Dravet syndrome/CDKL5, each caused by nonsense mutations, as well as our studies in spinal muscular atrophy and our cancer stem cell program, including statements regarding the timing of initiation, enrollment and completion of the trials and the period during which the results of the trials will become available;
- the rate and degree of market acceptance and clinical utility of Translarna;
- the ability and willingness of patients and healthcare professionals to access Translarna through alternative means if pricing and reimbursement negotiations in the applicable territory do not have a positive outcome, including whether patients in Germany will continue to be able to access Translarna via a reimbursed importation pathway provided under German law, while maintaining a sustainable price;
- the timing of and our ability to obtain additional marketing authorizations for Translarna and our other product candidates, and the ability of Translarna and our other product candidates to meet existing or future regulatory standards;

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- our ability to maintain the current label under the marketing authorization in the EEA or expand the approved product label of Translarna for the treatment of nmDMD, whether pursuant to our Phase 2 study of Translarna for nmDMD in pediatric patients, or otherwise;
- the timing of our planned closures of extension trials for Translarna for the treatment of nmCF;
- the potential receipt of revenues from future sales of Translarna and other product candidates, including our ability to earn a profit from sales or licenses of Translarna for the treatment of nmDMD;
- the potential impact that enrollment, funding and completion of Study 041 may have on our revenue growth;
- our sales, marketing and distribution capabilities and strategy, including the ability of our third-party manufacturers to manufacture and deliver Translarna in clinically and commercially sufficient quantities and the ability of distributors to process orders in a timely manner and satisfy their other obligations to us;
- our ability to establish and maintain arrangements for the manufacture of Translarna and our other product candidates that are sufficient to meet clinical trial and commercial launch requirements;
- our other regulatory submissions, including with respect to timing and outcome of regulatory review;
- our plans to pursue development of Translarna for additional indications;
- our ability to advance our earlier stage programs, including our cancer stem cell program;
- our plans to pursue research and development of other product candidates;
- whether we may pursue business development opportunities, including potential collaborations, alliances, and acquisition or licensing of assets;
- the potential advantages of Translarna;
- our intellectual property position;
- the impact of government laws and regulations;
- our competitive position; and
- our expectations with respect to the development and regulatory status of our product candidates and program directed against spinal muscular atrophy in collaboration with F. Hoffmann La Roche Ltd and Hoffmann La Roche Inc., which we refer to collectively as Roche, and the Spinal Muscular Atrophy Foundation, or the SMA Foundation, and our estimates regarding future revenues from achievement of milestones in that program.

We may not actually achieve the plans, intentions or expectations disclosed in our forward looking statements, and you should not place undue reliance on our forward looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in Part I, Item 1A. Risk Factors that we believe could cause actual results or events to differ materially from the forward looking statements that we make.

Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements whether as a result of new information, future events or otherwise, except as required by applicable law.

In this Annual Report on Form 10-K, unless otherwise stated or the context otherwise requires, references to “PTC,” “PTC Therapeutics,” “we,” “us,” “our,” “the Company,” and similar references refer to PTC Therapeutics, Inc. and, where appropriate, its subsidiaries. The trademarks, trade names and service marks appearing in this Annual Report on Form 10-K are the property of their respective owners.

All website addresses given in this Annual Report on Form 10-K are for information only and are not intended to be an active link or to incorporate any website information into this document.

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PART I

Item 1. Business

Overview

We are a global biopharmaceutical company focused on the discovery, development and commercialization of novel medicines using our expertise in RNA biology. The letters “PTC” in our corporate name are an acronym for post-transcriptional control processes, which are the regulatory events that occur in cells during and after a messenger RNA is copied from DNA through the transcription process. Our internally discovered pipeline addresses multiple therapeutic areas, including rare disorders and oncology. We have discovered all of our compounds currently under development using our proprietary technologies. We plan to continue to develop these compounds both on our own and through selective collaboration arrangements with leading pharmaceutical and biotechnology companies. We believe that systematically targeting post-transcriptional control processes represents an unexploited approach to drug discovery and development. Since our founding nearly 20 years ago, our mission has focused on developing treatments to fundamentally change the lives of patients living with rare genetic disorders.

Our lead product, Translarna™ (ataluren) received marketing authorization from the European Commission in August 2014 for the treatment of nonsense mutation Duchenne muscular dystrophy, or nmDMD, in ambulatory patients age 5 years and over in the 31 member states of the European Economic Area, or EEA. nmDMD is a rare, life threatening disorder. We have been generating revenue from sales of Translarna for the treatment of nmDMD through reimbursed early access programs, or EAP programs, or commercial sale, since the third quarter of 2014. During fiscal year 2016, Translarna achieved net sales of $81.4 million and is currently available for the treatment of nmDMD in over 25 countries.

Our marketing authorization in the EEA is subject to annual review and renewal by the European Commission following reassessment by the European Medicines Agency, or EMA, of the benefit-risk balance of the authorization and is further subject to a specific obligation to conduct and submit the results of a three-year clinical trial comprised of an18-month, placebo-controlled clinical trial, followed by an 18-month open-label extension, which we refer to together as Study 041.

Translarna is an investigational new drug in the United States. During the first quarter of 2017, we filed a New Drug Application, or NDA, for Translarna for the treatment of nmDMD over protest with the United States Food and Drug Administration, or FDA. The FDA has granted a standard review for the NDA and has set a target review date under the Prescription Drug User Fee Act, or PDUFA, of October 24, 2017. The PDUFA date is the goal date for the FDA to complete its review of the NDA, however, such date is not binding on the agency and there can be no assurance that the FDA will complete its review of our NDA by the PDUFA goal date.

Filing over protest is a procedural path permitted by FDA regulations that allows a company to have its NDA filed and reviewed when there is a disagreement with regulators over the acceptability of the NDA submission. The NDA, which seeks approval of Translarna for the treatment of nmDMD in the United States, was initially submitted by us in December 2015. In February 2016, following our initial submission, we received a Refuse to File letter from the FDA stating that our NDA was not sufficiently complete to permit a substantive review.

On March 2, 2017, we announced that the primary and secondary endpoints were not achieved in ACT CF, our Phase 3 double-blind, placebo-controlled, 48-week clinical trial comparing Translarna to placebo in nmCF patients six years of age or older not receiving chronic inhaled aminoglycosides. The safety profile of Translarna in the ACT CF study was consistent with previous studies and no new safety signals were identified. Based on the results of ACT CF, we plan to discontinue our current clinical development of Translarna for nmCF and close ongoing extension studies for Translarna for the treatment of nmCF. We have withdrawn our type II variation submission with the EMA, which sought approval of Translarna for the treatment of nmCF in the EEA.

Based on its understood mechanism of action, we believe that Translarna may have benefit in the treatment of patients with genetic disorders that arise as a result of a nonsense mutation. We are pursuing studies for Translarna in additional indications: mucopolysaccharidosis type I caused by nonsense mutation, or nmMPS I, nonsense mutation aniridia, and nonsense mutation Dravet syndrome/CDKL5.

We hold worldwide commercialization rights to Translarna for all indications in all territories. The EMA has designated Translarna as an orphan medicinal product and the FDA has granted orphan drug designation to Translarna

for the treatment of cystic fibrosis, or CF, Duchenne muscular dystrophy, or DMD, mucopolysaccharidosis type I, or MPS I, and aniridia.

We continue to advance the development of our spinal muscular atrophy, or SMA, collaboration with F. Hoffman-La Roche Ltd and Hoffman-La Roche Inc., which we refer to collectively as Roche, and the Spinal Muscular Atrophy Foundation, or SMA Foundation. The initiation in the fourth quarter of 2016 of Sunfish, a two-part clinical study in pediatric and adult type 2 and type 3 SMA patients was followed by the initiation of Firefish, a two-part clinical study in infants with type 1 SMA. Each of the

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Sunfish and Firefish studies are investigating the safety, tolerability and efficacy of the compound RG7916 in the applicable patient populations. Part one of each study is a dose-finding study with the primary objectives of evaluating the safety, pharmacokinetics, and pharmacodynamics of RG7916 in patients and to select the dose for part two of the applicable study. Part one of each study is expected to be followed by a pivotal part two with the primary objective of evaluating the efficacy of RG7916. The FDA has granted orphan drug designation to RG7916 for the treatment of patients with SMA.

In December 2016, the Phase 2 Moonfish study, which was evaluating the safety and efficacy of RG7800 (another compound within the SMA program), was terminated.

In addition, we have a pipeline of product candidates that are in early clinical and preclinical development, including our cancer stem cell program. Our preclinical and discovery programs are focused on the development of new treatments for multiple therapeutic areas, including neuromuscular disease and oncology. We have discovered all of our compounds currently under development using our proprietary technologies. We plan to continue to develop these compounds both on our own and through selective collaboration arrangements with leading pharmaceutical and biotechnology companies.

On March 16, 2017, we announced that we have entered into an asset purchase agreement with Marathon Pharmaceuticals, LLC, under which we have agreed to acquire all rights to Emflaza™ (deflazacort), subject to the satisfaction or waiver of certain conditions. Emflaza received approval from the FDA on February 9, 2017 as a treatment of Duchenne muscular dystrophy in patients five years of age and older. Additional information concerning the planned acquisition is discussed in Note 17. Subsequent Events in the consolidated financial statements and Item 1A. Risk Factors, each appearing elsewhere in this Annual Report on Form 10-K. Unless otherwise stated or the context otherwise requires, we have not reflected in this Annual Report on Form 10-K the changes to our business that may occur if we consummate the planned acquisition.

Product development programs

The following table summarizes key information about our most advanced product development programs that are being developed by us, or in collaboration with other pharmaceutical companies or independent investigators. All of the compounds in these programs are new chemical entities that we identified using our proprietary technologies.

Program	Development status
Translarna for nmDMD	• Marketing authorization granted in the EEA (1) • Finalized Study 041 protocol with the EMA (1) • October 24, 2017 PDUFA date set for NDA filed over protest (2) • Phase 2 pediatric safety and pharmacokinetics study in patients two to five years of age ongoing
Translarna for nmCF	• Discontinued
Translarna for nmMPS I	• Phase 2 study ongoing
Translarna for nonsense mutation aniridia	• Phase 2 study ongoing
Translarna for nonsense mutation Dravet syndrome/CDKL5	• Phase 2 study ongoing
Spinal muscular atrophy collaboration with Roche & the SMA Foundation	• Part one of Sunfish study (type 2/3 patients) ongoing • Part one of Firefish study (type 1 patients) ongoing
Cancer stem cell program (PTC596)	• Phase 1 dose-escalation safety and pharmacokinetics study completed (3)

(1)

The marketing authorization in the EEA includes the specific obligation to conduct and submit the results of Study 041 to the EMA by the end of the third quarter of 2021 and requires annual renewal by the European Commission following reassessment by the EMA of the benefit-risk profile of the authorization.

(2) We filed the NDA in the first quarter of 2017 using the FDA's file over protest regulations, which allow us to have the NDA filed and reviewed following receipt of the FDA's Refuse to File letter in February 2016 with respect to our initial NDA submission. The FDA has granted a standard review for the NDA and has set a target PDUFA review date of October 24, 2017, however, such date is not binding on the agency.

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(3) PTC596 was generally well tolerated as a monotherapy, producing systemic concentrations in patients similar to or exceeding those associated with preclinical activity. Though a protocol-defined maximum tolerated dose was not reached, the dose of 10 mg/kg was deemed intolerable due to pill burden and certain excipients that may have contributed to Grade 2 nausea, vomiting, and diarrhea in two of three patients.

Translarna™ (ataluren)

Mechanism of action

We discovered Translarna by applying our technologies to identify molecules that promote or enhance the suppression of nonsense mutations. Nonsense mutations are implicated in a variety of genetic disorders. Nonsense mutations create a premature stop signal in the translation of the genetic code contained in messenger RNA, or mRNA, and prevent the production of full-length, functional proteins. We believe that Translarna interacts with the ribosome, which is the component of the cell that decodes the mRNA molecule and manufactures proteins, to enable the ribosome to read through premature nonsense stop signals on mRNA and allow the cell to produce a full-length, functional protein. As a result, we believe that Translarna has the potential to be an important therapy for genetic disorders for which a nonsense mutation is the cause of the disease. Genetic tests are available for many genetic disorders, including those noted above, to determine if the underlying cause is a nonsense mutation. Translarna has been generally well tolerated in all of our clinical trials to date, which have enrolled over 1,000 individuals to date.

Nonsense mutation Duchenne muscular dystrophy (nmDMD)

Muscular dystrophies are genetic disorders involving progressive muscle wasting and weakness. DMD is the most common and one of the most severe types of muscular dystrophy. DMD occurs when a mutation in the dystrophin gene prevents the cell from making a functional dystrophin protein. Dystrophin is a muscle membrane associated protein and is critical to the structural and membrane stability of muscle fibers in skeletal, diaphragm and heart muscle. The absence of normally functioning dystrophin results in muscle fragility, such that muscle injury occurs when muscles contract or stretch during normal use. As muscle damage progresses, connective tissue and fat replace muscle fibers, resulting in inexorable muscle weakness.

Because the dystrophin gene is located on the X chromosome, DMD occurs almost exclusively in young boys. According to Parent Project Muscular Dystrophy, DMD occurs in approximately 1 in 3,500 live male births, while information from Moat, et al. (2013) in the European Journal of Human Genetics indicate prevalence of approximately 1 in 5,000 live male births. Genetic tests are available to determine if a patient's DMD is caused by a nonsense mutation. Based on information from Prior, et al. (1995) in the American Journal of Human Genetics, we estimate that a nonsense mutation is the cause of DMD in approximately 13% of patients. Overall, we estimate that there are approximately 7,000 nmDMD patients worldwide, with approximately 85% of such patients outside of the United States, including in Europe, Latin America, Asia Pacific, Middle East and Northern Africa regions. nmDMD is an ultra-rare, life threatening disorder. Without treatment, patients with DMD typically lose walking ability by their early teens, require ventilation support in their late teens and, eventually, experience premature death due to heart and lung failure. The average age of death for DMD patients is in their mid-twenties.

Marketing authorization matters for Translarna in nonsense mutation Duchenne muscular dystrophy

European Economic Area

We received marketing authorization from the European Commission in August 2014 for Translarna for the treatment of nmDMD in ambulatory patients aged five years and older in the 31 member states of the EEA. The marketing authorization is subject to annual review and renewal by the European Commission following reassessment by the EMA of the benefit-risk balance of continued authorization, which we refer to as the annual EMA reassessment, as well as our satisfaction of any specific obligation or other requirement placed upon the marketing authorization, including Study 041.

In January 2016, we submitted the final clinical study report from our Phase 3 clinical trial in nmDMD, which we refer to as ACT DMD, to the EMA in fulfillment of the initial specific obligation placed on our marketing authorization. The primary efficacy endpoint of ACT DMD was not achieved with statistical significance. We made our submission to the EMA as a type II variation request that sought to have this initial specific obligation to our marketing authorization removed and a full marketing authorization granted. In February 2016, we also submitted a marketing authorization renewal request with the EMA.

In January 2017, the European Commission renewed our marketing authorization based on the totality of the clinical data available from our trials and studies of Translarna for the treatment of nmDMD, including the safety and efficacy results of our Phase 2b and Phase 3 clinical trials, and our commitment to conduct and submit the results of Study 041 to the EMA by the end of the third quarter of 2021. Study 041 is a three-year clinical trial to confirm the efficacy and safety of Translarna in the approved patient population. The trial is comprised of two stages: an 18-month randomized, double-blind, placebo controlled

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clinical trial followed by an 18-month open label extension period. See “Item 1. Business—Planned and ongoing clinical development of Translarna in nonsense mutation Duchenne muscular dystrophy—Study 041” for further information regarding the specific obligation to the marketing authorization in the EEA.

Because the EMA did not grant our request for full marketing authorization, the authorization remains subject to the annual EMA reassessment. The marketing authorization renewal granted in January 2017 is effective, unless extended, through August 5, 2017. We submitted a marketing authorization renewal request to the EMA in February 2017.

Marketing authorization is required in order for us to engage in any commercialization of Translarna in the EEA, including through participation in the market access process and related pricing and reimbursement negotiations, on a country-by-country basis with each country in the EEA, and is also required to make Translarna available under EAP programs. See “Item 1. Business—Commercial Matters—Market Access Considerations” and “Item 1A. Risk Factors—Risks Related to the Development and Commercialization of our Product and our Product Candidates” and “—Risks Related to Regulatory Approval of our Product and our Product Candidates” for further information regarding the marketing authorization in the EEA, the market access process and related risks.

As the marketing authorization holder, we are obligated to monitor the use of Translarna for nmDMD to detect, assess and take required action with respect to information that could impact Translarna’s safety profile and to report this information, through pharmacovigilance submissions, to the EMA. Following its assessment of these submissions, the EMA can recommend to the European Commission actions ranging from the continued maintenance of the marketing authorization to its withdrawal.

United States

We submitted our completed NDA to the FDA in December 2015 with our ACT DMD analyses, after commencing our submission on a rolling basis in December 2014.

On February 22, 2016, we received a Refuse to File letter from the FDA stating that our NDA was not sufficiently complete to permit a substantive review in particular because, in the view of the FDA, both the Phase 2b and Phase 3 ACT DMD trials were negative and do not provide substantial evidence of effectiveness and that our NDA does not contain adequate information regarding the abuse potential of Translarna. Additionally, the FDA stated that we had proposed a post-hoc adjustment of ACT DMD that eliminates data from a majority of enrolled patients. While other comments and requests were noted in the letter as items to be addressed if the NDA were to be resubmitted, the FDA specified that they were not related to its refusal to file our NDA.

Following the FDA’s refusal to file our NDA, we initiated dialogue with the FDA to discuss and clarify the matters set forth in the letter and determine our best path forward. In accordance with the formal dispute resolution process that exists within the FDA’s Center for Drug Evaluation and Research, we filed a formal appeal of the Refuse to File letter, which was denied in October 2016. In the first quarter of 2017, we filed our Translarna NDA for nmDMD via the FDA’s file over protest regulations. We included additional retrospective and post hoc analyses from our clinical trials with the NDA filed in 2017, including analyses of the 6-minute walk test using alternative statistical and analytical methods and new analyses from the North Star Ambulatory Assessment test, a functional scale designed for boys affected by DMD. Filing over protest is a procedural path permitted by FDA regulations that allows a company to have its NDA filed and reviewed when there is a disagreement with regulators over the acceptability of the NDA submission.

The FDA has notified us that it has granted a standard review for the NDA and has set a target PDUFA review date of October 24, 2017. The PDUFA date is the target date for the FDA to complete its review of the NDA, however, such date is not binding on the agency and there can be no assurance that the FDA will complete its review of our NDA by the PDUFA date.

There is significant risk that, notwithstanding any dialogue we have had or any further dialogue we may be able to initiate with the FDA, pursuant to the file over protest process or otherwise, the agency will continue to disagree with our interpretation of the results of ACT DMD and the totality of clinical data from our trials, and will not grant marketing approval for Translarna for the treatment of nmDMD.

See “Item 1. Business—Government Regulation—The new drug approval, or NDA, process” below for further discussion with respect to the NDA process. See “Item 1. Business—Translarna™ (ataluren)” and “Item 1A. Risk Factors—Risks Related

to the Development and Commercialization of our Product and our Product Candidates" and "—Risks Related to Regulatory Approval of our Product and our Product Candidates" for further detail regarding the results of our completed trials and studies of Translarna for the treatment of nmDMD, the Refuse to File letter, our regulatory strategy in the United States, and the related risks to our business.

History of FDA Interactions. As previously disclosed, in February 2012, we discussed the design of a proposed Phase 3 clinical trial, which became ACT DMD, with the FDA. In that meeting, although the FDA indicated that the adequacy of data

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for filing and approval of an NDA would remain review issues, the FDA had no objections to key elements of our proposed trial design, including the eligibility criteria for patients based on baseline 6-minute walk distance, use of the 6-minute walk test as the primary efficacy endpoint and inclusion of timed tests of muscle function as key secondary endpoints, or the absence of any measure of dystrophin. We met with the FDA in August 2014 to discuss our proposed rolling NDA submission and initiated that submission in December 2014. We submitted our draft statistical analysis plan to the FDA in the spring of 2015, which included pre-specified, sub-group, and meta-analyses. We subsequently received comments from the FDA, which were incorporated before submitting our final statistical analysis plan, and prior to our unblinding of the study.

In 2010, in connection with our NDA based on our Phase 2b data, we had received a refuse to file letter from the FDA. The FDA refused to file this NDA on the grounds that the single placebo controlled Phase 2b clinical trial contained in the NDA did not achieve statistical significance in the pre-specified analysis. In December 2011, we filed with the FDA a formal dispute resolution request concerning the NDA. We requested review of the issues related to the FDA's refusal to file the NDA and a prospective resubmission of the NDA with updated information and analyses. In January 2012, the FDA reaffirmed the appropriateness of its earlier decision to refuse to file the 2010 NDA. In the current Refuse to File letter, the FDA referenced its prior refusal to file relative to the Phase 2b data and our discussions with the FDA, reiterating the views previously disclosed.

Other Territories

Translarna received marketing authorization for the treatment of nmDMD in Israel and South Korea in 2015 and these licenses are currently active. Many territories outside of the EEA, including Israel and South Korea, reference and depend on the determinations by the EMA when considering the grant of a marketing authorization. It is unlikely that we would be able to maintain our marketing authorizations in these regions in the event the EMA determined not to renew or otherwise modified or withdrew our marketing authorization in the EEA.

We have been pursuing and expect to continue to pursue marketing authorizations for Translarna for the treatment of nmDMD in other regions. In March 2016, we withdrew our New Drug Submission, or NDS, with Health Canada for Translarna for nmDMD. We are considering our best path forward for re-submitting the NDS in Canada and for progressing with our marketing authorization submissions in other territories, subject to our progress with regulatory matters in the United States and the EEA, as described above.

Planned and ongoing clinical development of Translarna in nonsense mutation Duchenne muscular dystrophy

Phase 2 pediatric study

As part of our pediatric development commitments under our marketing authorization in the EEA and to support the potential expansion of Translarna's labeling to younger patients with nmDMD, we initiated a Phase 2 pediatric clinical study to evaluate the safety and pharmacokinetics of Translarna in patients two to five years of age. The study, initiated in June 2016, includes a four-week screening period, a four-week study period, and a 48-week extension period for patients who complete the four-week study period (52 weeks total treatment).

Study 041

Overview. As a specific obligation to our marketing authorization in the EEA, we are required to conduct and submit to the EMA the results of a three-year clinical trial to confirm the efficacy and safety of Translarna in the treatment of ambulatory patients with nmDMD aged five years or older. The trial is comprised of two stages: an 18-month randomized, double-blind, placebo controlled clinical trial followed by an 18-month open label extension period. We refer to the 18-month clinical trial portion as "Stage 1" and the 18-month extension period as "Stage 2". We refer to Stage 1 and Stage 2 together as Study 041. As a condition to our marketing authorization, we are required to submit the results of Study 041 to the EMA by September 2021. The protocol for Study 041 has been approved by the CHMP. For a discussion of the risks related to conducting clinical trials, in general, and Study 041, in particular, please see "Item 1A. Risk Factors—Risks Related to the Development and Commercialization of our Product and our Product Candidates" ands "—Risks Related to Regulatory Approval of our Product and our Product Candidates".

Enrollment. According to the study protocol, Study 041 will enroll nmDMD patients aged five years and above who achieve a 6-minute walk distance, or 6MWD, equal to or greater than 150 meters at three pre-treatment evaluation times (screening, baseline day one and baseline day two), tested as set forth in the protocol. Qualified participants will also need to perform timed function tests of running/walking 10 meters, climbing/descending four stairs and standing

from supine within 30 seconds at both screening and baseline and meet the other criteria set forth in the protocol. Of the approximately 250 patients planned to be enrolled in Study 041, approximately 160 patients are expected to meet the criteria for inclusion in the primary analysis population, which we refer to as the modified intention-to-treat population, or mITT. Patients included in the mITT must be at least 7, but less than 16, years old, with a 6MWD of equal to or greater than

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300 meters and a stand from supine time of five seconds or more, each as tested at screening and baseline.

Objectives and endpoints. The primary objective of Study 041 is to evaluate the effect of Translarna on ambulation and endurance as assessed by the 6-minute walk test, or 6MWT. The primary analysis of Stage 1 will evaluate the difference in slope of change in 6MWD from baseline to week 72 between Translarna and placebo in the mITT population. Data from participants who do not qualify for inclusion in the mITT will be used for summary and analysis of efficacy endpoints.

Slope of change in 6MWD over 144 weeks will also be assessed as a secondary endpoint at the conclusion of Stage 2, and the consistency of the results at 144 weeks against week 72 will be assessed. Changes in 6MWD from baseline to week 72 and week 144 respectively will also be assessed as secondary endpoints.

A secondary objective of Study 041 is to determine the effects of Translarna on ambulation and burst activity as assessed by timed function tests (10-meter run/walk, 4-stair stair-climb, and 4-stair stair descend). Each timed function test will be analyzed as a secondary endpoint for both the mITT and ITT populations, at the end of Stage 1 and Stage 2. A separate analysis will evaluate 10-meter run/walk results in participants with a baseline 6MWD below 300 meters. An additional analysis will evaluate a composite endpoint of average change in times to run/walk 10 meters, climb 4 stairs, and descend 4 stairs. We will also assess each of time to loss of ambulation, stair-climbing and stair-descending over 72 weeks and over 144 weeks.

Determination of the effects of Translarna on lower-limb muscle function as assessed by the North Star Ambulatory Assessment, or NSAA, a functional scale designed for boys affected by DMD, will serve as an additional secondary objective. NSAA scores will be analyzed as secondary endpoints for both the mITT and ITT populations, at the end of Stage 1 and Stage 2. A separate analysis for Stage 2 will evaluate changes in total score in participants with a baseline 6MWD of equal to or greater than 400 meters and under 7 years of age. We will also assess the risk of loss of NSAA items over 72 weeks and 144 weeks.

The safety profile of Translarna also will be evaluated throughout Stage 1 and Stage 2 as a secondary objective.

Certain exploratory endpoints will also be assessed in Study 041. In patients aged 7 years and above, change from baseline in upper limb function will be assessed using both functional testing and parent/ caregiver-reported questionnaires. In patients under 7 years of age, muscle strength will be assessed by change from baseline in myometry parameters. At pre-qualified sites only, magnetic resonance imaging will be used to assess change from baseline in muscle fat fraction. The effects of Translarna on pulmonary function will be assessed by change from baseline in forced vital capacity. In addition, subject- and parent/caregiver-reported questionnaires and at-home diaries will assessed to evaluate the effect of Translarna on health-related quality of life (HRQL) changes from baseline.

Stratification. In Stage 1, participants will be randomized 1:1 to placebo or Translarna (10, 10, 20 mg/kg). The randomization will be stratified based on type of concomitant corticosteroid used at baseline (deflazacort versus prednisone/prednisolone), maximum of the two valid 6-minute walk tests performed at baseline day 1 and day 2 (<300 meters versus ≥300 to <350 meters, versus ≥350 to <400 meters, versus ≥400 meters), and time to stand from supine at baseline (<5 seconds versus ≥5 seconds).

Observational study, data collection, and open label, extension trials of Translarna for treatment of nmDMD

We are undertaking a multi-center, observational post-approval study of patients receiving Translarna on a commercial basis, as required by the Pharmacovigilance Risk Assessment Committee of the EMA and in collaboration with TREAT-NMD and the Cooperative International Neuromuscular Research Group. During the study we will gather data on Translarna safety, effectiveness, and prescription patterns in routine clinical practice.

Pursuant to the five-year managed access agreement entered into in July 2016 between us, the U.K. National Institute for Health and Care Excellence, or NICE, National Health Services England, or NHS England, and other interested parties, the NorthStar Network is collecting data on the efficacy of Translarna for the treatment of nmDMD as measured by the NorthStar Ambulatory Assessment test. Patients receiving Translarna will be compared to an historical natural history population as well as a matched control group in order to assess response to treatment over the period specified in the managed access agreement.

An open label, extension trial involving patients who participated in ACT DMD is also ongoing, across multiple sites in the United States, Europe and other territories. Two open label, extension trials involving patients from the United States, Europe, Israel, Australia, and Canada who had participated in our prior trials for nmDMD are also ongoing. In

certain limited territories where Translarna is available via a commercial or EAP program, we have begun to wind down the studies and are investigating the potential impact that additional site closures may have on our research and development expense.

Completed clinical trials of Translarna in nonsense mutation Duchenne muscular dystrophy

Phase 3 clinical trial of Translarna for nmDMD (ACT DMD)

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In October 2015, we announced results from ACT DMD, also referred to as Study 020, our Phase 3, double-blind, placebo-controlled, 48-week clinical trial to evaluate the safety and efficacy of Translarna in patients with nmDMD. ACT DMD involved 228 patients at 53 sites across 18 countries.

In the overall intent-to-treat, or ITT, study population, the primary endpoint of change from baseline at week 48 in the 6MWT, showed a 15 meter benefit in favor of Translarna, which did not meet statistical significance.

A summary of the safety and efficacy results from ACT DMD is outlined below.

Safety and tolerability. The results of ACT DMD confirmed the favorable safety profile of Translarna seen in our 48-week, 174-patient Phase 2b double-blind, placebo controlled clinical trial evaluating the long-term safety and efficacy of Translarna in patients with nmDMD completed in 2009, or the Phase 2b trial.

Translarna was generally well tolerated in ACT DMD. There were two study discontinuations due to adverse events, including one in the Translarna arm (constipation) and one in the placebo arm (disease progression). Most treatment-emergent adverse events were mild or moderate in severity. The most common adverse events in this trial were vomiting (20.4% overall), nasopharyngitis (20.0%), headache (18.3%), and fall (17.8%). These events were generally balanced across treatment arms and are typical of pediatric illnesses and/or patients with DMD. Adverse events with at least a 10% incidence in either treatment arm that were seen with increased frequency from the placebo group to the Translarna 40 mg dose group were vomiting (18.3% for placebo, 23.6% for the Translarna 40 mg group), nasopharyngitis (19.1% for placebo, 20.9% for the Translarna 40 mg group), fall (17.4% for placebo, 18.3% for the Translarna 40 mg group), cough (11.3% for placebo, 16.5% for the Translarna 40 mg group) diarrhea (8.7% for placebo, 17.4% for the Translarna 40 mg group), and pyrexia (10.4% for placebo, 13.9% for the Translarna 40 mg group). An overview of adverse events in this trial is shown in the table below.

Overview of treatment-emergent adverse events in Phase 3 clinical trial (as-treated population)

Parameter	Placebo N=115	Translarna 40 mg group N=115	All patients N=230
Patients with ≥1 adverse event	101 (87.8)%	103 (89.6)%	204 (88.7)%
Adverse events by severity			
Grade 1 (mild)	54 (47.0)%	61 (53.0)%	115 (50.0)%
Grade 2 (moderate)	37 (32.2)%	35 (30.4)%	72 (31.3)%
Grade 3 (severe)	9 (7.8)%	7 (6.1)%	16 (7.0)%
Grade 4 (life-threatening)	—	—	—
Adverse events by relatedness			
Unrelated	47 (40.9)%	44 (38.3)%	91 (39.6)%
Unlikely	30 (26.1)%	20 (17.4)%	50 (21.7)%
Possible	18 (15.7)%	27 (23.5)%	45 (19.6)%
Probable	6 (5.2)%	12 (10.4)%	18 (7.8)%
Discontinuations due to adverse events	1 (0.9)%	1 (0.9)%	2 (0.9)%
Serious adverse events	4 (3.5)%	4 (3.5)%	8 (3.5)%
Deaths	—	—	—

There were no serious adverse events observed during the trial that were considered possibly or probably related to Translarna. Determination of relatedness of the serious adverse event to Translarna was made by the trial investigator, based on his or her judgment.

Intent to Treat (ITT) Population. The primary efficacy endpoint in ACT DMD was change in 6MWD from baseline to week 48. In the ITT population, a 15 meter benefit (p=0.213) was observed in the primary endpoint which did not meet statistical significance.

Secondary endpoints in the trial included the proportion of patients with at least 10% worsening in 6MWD at week 48 of the trial compared to baseline, or 10% 6MWD worsening, and change in timed function tests of time to run/walk 10 meters, climb four stairs and descend four stairs. The hazard ratio for Translarna versus placebo was 0.75 (p=0.160) for 10% 6MWD worsening. Benefits trended in favor of Translarna over placebo in the timed function tests in the ITT population, including observed results in time to run/walk 10 meters (1.2 seconds; p=0.117), time to climb four stairs

(1.8 seconds; p=0.058), and time to descend four stairs (1.8 seconds; p=0.012).

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Additional endpoints included the NSAA test and the Pediatric Outcomes Data Collection Instrument, or PODCI, a validated tool for measuring quality of life in pediatric patients with orthopedic conditions. These additional endpoints favored Translarna in the ITT population but did not meet statistical significance.

Pre-Specified Analyses. The statistical analysis plan submitted to the FDA for ACT DMD set forth pre-specified analyses of efficacy to be conducted, including subgroups of patients with baseline 6MWD less than 350 meters and patients with baseline 6MWD of greater than or equal to 300 and less than 400 meters, which we refer to as our key subgroups.

The pre-specification of our key subgroups was scientifically justified based upon knowledge of the biology of the disease and the evolving understanding of the natural history of the six minute walk test in DMD patients. We considered the pre-specified less than 350 meter baseline 6MWD population as a key subgroup based on the knowledge that 350 meters represents a transition point for patients towards a more rapid decline in walking ability as supported by analysis from our Phase 2b trial. Furthermore, we considered the pre-specified 300 to 400 meter baseline 6MWD population as a key subgroup based on an increasing understanding of the sensitivity limitations of the six minute walk test as an endpoint in 48-week studies. Natural history data suggests that the 6MWT may not be the optimal tool to demonstrate efficacy in patients with either a baseline 6MWD of less than 300 meters, as these patients have significant muscle loss as monitored by magnetic resonance spectroscopy and are at high risk for losing ambulation regardless of treatment, or in high walking patients, such as those with a baseline 6MWD at or greater than 400 meters, as these patients are likely to remain stable over a 48 week testing period.

By defining these key subgroups, we thereby also defined corresponding complement subgroups of patients with baseline 6MWD greater than or equal to 350 meters, greater than or equal to 400 meters, and less than 300 meters. We also pre-specified a meta-analysis of the combined results from ACT DMD and the Phase 2b ambulatory decline phase patients.

Pre-specified sub-group analysis. We saw strong evidence of clinical benefit in the pre-specified subgroup of patients with baseline 6MWD between 300 and 400 meters. Specifically, we observed a benefit in Translarna-treated patients of 47 meters (nominal p=0.007) in the 6MWT in this subgroup. This benefit was consistent with an observed benefit of 49 meters (nominal p=0.026) in our Phase 2b clinical trial in the 300 to 400 meters baseline 6MWD population. We also saw clinically meaningful benefit for Translarna over placebo in each of the timed function tests, including observed results in time to run/walk 10 meters (2.1 seconds; nominal p=0.066), time to climb four stairs (3.6 seconds; nominal p=0.003), and time to descend four stairs (4.3 seconds; nominal p<0.001). The hazard ratio for Translarna versus placebo was 0.79 (nominal p=0.418) for 10% 6MWD worsening. In addition, a benefit of 4.5 points over placebo (nominal p=0.041) was observed in the NSAA test, which we believe is clinically meaningful. We believe that the benefits observed in this key pre-specified subgroup support the use of the 6MWT in the patients with a walking ability in the 300 to 400 meters range and the understanding that the reliability of the 6MWT over a 48 week period was limited at both the lower and upper ends of our 6MWD enrollment range.

In the pre-specified subgroup of patients with baseline 6MWD less than 350 meters, we observed a benefit of 24 meters (nominal p=0.210) in favor of Translarna in the 6MWT. An analysis of the results from our Phase 2b clinical trial in the less than 350 meters baseline 6MWD population, defined post-hoc, demonstrated a 68 meter benefit in the 6MWT (nominal p=0.006). In the timed function tests for the subgroup of ACT DMD patients with baseline 6MWD less than 350 meters, we observed benefits for Translarna over placebo in time to run/walk 10 meters (2.3 seconds; nominal p=0.033), time to climb four stairs (4.2 seconds; nominal p=0.019) and time to descend four stairs (4.0 seconds; nominal p=0.007).

As described above, we believe the 6MWT lacks sensitivity to detect a clinical effect in patients with baseline less than 300 meters in a 48-week trial. However, the timed function tests trended in favor of patients treated with Translarna with a baseline 6MWD below 300 meters, including observed benefit over placebo in time to run/walk 10 meters (2.5 seconds; nominal p=0.066), time to climb four stairs (2.4 seconds; nominal p=0.790), and time to descend four stairs (2.1 seconds; nominal p=0.595). We believe the positive trends in this population reflect that short muscle burst activity tests may be a better clinical measure for patients that are at a more advanced stage of disease progression. Consistent with the natural history of ambulatory DMD patients with 6MWD greater than 400 meters, which indicates stability in walking ability over a 48 week period, we observed no meaningful difference in 6MWT

between patient groups. Similarly, we observed no meaningful difference in 6MWT between patient groups with baseline 6MWD greater than 350 meters.

Pre-specified meta-analysis. The meta-analysis combined efficacy results from the ACT DMD ITT population and Phase 2b ambulatory decline phase subgroup. The Phase 2b ambulatory decline phase patients includes the patients from our randomized, double-blind, placebo controlled, Phase 2b clinical trial in patients with nmDMD who would have met the enrollment criteria of ACT DMD.

Results from the meta-analysis showed a statistically significant 21 meter improvement in 6MWD ($p = 0.015$) favoring Translarna.

Additionally, the meta-analysis showed statistically significant benefit for Translarna over placebo across each timed function test including time to run/walk 10 meters (1.4 seconds; $p=0.025$), time to climb four stairs (1.6 seconds; $p=0.018$) and time to

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descend four stairs (2.0 seconds; p=0.004). The hazard ratio for Translarna versus placebo was 0.66 (p=0.023) for 10% 6MWD worsening. We believe that we are able to demonstrate a statistically significant efficacy outcome in the 6MWD in the meta-analysis, despite the significant variability in baseline 6MWD among patients in both ACT DMD and the Phase 2b ambulatory decline phase, due to the substantially larger patient population available in the pooled analysis.

Retrospective Analysis. We also looked back at the observed results in the meta-analysis for all patients with a baseline 300 to 400 meter 6MWD from ACT DMD and the Phase 2b trial. The meta-analysis of this data demonstrated a 45 meter benefit (nominal p<0.001) in the 6MWT as well as clinically meaningful benefits across each secondary endpoint timed function test, including benefit over placebo in time to run/walk 10 meters (2.2 seconds; nominal p=0.008), time to climb four stairs (3.4 seconds; nominal p<0.001) and time to descend four stairs (4.3 seconds; nominal p<0.001). This meta-analysis of patients with baseline 6MWD of 300 to 400 meters was not pre-specified and is defined post-hoc.

Statistical Considerations. The pre-specified meta-analysis results, which favored Translarna in the 6MWT and each of the timed function tests, are considered statistically significant. In the pre-specified subgroups of ACT DMD patients with a baseline 6MWD less than 350 meters and 300 to 400 meters, the p-values for the 6MWT and each of the timed function tests are considered nominal. For information with respect to the use of nominal p-values and post-hoc analyses, see Item 1A. Risk Factors, “Our conclusions regarding the activity and potential efficacy of Translarna in nmDMD are primarily based on retrospective, subgroup and meta-analyses of the results of our Phase 2b and ACT DMD clinical trials of Translarna for the treatment of nmDMD. Other than with respect to certain of our meta-analyses, results of our analyses are expressed as nominal p-values, which are generally considered less reliable indicators of efficacy than adjusted p-values. In addition, retrospective analyses are generally considered less reliable than pre-specified analyses.”

Participation Criteria and Stratification. Certain key inclusion criteria were specified in the ACT DMD trial protocol for enrollment: the patient had to be 7 through 16 years of age; at the screening visit the patient had to be able to walk no more than 80% of predicted 6MWD compared to healthy boys matched for age and height, but have the ability to walk at least 150 meters during the 6MWT; and the patient must have used systemic corticosteroids for a minimum of six months prior to start of treatment. The ACT DMD trial protocol provided for the exclusion of patients from the trial if, among other things, they recently used systemic aminoglycoside antibiotics, recently initiated or changed corticosteroid therapy or previously received Translarna treatment. Patients enrolled in ACT DMD underwent 48 weeks of blinded treatment prior to the final analysis and the randomization was stratified based on age (<9 years versus ≥9), baseline 6MWD (<350 versus ≥350 meters), and duration of prior use of corticosteroids (<12 months versus ≥12 months).

Phase 2b clinical trial of Translarna for nmDMD

Overview. In March 2010, we announced the results of a randomized, double-blind, placebo controlled, dose ranging Phase 2b clinical trial evaluating the long term efficacy and safety of Translarna in patients with nmDMD as confirmed by gene sequencing. We conducted this clinical trial in 174 patients in 11 countries. The primary objective of this trial was to evaluate the effect of Translarna on ambulation using 6MWD at week 48 of the trial compared to baseline as the primary efficacy endpoint. Supportive analyses of ambulation consisted of the proportion of patients with at least 10% worsening in 6MWD at week 48 of the trial compared to baseline and time to persistent 6MWD 10% worsening from baseline. Multiple additional secondary and exploratory endpoints, including, among others, tests of muscle function based on time to climb four stairs, descend four stairs, run/walk 10 meters and stand from supine, were monitored for the primary purpose of gaining a greater understanding of clinical trial design in DMD. We assessed safety through collection of adverse event information, measurement of laboratory parameters and performance of electrocardiograms, or ECGs. We also evaluated study drug compliance and Translarna plasma concentrations.

Patients enrolled in this trial were at least five years of age, had the ability at baseline to walk at least 75 meters unassisted during a 6MWT, had onset of disease signs/symptoms prior to age nine, had elevated creatine kinase levels, and had ongoing difficulty with walking. Patients were excluded from the trial if they had a prior or ongoing clinically significant illness, had a positive hepatitis B or hepatitis C test or had recently used systemic aminoglycosides.

Patients receiving corticosteroid therapy were required to have initiated therapy more than six months prior to enrollment and to be on a stable dosing regimen for at least three months prior to entering the trial. The trial protocol specified a clinic visit every six weeks to assess efficacy and safety and an interim laboratory visit every three weeks for the first 24 weeks of the trial. The treatment duration was 48 weeks.

Patients were stratified based on age, baseline 6MWD, and use of corticosteroids. Patients were randomized in a 1:1:1 ratio to receive (i) placebo; (ii) daily dose of 40 mg/kg of Translarna, or the 40 mg group; and (iii) daily dose of 80 mg/kg of Translarna, or the 80 mg group.

Pre-specified analysis in ITT population. We performed the primary analysis of the mean change in 6MWD from baseline to 48 weeks specified in the trial protocol in the ITT population. The ITT population included all 174 randomized patients with a valid 6MWT available at baseline and at least one post-baseline visit. Analysis of the results of the ITT population showed that

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patients in the 40 mg group had notably less decline in their walking ability than the patients taking placebo, with a difference of 29.7 meters between the 40 mg group and placebo in mean change in 6MWD over 48 weeks. Although this result was consistent with the clinically meaningful treatment effect of 30 meters specified in the trial protocol, the resulting nominal p-value of 0.149 was not statistically significant at the pre-specified level of less than 0.05. Typically, a trial result is statistically significant if the chance of it occurring when the treatment is like placebo is less than one in 20, resulting in a p-value of less than 0.05. A p-value is called nominal if it is the result of one particular comparison when more than one comparison is possible, such as when two active treatments are compared to placebo or when two or more subgroups are analyzed.

In addition, ITT population analysis showed that there was no difference between patients in the 80 mg group from placebo in mean change in 6MWD over 48 weeks. Although unanticipated, this finding is consistent with a bell-shaped dose-response curve that we observed in four subsequent non-clinical studies of Translarna in DMD and other genetic disorders. Under analysis of the ITT population, pre-specified measurements of supportive analyses of ambulation were not reached in any of the three treatment arms of the trial.

Post-hoc analyses of Phase 2b clinical trial data. Based on our further evaluation of the data from our Phase 2b clinical trial after unblinding the results, we identified three issues affecting the pre-specified statistical analyses. We addressed these issues in a post-hoc, retrospective refinement to the pre-specified statistical analysis plan, resulting in what we refer to as a corrected ITT analysis.

- Our pre-specified statistical model used to calculate the p-value and significance of the trial results omitted a specific statistical term designed to address the potential relationship between the 6MWD results at baseline and at each subsequent patient visit. As has now become standard practice in analyses of repeated-measures data, we adjusted our statistical model to add this statistical term in preparing the corrected ITT analysis.
- Because the 6MWD data were non-normally distributed, our pre-specified analysis used rank-transformed data in which the 6MWD values for each patient were ordered from smallest to largest and ranked from one to 174. However, ranking the data in this way did not fully reflect the large variability as measured in meters that we observed in the original 6MWD data. In the corrected ITT analysis, we used a re-randomization test, rather than rank transformation of the data, to address non-normality of the trial data. This re-randomization test allowed analysis of the 6MWD results in meters, rather than ranking the results relative to one another, to more accurately reflect the large variability in walking distances.
- Two patients had lower limb injuries after screening but prior to their baseline assessment. These injuries substantially affected their walking ability and led to aberrantly low baseline 6MWD values that did not accurately reflect their pre-treatment ambulatory ability. These baseline 6MWT were incorrectly classified as valid by the investigative site, and the resulting data should not have been included in the ITT analysis. In the corrected ITT analysis, we replaced the baseline values for these two patients with their valid screening values.

The results of our post-hoc analysis of the primary efficacy endpoint of this trial are shown in the table below.

Change in 6-minute walk distance from baseline to week 48 (corrected ITT analysis)

	Treatment arm		
Summary of change from baseline to week 48	Placebo N=57	Translarna 40 mg/kg/day N=57	Translarna 80 mg/kg/day N=60
Mean (standard deviation), meters	–44.1 (88.0)	-12.9 (72.0)	–44.8 (84.8)
Mean difference from placebo, meters		31.3	–0.7
Nominal p-value (vs. placebo)		0.0281	0.912
Adjusted p-value (vs. placebo)		0.0561	0.991

In the corrected ITT analysis, the difference between the 40 mg group and placebo in mean change in 6MWD over 48 weeks was 31.3 meters. We observed clear separation between the 40 mg group and placebo, with the difference between the arms increasingly favoring the 40 mg group over time. The resulting nominal p-value for the comparison of mean change in 6MWD from baseline to week 48 for the 40 mg group versus placebo was 0.0281. However, because two dose levels were compared to placebo, we were required to apply a multiplicity adjustment, which

yielded a final adjusted p-value of 0.0561 for the 40 mg group versus placebo.

Although we believe that our additional analyses of the trial results were warranted, a retrospective analysis performed after unblinding trial results can result in the introduction of bias if the analysis is inappropriately tailored or influenced by knowledge of the data and actual results. In addition, nominal p-values cannot be compared to the benchmark p-value of 0.05 to

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determine statistical significance without being adjusted for the testing of multiple dose groups or analyses of subgroups. Because of these limitations, regulatory authorities typically give greatest weight to results from pre-specified analyses and adjusted p-values and less weight to results from post-hoc, retrospective analyses and nominal p-values.

Secondary endpoints. Patients in the 40 mg group trended better than the placebo group in several of the secondary endpoints tracked during this trial, however the trial was not powered to detect statistically significant differences in secondary endpoints. Patients in the 40 mg group and exceeded the clinically meaningful threshold of 1.5 seconds for stair-climbing and stair- descending in the ITT analysis and for running/walking in the corrected ITT analysis. In a supine to stand test, we did not observe any difference between Translarna and placebo. Other secondary endpoints showed trends favoring patients treated with Translarna, but at levels below a threshold considered to be clinically meaningful, including: muscle strength (tested through myometric evaluations), frequency of falls (based on patients/caregiver notation), and health related quality of life and treatment satisfaction (based on patient reports).

Safety and tolerability. Translarna was generally well tolerated at both dose levels in our Phase 2b clinical trial. There were no study discontinuations due to adverse events. Most treatment-emergent adverse events were mild or moderate in severity. Investigators' attributions of drug-related adverse effects were generally similar across the placebo and Translarna arms. The most common adverse events in this trial were vomiting (46.6% overall), headache (29.3%), diarrhea (24.1%), nasopharyngitis (20.7%), fever (19.0%), cough (19.0%) and upper abdominal pain (17.8%). These events were generally balanced across treatment arms and are typical of pediatric illnesses. Adverse events with at least a 10% incidence in any treatment arm that were seen with increased frequency from the placebo group to the Translarna 40 mg dose group to the Translarna 80 mg dose group were nausea (12.3% for placebo, 14.0% for the Translarna 40 mg group and 16.7% for the Translarna 80 mg group), abdominal pain (7.0% for placebo, 12.3% for the Translarna 40 mg group and 16.7% for the Translarna 80 mg group), pain in extremity (10.5% for placebo, 12.3% for the Translarna 40 mg group and 13.3% for the Translarna 80 mg group), flatulence (7.0% for placebo, 8.8% for the Translarna 40 mg group and 11.7% for the Translarna 80 mg group) and nasal congestion (7.0% for placebo, 8.8% for the Translarna 40 mg group and 10.0% for the Translarna 80 mg group). An overview of adverse events in this trial is shown in the table below.

Overview of treatment-emergent adverse events in Phase 2b clinical trial (as-treated population)

Parameter	Treatment arm			
	Placebo N=57	Translarna 40 mg group N=57	Translarna 80 mg group N=60	All patients N=174
Patients with ≥ 1 adverse event	56 (98.2)%	55 (96.5)%	57 (95.0)%	168 (96.6)%
Adverse events by severity				
Grade 1 (mild)	21 (36.8)%	16 (28.1)%	20 (33.3)%	57 (32.8)%
Grade 2 (moderate)	26 (45.6)%	31 (54.4)%	27 (45.0)%	84 (48.3)%
Grade 3 (severe)	9 (15.8)%	8 (14.0)%	10 (16.7)%	27 (15.5)%
Grade 4 (life-threatening)	—	—	—	—
Adverse events by relatedness				
Unrelated	14 (24.6)%	8 (14.0)%	11 (18.3)%	33 (19.0)%
Unlikely	16 (28.1)%	17 (29.8)%	13 (21.7)%	46 (26.4)%
Possible	20 (35.1)%	25 (43.9)%	29 (48.3)%	74 (42.5)%
Probable	6 (10.5)%	5 (8.8)%	4 (6.7)%	15 (8.6)%
Discontinuations due to adverse events	—	—	—	—
Serious adverse events	3 (5.3)%	2 (3.5)%	2 (3.3)%	7 (4.0)%
Deaths	—	—	—	—

There were no serious adverse events observed during the trial that were considered possibly or probably related to Translarna. Determination of relatedness of the serious adverse event to Translarna was made by the trial investigator, based on his or her judgment.

Phase 2a clinical trial of Translarna for nmDMD

In October 2007, we announced the results of an open label Phase 2a clinical trial evaluating Translarna in 38 patients with nmDMD. The primary objective of this trial was to obtain indications of pharmacological activity. The primary efficacy endpoint in this trial was the change from baseline measurement of dystrophin levels in a muscle in the foot known as the extensor digitorum brevis. nmDMD patients enrolled in this trial were at least five years of age, had increased levels of serum

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creatine kinase, or CK, and had absent or diminished dystrophin protein on muscle biopsy. All participants in the trial received Translarna treatment for 28 days at one of three varying doses (12 mg/kg/day, 40 mg/kg/day and 80 mg/kg/day). In this trial, Translarna induced a mean 11.0% increase in muscle dystrophin expression over the 28 days of treatment, with 23 of the 38 patients (61%) showing an increase from baseline. We observed serum CK reductions in 35 of the 38 patients (92%) at the end of treatment. With cessation of Translarna treatment, mean serum CK concentrations reverted toward baseline. Changes in myometry scores and timed function tests were small and not statistically significant with 28 days of Translarna treatment. Anecdotal reports from the parents and teachers of several boys noted evidence of greater activity, increased endurance and less fatigue during Translarna administration. Pharmacokinetic results from this trial indicated that both the 40 mg/kg/day and the 80 mg/kg/day dose regimens achieved plasma concentrations of Translarna that were predicted to have a therapeutic effect, based on preclinical data. The 12 mg/kg/day regimen did not consistently achieve these levels, and as a result we did not include this dosing regimen in our subsequent Phase 2b clinical trial.

Nonsense mutation cystic fibrosis (nmCF)

On March 2, 2017, we announced that the primary and secondary endpoints were not achieved in ACT CF, our Phase 3 double-blind, placebo-controlled, 48-week clinical trial comparing Translarna to placebo in nmCF patients six years of age or older not receiving chronic inhaled aminoglycosides. The safety profile of ataluren in the ACT CF study was consistent with previous studies and no new safety signals were identified.

Based on the results of ACT CF, we plan to discontinue our current clinical development of Translarna for nmCF. In connection with this discontinuation, we intend to close the two open label extension trials previously made available to patients who successfully completed blinded treatment in our prior Phase 3 clinical trials for Translarna in nmCF. We have also withdrawn our type II variation submission with the EMA, which sought approval of Translarna for the treatment of nmCF in the EEA.

Phase 3 clinical trial of Translarna for nmCF (ACT CF)

In the intent-to-treat population, the primary endpoint of lung function as measured by absolute change from baseline in percent-predicted forced expiratory volume in one second assessed as an average at Week 40 and at Week 48 showed a 0.6% difference in favor of Translarna versus placebo (-1.4% change on Translarna versus -2.0% change on placebo; p=0.534). For the secondary endpoint of rate of pulmonary exacerbations, there was a trend in favor of Translarna, with the rate in the Translarna group being 14% lower than the placebo group (p=0.401). These results were not statistically significant.

ACT CF was conducted in 16 countries and enrolled 279 patients who were randomized to receive either Translarna or placebo.

Safety and tolerability. The preliminary results of ACT CF confirmed the safety profile of Translarna with no new safety signals identified. Translarna was generally well tolerated in the clinical trial. There were seven (2.5%) study discontinuations due to adverse events, including three (2.1%) in the Translarna 40 mg group (chest discomfort/pain of extremities/flushing in one patient, dizziness/headache in a second patient and dysuria in a third patient) and four (2.9%) in the placebo group (pulmonary exacerbation in one patient, cough/dyspnea in a second patient, depressed mood in a third patient and gama glutamyltransferase elevation in a fourth patient). Most treatment-emergent adverse events were mild or moderate in severity.

The most common adverse events (regardless of treatment group) in this trial were infective pulmonary exacerbations (63.1%), cough (18.3%), viral upper respiratory tract infection (17.2%), and upper respiratory tract infection (15.1%). These events were mostly balanced across treatment arms and are typical adverse events in patients with cystic fibrosis. Adverse events with at least a 10% incidence in either treatment arm that were seen with increased frequency in the Translarna 40 mg group compared to the placebo group were viral upper respiratory tract infection (15.1% for placebo, 19.3% for the Translarna 40 mg group), cough (18.0% for placebo, 18.6% for the Translarna 40 mg group), sinusitis (9.4% for placebo, 11.4% for the Translarna 40 mg group), and hemoptysis (7.9% for placebo, 10.0% for the Translarna 40 mg group).

Prior Phase 3 clinical trial of Translarna for nmCF (Study 009)

The study population that we used in ACT CF was based on, and reflected our analysis of the results of, our randomized, double-blind, placebo controlled, Phase 3 clinical trial evaluating the long-term safety and efficacy of

Translarna in patients with nmCF completed in 2011, or Study 009. Although the primary endpoint of relative change in percent-predicted forced expiratory volume in one second was not achieved in Study 009, we believe the outcomes observed in multiple endpoints between the subgroup of patients who were not prescribed chronic inhaled tobramycin and the subgroup of patients who were prescribed chronic inhaled tobramycin as well as post-hoc in vitro testing showing the interference of aminoglycoside antibiotics with Translarna activity supported the hypothesis that inhaled tobramycin may interfere with Translarna's mechanism of action.

Translarna was generally well tolerated in Study 009, and there were generally similar adverse event profiles in patients treated with Translarna and patients treated with placebo. Most serious adverse events were cystic fibrosis pulmonary exacerbations

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unrelated to study drug treatment. Most treatment-emergent adverse events were mild or moderate in severity. Investigators' attributions of severity and drug-relatedness were generally similar across the placebo and Translarna arms. The most common adverse events during this trial were cystic fibrosis pulmonary exacerbation (78.2% overall), cough (25.6%) and viral upper respiratory tract infection (21.0%). These events were slightly more frequent in the placebo arm and are typical of cystic fibrosis. Adverse events with at least a 10% incidence in any treatment arm that were seen with higher frequency in the Translarna arm were headache (11.9% for placebo and 16.7% for Translarna), abdominal pain (12.7% for placebo and 15.0% for Translarna), sinusitis (11.9% for placebo and 12.5% for Translarna) and vomiting (8.5% for placebo and 11.7% for Translarna). Eleven patients prematurely discontinued treatment because of adverse events, including eight in the Translarna arm and three in the placebo arm.

There were 19 patients with at least one treatment-emergent renal adverse event, including 15 patients receiving Translarna and 4 patients receiving placebo. In the Translarna arm, five adverse events that involved the renal system led to discontinuation. As compared to the placebo group, the Translarna treatment arm also had a higher incidence of adverse events of creatinine elevations, which can be an indication of impaired kidney function. These adverse events of creatinine elevations were generally mild and transient. In the Translarna treatment arm, clinically meaningful creatinine elevations of grade 3 or grade 4 were reported in conjunction with cystic fibrosis pulmonary exacerbations. These creatinine elevations were associated with concomitant treatment with antibiotics associated with impaired kidney functions, such as aminoglycosides or vancomycin. This led to the subsequent prohibition of concomitant use of Translarna and these potentially nephrotoxic antibiotics, which was successful in addressing this issue. The incidence of new-onset kidney stones was similar in both arms, with five patients in the Translarna arm and four patients in the placebo arm.

The serious adverse events observed during the trial that were considered possibly related to Translarna were biliary colic, elevated creatinine, pancreatitis, renal failure, urinary tract infection and urinary retention. Determination of relatedness of the serious adverse event to Translarna was made by the trial investigator, based on his or her judgment.

Translarna™ for additional indications

Over the last seven years multiple independent investigators have conducted preclinical studies in which Translarna enabled readthrough of the premature stop codons from a large set of nonsense mutations across a diverse group of experimental models exhibiting various genetic disorders. The studies evaluated Translarna's ability to read through premature stop codons in mRNA in cell-free systems, transfected cell lines, mouse models and patient cells. Based on these studies by independent investigators in addition to our own trials and studies, we expect to continue to pursue additional indications for Translarna, including nmMPS I and aniridia caused by nonsense mutation and, via an investigator initiated study, Dravet syndrome/CDKL5 caused by nonsense mutation.

Nonsense mutation aniridia

Aniridia is a genetic disorder due to mutations in the PAX6 gene associated with loss of eyesight and other symptoms. We estimate that approximately one-third of all aniridia cases are due to a nonsense mutation. In a prior study conducted by an independent investigator, Translarna-treated mice with nonsense mutation aniridia showed a significant increase in the PAX6 protein in a nonsense mutation PAX6 gene, but not in mice with a PAX6 gene harboring a splice-site mutation. The investigators in this study found that Translarna not only inhibited disease progression, but also reversed corneal, lens and retinal malformation defects and restored electrical responses of the retina.

The first patient in our clinical study of Translarna in nonsense mutation aniridia, which we refer to as STAR, was dosed in February 2016. STAR is a Phase 2, randomized, double-masked, placebo-controlled study of Translarna in patients with aniridia caused by a nonsense mutation, followed by an open-label extension study. Patients will receive masked study drug for 48 weeks followed by open-label Translarna for another 48 weeks. Safety and efficacy will be assessed.

Nonsense mutation Dravet syndrome/CDKL5

Dravet syndrome and CDKL5 are two different genetically defined disorders of epilepsy. Dravet syndrome, also called severe myoclonic epilepsy of infancy, is a debilitating form of epilepsy caused by defects in the sodium voltage gated channel a1 subunit gene required for the proper function of brain cells. People with Dravet syndrome experience frequent seizures and developmental delays. CDKL5 is caused by a mutation of the Cyclin-dependent kinase-like 5

(CDKL5) gene leading to a lack of the protein critical in brain development. CDKL5 is characterized by in seizures starting early in life and severe developmental impairment.

A clinical study assessing Translarna in nonsense mutation Dravet syndrome/CDKL5 was initiated in the first quarter of 2017.

Nonsense mutation Mucopolysaccharidosis type I (nmMPS I)

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MPS I is an inherited genetic disorder caused by a deficiency in an essential enzyme that is responsible for the breakdown of byproducts of chemical reactions in the body's cells. It is estimated that 60 percent to 80 percent of cases of MPS I are caused by a nonsense mutation. While enzyme replacement therapies are on the market, there remains significant unmet medical need for the development of new treatments that can target the underlying cause of the disorder.

During the first quarter of 2015, we amended the trial design for our Phase 2, multicenter, proof-of-concept study to evaluate the safety and pharmacokinetics of Translarna for the treatment of nmMPS I to include patients currently on enzyme replacement therapy, which contributed to delays in site initiation and patient accrual. We have continued to encounter difficulties identifying qualified patients for this study. Patients enrolled will participate in the study for approximately 12 weeks of Translarna treatment. The pharmacodynamic activity of Translarna in nmMPS I will also be explored via assessment of GAG levels in cerebrospinal fluid, urine, and blood.

Spinal muscular atrophy program

Spinal muscular atrophy, or SMA, is a genetic neuromuscular disease characterized by muscle wasting and weakness. The disease generally manifests early in life. SMA is caused by defects in the Survival Motor Neuron 1, or SMN1, gene that encodes the survival motor neuron, or SMN, protein. The SMN protein is critical to the health and survival of the nerve cells in the spinal cord responsible for muscle contraction. A second gene, SMN2, is very similar to SMN1, except that SMN2 is alternatively spliced and mostly produces an ineffective SMN protein that is missing a particular nucleotide sequence known as exon 7. According to the SMA Foundation, SMA is the leading genetic cause of death in infants and toddlers. We estimate that SMA affects approximately 20,000 to 30,000 children and adults in the United States, Europe and Japan and that one in 11,000 children are born with the disease.

Using our alternative splicing technology and in collaboration with the SMA Foundation, we identified highly potent small molecule splicing modifiers that in non-clinical studies in cultured cells isolated from patients with SMA increased both the inclusion of exon 7 in the SMN2 mRNA and the levels of SMN protein produced by SMN2. Importantly, in studies in transgenic mice carrying only the SMN2 gene, these orally bioavailable compounds, penetrate the blood-brain barrier and increase the levels of full-length SMN2 mRNA and protein in brain, spinal cord, muscle and other tissues. In these same mouse studies, treatment with these compounds resulted in increased survival, restoration of body weight, prevention of motor neuron loss and improved motor function.

In November 2011, we entered into a collaboration and licensing agreement with Roche which included a $30 million upfront payment, the potential for up to $460 million in milestone payments and royalties on net sales. Roche is responsible for pursuing clinical development of compounds from the research program under the collaboration and then commercializing any resulting products. A lead development compound, RG7800, was selected to move into IND-enabling studies in August 2013, triggering a milestone payment to us from Roche of $10 million. In 2014, we received two milestone payments from Roche totaling $17.5 million, one in January 2014 upon the initiation of a Phase 1 clinical study of RG7800 and in November 2014, upon the initiation of a Phase 2 clinical study of RG7800. We also previously received $13.3 million in sponsored research funding for this program from the Spinal Muscular Atrophy Foundation.

RG7800 was formerly the subject of a Phase 2 randomized, double blind, placebo controlled study called Moonfish in adult and pediatric patients with SMA. Results from the first cohort in Moonfish, which included 13 adult and adolescent SMA patients, demonstrated that SMN protein can be increased with RG7800, providing proof of mechanism for oral small molecule SMN2 splicing modifiers. Up to three-fold increases in the ratio of full length SMN2 mRNA to SMN2Δ7 mRNA and up to two-fold increases in SMN protein were observed versus baseline, as measured in whole blood. RG7800 was well tolerated over 12 weeks at a dose of 10 mg once daily. In addition, a dose-dependent effect on SMN2 alternative splicing was observed in a previous Phase 1 clinical study of RG7800 in healthy volunteers.

Dosing in the Moonfish trial was suspended in April 2015 and the trial was placed on clinical hold to investigate a non-clinical safety finding observed in a longer term animal study. Although RG7800 remains a potential product candidate under the SMA program, the Moonfish trial was terminated in December 2016.

A different compound in the SMA collaboration, RG7916, is currently being advanced in development. In October 2016, a two-part clinical study, called Sunfish, initiated in pediatric and adult type 2 and type 3 SMA patients to

investigate the safety, tolerability and efficacy of RG7916. Both parts of Sunfish will be double-blinded, placebo-controlled, and randomized. Part one of the study is a dose-finding study in approximately 36 type 2 and type 3 SMA patients for a minimum of 12 weeks with the primary objective of evaluating the safety, pharmacokinetics, and pharmacodynamics of RG7916 in patients, and to select the dose for the second part of the study. The pivotal part two of Sunfish will be a confirmatory study in approximately 150 type 2 and type 3 SMA patients for up to 24 months with the primary objective of evaluating the efficacy of RG7916 compared to placebo, followed by an open-label extension study.

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A two-part clinical study, called Firefish, also recently initiated in infants with type I SMA. Part one of Firefish is an open-label, dose escalation study in at least 8 infants for a minimum of 4 weeks. The primary objective of part one is to assess the safety profile of RG7916 in infants and determine the dose for part two. Part two is an open-label, single-arm study in approximately 40 infants with type I SMA for 24 months. The primary objective of part two is to assess the efficacy of RG7916 at the selected dose over a 12-month treatment period.

Commencement of the pivotal part two portion of either Sunfish or Firefish will trigger a single $20 million milestone payment to us from Roche. We anticipate that both Sunfish and Firefish will move into the pivotal second part of the respective study during 2017.

A Phase 1 study for RG7916 in healthy volunteers to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics completed in 2016. Results indicated that RG7916 was well tolerated and treatment resulted in dose-dependent increases of full length SMN2 mRNA and decreases of SMN2 mRNA without exon 7 (SMNΔ7), which may be interpreted as proof of mechanism in terms of the expected pharmacodynamic effect.

Cancer stem cell program

Cancer stem cells have been identified in numerous tumor types as a subpopulation of tumor cells that have the ability to initiate a tumor, produce other cancer cell types, move freely and proliferate throughout the body without attaching to other cells or surfaces and resist chemotherapy and radiotherapy. Many researchers believe that the resistance of cancer stem cells to chemotherapy and radiotherapy is a key factor in the failure of current cancer treatments. The BMI1 protein, which is overexpressed in many tumor subtypes, is a critical component of the polycomb repressive complex 1, or PRC1. PRC1 modulates expression of genes that are important for cancer stem cell survival, maintenance, stabilization and differentiation. PRC1 is an epigenetic enzyme complex, meaning that it is able to modify DNA directly to modulate gene expression without altering the nucleotide sequence in the genetic code. As a critical and rate limiting component of PRC1, the BMI1 protein regulates the self-renewal of adult blood and central nervous system stem cells that regulate cell growth.

Our product candidate in the cancer stem cell program, PTC596, is a first-in-class, orally bioavailable and potent small molecule that targets tumor stem cell populations by reducing the activity and amount of a protein called BMI1. Elevated levels of BMI1 are associated with more aggressive tumors and a poor prognosis in a wide variety of cancers, including glioblastoma. In in vitro assays, PTC596 preferentially depleted cancer stem cells derived from glioblastoma, fibrosarcoma, prostate and colon cancers. In contrast, the widely used cytotoxic chemotherapeutic agents carboplatin, temozolomide, methotrexate and indibulin enriched the population of cancer stem cells in these same assays.

In animal cancer models using human tumors, 2x/week oral dosing of PTC596 provided tumor control, including reduction of tumor size. PTC596 and the commonly used chemotherapeutic agent, paclitaxel, both effectively controlled tumor growth in these animal models. However, PTC596, but not paclitaxel, decreased BMI1 levels, indicating a reduction in cancer stem cells. Consistent with this reduction in BMI1 levels, tumors treated with PTC596 had lower levels of cancer stem cells capable of initiating a new tumor than did either untreated tumors or tumors treated with paclitaxel when transplanted into a naïve mouse. PTC596 is well tolerated at therapeutically effective doses in animals. Preliminary data from animal models suggest that PTC596 may preferentially target cancer stem cells without targeting normal stem cells.

We believe that reducing levels of BMI1 therefore represents a promising new therapeutic strategy to treat drug and radiation- resistant cancers.

A Phase 1 first-in-human, dose-escalation safety and pharmacokinetic open-label clinical study in advanced cancer patients with solid tumors initiated for PTC596 in April 2015 and completed in the first quarter of 2017. PTC596 was generally well tolerated as a monotherapy, producing systemic concentrations in patients similar to or exceeding those associated with preclinical activity. Though a protocol-defined maximum tolerated dose was not reached, the dose of 10 mg/kg was deemed intolerable due to pill burden and certain excipients that may have contributed to Grade 2 nausea, vomiting, and diarrhea in two of three patients. Data from this study and continued clinical development of PTC596, including reformulation efforts, are expected during 2017.

We received grant funding of $5.4 million for our cancer stem cell program from the Wellcome Trust prior to 2014. To the extent that we develop and commercialize program intellectual property on a for-profit basis ourselves or in

collaboration with a partner (provided we retain overall control of worldwide commercialization), we may become obligated to pay to Wellcome Trust development and regulatory milestone payments. Our first such milestone payment of $0.8 million to Wellcome Trust occurred in the second quarter of 2016. For additional information, see "Item 1. Business - Our Collaborations and Funding Arrangements".

Pre-clinical and other programs

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We continue to invest in our pre-clinical product pipeline by committing significant resources to research and development programs and business development opportunities within our areas of scientific expertise, including potential collaborations, alliances, and acquisitions or licensing of assets that complement our strategic mission to leverage our knowledge of RNA biology to bring novel therapeutics to patients affected by rare and neglected disorders.

Scientific Background of Post-Transcriptional Control Processes

Post-transcriptional control processes are the events that occur in a cell following the transcription of DNA to make RNA. These processes regulate, for example, how long an RNA molecules last in the cell, how precursor messenger RNA, or pre-mRNA, molecules undergo splicing, and how efficiently mRNA molecules are translated to produce a protein.

The majority of human protein-encoding genes are not contiguous but have an interrupted structure consisting of nucleotides that comprise the mRNA, called exons. The genetic information encoded within a gene is composed of exons which are interrupted by stretches of nucleotides called introns that are removed immediately after the gene is transcribed from DNA to pre-mRNA. The process of intron removal is called splicing.

A mRNA contains multiple regions that have specific functions. Although the protein coding region of mRNA contains the instructions to manufacture the protein, portions of mRNA that do not code for the protein, known as untranslated regions, or UTRs, are unique to specific mRNAs and are directly involved in the post-transcriptional control of protein production. Interactions of factors in the cell with the UTRs on the mRNA determine when and how much protein is produced as well as how mRNA is degraded and eliminated from the cell.

Our Approach

Our approach to drug discovery and development is to target systematically post-transcriptional control processes by small molecule therapeutics. We believe that focusing on post-transcriptional control processes will enable us both to address known drug targets through new mechanisms of action and to pursue a broad range of targets that have previously not been amenable to drug discovery. We believe that a large number of promising post-transcriptional control drug targets remain unexploited, providing a significant opportunity for our integrated and systematic approach to drug discovery. This technology also has broad applicability to address intractable drug targets in a wide variety of diseases for which there is an unmet medical need, including genetic disorders, cancer, and musculoskeletal disorders, as well as inflammation, metabolic disorders, cardiovascular conditions and neurological disorders.

Our RNA Biology Focused Small Molecule Technology Platform

We have developed and assembled an integrated set of proprietary technologies focused on our understanding of RNA biology for the discovery of small molecules that target post-transcriptional control processes. Our technologies allow us to screen our compound library against targets in many different therapeutic areas in an expeditious and cost-effective manner. Our efforts span from target identification and characterization to the identification of selective lead molecules. From these lead molecules, our research team undertakes a chemical optimization program designed to select an appropriate development candidate. We refer to our technologies as GEMS (gene expression modulation by small-molecules), alternative splicing, and nonsense suppression.

GEMS

We use our GEMS technology to identify molecules that modulate gene expression by targeting the post-transcriptional control processes that act through the UTRs of mRNA molecules. The UTRs of mRNA can have important roles in regulating protein production because they contain the instructions for determining the protein production efficiency and how long a given mRNA molecule will live within the cell.

Target proteins of potential biological and medical relevance to human disease are assessed for the prevalence of regulation through the unique UTRs. Once a target is selected, we precisely define the UTR and generate proprietary assays to screen our library of over 300,000 compounds to identify those that enhance or inhibit expression of the target gene by modulating the post-transcriptional control processes that act through the 5’- and 3’- UTRs of the target mRNA.

Alternative splicing

We use our alternative splicing technology to identify molecules that modulate mRNA splicing. Pre-mRNA splicing is a multi-step biochemical reaction. Approximately 94% of all human genes undergo splicing. In addition, through

alternative splicing, one gene can often generate several mRNA products by including or excluding exons that can result in the mRNA being regulated differently or a different protein being produced. Altered regulation of alternative splicing is the direct cause of many human diseases, including many forms of cancer, Riley-Day syndrome (familial dysautonomia), myotonic dystrophy and SMA.

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We have developed a powerful high-throughput drug discovery technology that enables us to identify small molecule modifiers of pre-mRNA splicing. The technology relies on a sensitive quantification of mRNA directly in human cells or tissue samples. Using this technology, we have successfully identified orally bioavailable small molecules that correct splicing of the Survival Motor Neuron 2, or SMN2, gene, which is implicated in the genetic disorder SMA. Based on this experience, we believe that other small molecule drug candidates can be rapidly identified that correct alternative splicing of genes, promote inclusion of specific exons into mRNA or force skipping of undesired exons from the mature mRNA. We believe that this technology is potentially widely applicable to a large number of target genes in all therapeutic areas.

Nonsense suppression

We use our nonsense suppression technology to identify molecules that promote or enhance readthrough of premature stop codons. The presence of a premature stop codon results in translation termination before a full-length protein can be produced. Our nonsense suppression technologies identify small molecules that increase readthrough at the premature stop codon by facilitating the incorporation of a defined set of amino acids at the site of the premature stop codon to enable production a full-length protein. We believe this approach is applicable to a wide variety of therapeutic areas.

In addition to identifying molecules that increase readthrough, we are identifying molecules that can enhance the nonsense suppression effect of Translarna and other readthrough agents by preventing the decay of nonsense-containing mRNAs, which we refer to as nonsense mediated decay. We have developed a high throughput screen to identify molecules that increase the level of nonsense-containing mRNAs. We can evaluate the effect of these molecules alone and in combination with Translarna in cell-based models of disease, identify lead compounds and initiate a chemical optimization program. We are currently in the process of evaluating compounds as single agents and in combination with readthrough compounds in preparation for an optimization program.

Our Collaborations and Funding Arrangements

We currently have ongoing collaborations with Roche and the SMA Foundation. We also have received grant funding from Wellcome Trust pursuant to funding agreements under which we have continuing obligations. In addition to these material collaboration and funding agreements, which are described in more detail below, we have a collaboration focused on translational research for discovering and developing new treatments for orphan disorders with the University of Pennsylvania’s Center for Orphan Disease Research & Therapy. In addition, during 2015 we announced our research collaboration with Massachusetts General Hospital, or MGH, a Partners Healthcare hospital, for the treatment of rare genetic disorders resulting from pre-mRNA splicing defects pursuant to which we have certain licensing, development and commercialization obligations to MGH.

Roche and the SMA Foundation

Overview. In November 2011, we entered into a license and collaboration agreement with Roche and the SMA Foundation to further develop and commercialize compounds identified under our SMA sponsored research program with the SMA Foundation and to research other small molecule compounds with potential for therapeutic use in patients with SMA. The research term of this agreement was terminated effective December 31, 2014. The ongoing collaboration is governed by a joint steering committee consisting of an equal number of representatives of us, the SMA Foundation and Roche. We, the SMA Foundation and Roche have agreed to endeavor to make decisions by consensus, but if the joint steering committee cannot reach agreement after following a specified decision resolution procedure, Roche’s decision will control. However, Roche may not exercise its final decision-making authority with respect to certain specified matters, including any decision that would increase our or the SMA Foundation’s obligations, reduce our or the SMA Foundation’s rights, expand Roche’s rights, or reduce Roche’s obligations under the license and collaboration agreement.

Commercialization. We have granted Roche worldwide exclusive licenses, with the right to grant sublicenses, to our patent rights and know-how with respect to such compounds and products. Roche is responsible for pursuing worldwide clinical development of compounds from the research program and has the exclusive right to develop and commercialize compounds from the collaboration.

Payments and Contingent Payments. Pursuant to the license and collaboration agreement, Roche paid us an upfront non-refundable payment of $30.0 million. During the research term, which was terminated effective December 31,

2014, Roche provided us with funding, based on an agreed- upon full-time equivalent rate, for an agreed-upon number of full- time equivalent employees that we contributed to the research program. We are eligible to receive up to an aggregate of $135 million in payments if specified development and regulatory milestones are achieved and up to an aggregate of $325 million in payments if specified sales milestones are achieved. As of December 31, 2016, we have earned $27.5 million of these development and regulatory milestone payments based on the progression of the collaboration from the pre-clinical stage to Phase 2 clinical study in SMA patients. We are also entitled to tiered single-digit to mid-teen royalties on worldwide net product sales of products developed pursuant to the collaboration. Roche’s obligation to pay us royalties will expire generally

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on a country-by- country basis at the latest of the expiration of the last-to-expire patent covering a product in the given country, the expiration of regulatory exclusivity for that product in such country or 10 years from the first commercial sale of that product in such country. However, the royalties payable to us may be decreased in certain circumstances. For example, the royalty rate in a particular country is reduced if the product is not protected by patents in that country and no longer entitled to regulatory exclusivity in that country. We remain responsible for making any payments to the SMA Foundation that may become due under our pre-existing sponsored research agreement with the SMA Foundation.

Termination. Unless terminated earlier, the license and collaboration agreement will expire on the date when no royalty or other payment obligations are or will become due under the agreement. Roche's termination rights under the license and collaboration agreement includes the right to terminate the agreement at any time after November 22, 2013 on a product-by-product and country-by-country basis upon three months' notice before the launch of the applicable product or upon nine months' notice thereafter; and the right to terminate the agreement in specified circumstances following a change of control of us. The license and collaboration agreement provides that we or Roche may terminate the agreement in the event of an uncured breach by the other party of a material provision of the agreement, or in the event of the other party's bankruptcy or insolvency. Upon termination of the collaboration agreement by Roche for convenience or termination by us as a result of Roche's breach, bankruptcy, change of control or patent challenge, we have the right to assume the development and commercialization of product candidates arising from the license and collaboration agreement. In that event, we may become obligated to pay royalties to Roche on sales of any such product.

SMA Foundation

Overview. In June 2006, we entered into a sponsored research agreement with the SMA Foundation under which we and the SMA Foundation have collaborated in the research and preclinical development of small molecule therapeutics for SMA. As discussed above, we are also collaborating with the SMA Foundation and Roche to further develop these compounds. Pursuant to the sponsored research agreement, as amended, the SMA Foundation provided us with $13.3 million in funding. The SMA Foundation is not obligated to provide any further funding under this agreement.

Continuing financial obligations. We may become obligated to pay the SMA Foundation single-digit royalties on worldwide net product sales of any collaboration product that we successfully develop and subsequently commercialize or, if we outlicense rights to a collaboration product, a specified percentage of certain payments we receive from our licensee. As discussed above, we have outlicensed rights to Roche pursuant to a license and collaboration agreement. We are not obligated to make such payments unless and until annual sales of a collaboration product exceed a designated threshold. Our obligation to make such payments would end upon our payment to the SMA Foundation of a specified amount, which we refer to as the repayment amount.

Reversion rights. In specified circumstances, including those involving our decision to discontinue development or commercialization of a collaboration product, our uncured failure to meet agreed timelines or those that might arise following our change of control, we may be obligated to grant the SMA Foundation exclusive or non-exclusive sublicensable rights under our intellectual property, in certain collaboration products, among other rights, to assume the development and commercialization of such collaboration products and to provide the SMA Foundation with other transitional assistance, which we refer to as a reversion. In some such cases, we may be entitled to receive licensing fee payments from the SMA Foundation and single-digit royalties on sales of the applicable collaboration product, which amounts we collectively refer to as reversion payments. In other cases, the SMA Foundation is not required to make any payments to us in connection with the licenses it receives from us.

Termination. Unless terminated earlier, the sponsored research agreement will continue until the earliest of the SMA Foundation's receipt of the repayment amount or, if there was a reversion, either our receipt of all reversion payments that the SMA Foundation may be obligated to make to us or, if the SMA Foundation is not obligated to make reversion payments, the expiration of the last-to-expire patent we licensed to the SMA Foundation in connection with such reversion. The sponsored research agreement provides that either party may terminate the agreement in the event of an uncured material breach by the other party or in the event of the other party's bankruptcy or insolvency.

Wellcome Trust (cancer stem cell and antibacterial programs)

We have two separate funding agreements with Wellcome Trust. The materials terms of these funding agreements are similar in substance, except as described below.

One agreement, entered into in May 2010, relates to the research and development of small molecule compounds that selectively decrease the production of BMI1 expression in tumor stem cells, which we refer to as our cancer stem cell program. Pursuant to this agreement, Wellcome Trust awarded us a $5.4 million grant, of which approximately $0.9 million was paid in connection with execution of the agreement and the balance of which was paid based on our achievement of specified milestones.

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The other agreement, entered into in December 2011, relates to the research and development of small molecule compounds that target life-threatening infections caused by multidrug-resistant Gram-negative bacteria. Pursuant to this agreement, Wellcome Trust awarded us a $5.0 million grant, of which approximately $1.7 million was paid in connection with execution of the agreement. In connection with the achievement of a specified milestone, we received $1.6 million in 2013, $0.8 million in 2014 and $0.7 million in 2015. We are no longer actively pursuing an antibacterial program and do not expect to receive additional funding under this agreement.

Development and commercialization. We own all intellectual property that arises from the conduct of the research programs under these funding agreements, which we refer to as program intellectual property, and are responsible for developing and commercializing the program intellectual property, including PTC596 (for our cancer stem cell program), and other compounds. However, we will require Wellcome Trust's written consent prior to any such development or commercialization. If Wellcome Trust withholds such consent and we and Wellcome Trust are not able to resolve Wellcome Trust's concerns, the parties have agreed to follow a specified dispute resolution procedure that gives neither party final decision-making authority.

Reversion rights. Under both funding agreements, if we fail to take reasonable steps to develop or commercialize program intellectual property during specified timeframes, we may be obligated to grant exclusive rights to Wellcome Trust or its nominee under the program intellectual property, along with non-exclusive rights under our background intellectual property, so that Wellcome Trust or its nominee can assume such development and commercialization. If we grant such a license, we would be entitled to a share of any consideration received by Wellcome Trust in connection with any subsequent development or commercialization of program intellectual property on a for-profit basis, which share would be proportionate to our contribution to the development and commercialization.

Continuing financial obligations-cancer stem cell program. To the extent that we develop and commercialize program intellectual property on a for-profit basis ourselves or in collaboration with a partner (provided we retain overall control of worldwide commercialization), we may become obligated to pay to Wellcome Trust development and regulatory milestone payments and single-digit royalties on sales of any research program product under our cancer stem cell program. We made the first development milestone payment of $0.8 million to Wellcome Trust under this agreement during the second quarter of 2016. Additional development and regulatory milestone payments up to an aggregate of $22.4 million may become payable by us under the agreement. For example, in the event a Phase 2 clinical study of a research program candidate, such as PTC596, is commenced, a milestone payment of $2.5 million would become payable by us to Wellcome Trust upon the earlier to occur of the first dose administered to the last patient enrolled in the study or the termination of dosing of all patients in the study.

If we had continued development under our former antibacterial program, similar milestone and royalty payments from us to Wellcome Trust would have applied under that agreement.

Additional continuing financial obligations. Our obligation to pay the royalties describe above would continue on a country-by-country basis until the longer of the expiration of the last patent in the program intellectual property in such country covering the research program product and the expiration of market exclusivity of such product in such country. To the extent that we develop and commercialize program intellectual property on a for-profit basis through outlicensing, we will be obligated to pay to Wellcome Trust a specified share of any consideration we receive from our licensee, provided that Wellcome Trust would be entitled to receive a minimum amount equal to its original contribution. We would incur no payment obligations to Wellcome Trust to the extent that we elect to develop and commercialize program intellectual property on a non-profit basis.

Termination. Unless terminated earlier, each funding agreement will continue until we have received the full amount of the grant, the research program has ended, the last-to-expire of the patents in the program intellectual property has expired, any agreement entered into for the exploitation of the program intellectual property or our background intellectual property has expired, and there are no remaining payment obligations relating to the exploitation of the program intellectual property or our background intellectual property. Each funding agreement provides that either party may terminate the agreement in the event of an uncured material breach by the other party or in the event of the other party's bankruptcy or insolvency and that Wellcome Trust may terminate the agreement under specified circumstances, including, among others, in specified circumstances following a change in control of us or if Wellcome Trust believes that an uncorrected serious failure exists in the progress, management or conduct of the research

program or that an act or omission by us is incompatible with or has an adverse effect on Wellcome Trust's charitable objectives or reputation.

If Wellcome Trust terminates either or both funding agreements in specified circumstances, including as a result of our material breach, bankruptcy or insolvency, or following our change of control, we may be obligated to assign to Wellcome Trust ownership of the applicable program intellectual property, grant to Wellcome Trust royalty-free non-exclusive rights under the applicable background intellectual property for the continuation of the research program (if applicable) and the development and commercialization of the applicable program intellectual property, and provide Wellcome Trust with other specified transitional assistance.

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Certain specified rights and obligations of the parties will generally survive termination of the funding agreements, including Wellcome Trust's right to receive payments from us with respect to development and commercialization of program intellectual property on a for-profit basis.

If a funding agreement terminates prior to the end of a research program, we are obligated to return all funding we received from Wellcome Trust that is unspent at the date of termination (after deduction of costs and non-cancellable commitments incurred prior to such date).

Intellectual Property

Patents and trade secrets

Our success depends in part on our ability to obtain and maintain proprietary protection for our product candidates, technology and know-how, to operate without infringing the proprietary rights of others and to prevent others from infringing our proprietary rights. Our policy is to seek to protect our proprietary position by, among other methods, filing U.S. and certain foreign patent applications related to our proprietary technology, inventions and improvements that are important to the development of our business, where patent protection is available. We also rely on trade secrets, know-how, continuing technological innovation and in-licensing opportunities to develop and maintain our proprietary position.

As of January 12, 2017, our patent portfolio included a total of 92 U.S. patents and 47 U.S. patent applications, including original filings, continuations and divisional applications, as well as numerous foreign counterparts to many of these patents and patent applications. We own or exclusively in-license these patents and patent applications with claims directed to the composition of matter, pharmaceutical formulation and methods of use of many of our compounds, including ataluren, the active ingredient in the formulated product Translarna™.

The patent rights relating to Translarna™ (ataluren) owned by us consist of 27 issued U.S. patents relating to composition of matter, methods of use, formulation, dosing and methods of manufacture and multiple pending patent applications relating to composition of matter, methods of use, formulation, dosing and methods of manufacture. We do not license any material patent rights relating to ataluren to unaffiliated parties. The issued U.S. patents relating to composition of matter are currently scheduled to expire in 2024 and all U.S. patents that issue from U.S. patent applications arising from the composition of matter would also be scheduled to expire in 2024. Issued U.S. patents relating to therapeutic method of use are currently scheduled to expire in 2026 and 2027, including patent term adjustment. We have patent rights that are the subject of granted patents or pending counterpart patent applications in a number of other jurisdictions, including Canada, South America, Europe, Africa, Asia and Eurasia. We own five granted European patents relating to composition of matter, uses, dosing and methods of manufacture of ataluren, as well as multiple pending European patent applications relating to composition of matter, uses and formulations. The expiration dates of the granted and allowed European patents occur for composition of matter in 2024, for dosing regimens in 2026 and 2027, and for the manufacturing process in 2027. Except as indicated above, the anticipated expiration dates referred to above are without regard to potential patent term extension, patent term adjustment or other marketing exclusivities that may be available to us.

The term of individual patents depends upon the legal term for patents in the countries in which they are obtained. In most countries, including the United States, the patent term is 20 years from the earliest filing date of a non-provisional patent application. In the United States, a patent's term may, in certain cases, be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier filed patent. The term of a U.S. patent that covers a drug, biological product or medical device approved pursuant to a pre-market approval, or PMA, may also be eligible for patent term extension when FDA approval is granted, provided statutory and regulatory requirements are met. The length of the patent term extension is related to the length of time the drug is under regulatory review while the patent is in force. The Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, permits a patent term extension of up to five years beyond the expiration date set for the patent. Patent extension based on Hatch-Waxman cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent applicable to each regulatory review period may be granted an extension and only those claims reading on the approved drug may be extended.

Similar provisions are available in Europe and certain other foreign jurisdictions to extend the term of a patent that covers an approved drug. One means of patent term extension in Europe after EMA approval is based on obtaining a Supplementary Protection Certificate (SPC). We have applied for SPCs for ataluren in all applicable European countries in which we have a European patent and expect that all will be granted. The maximum patent term extension provided by an SPC is a total of 5 years from the date of patent term expiration. In the future, if and when our product candidates receive approval by the FDA or other non-European foreign regulatory authorities, we expect to apply for patent term extensions on issued patents covering those products, depending upon the length of the clinical trials for each drug and other factors.

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We may rely, in some circumstances, on trade secrets to protect our technology. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, in part, by confidentiality agreements with our employees, consultants, scientific advisors and contractors. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our consultants, contractors or collaborators use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

License agreements

We are a party to a number of license agreements under which we license patents, patent applications and other intellectual property from third parties. We enter into these agreements to augment our proprietary intellectual property portfolio. The licensed intellectual property covers some of the compounds that we are researching and developing, some post-transcriptional control targets and some of the scientific processes that we use. These licenses impose various diligence and financial payment obligations on us. We expect to continue to enter into these types of license agreements in the future.

Manufacturing

We do not own or operate manufacturing or distribution facilities for the production of clinical or commercial quantities of Translarna or for our other product candidates or compounds that we are testing in our preclinical programs. We currently rely, and expect to continue to rely, on third parties for the manufacture, packaging, labeling and distribution of clinical and commercial supplies of Translarna as well as any other product or product candidate that we may develop, other than small amounts of compounds that we may synthesize ourselves for preclinical testing. The active pharmaceutical ingredients in Translarna and our product candidates are provided by third-parties. We currently rely on a single source for the production of some of our raw materials and we obtain our supply of the bulk drug substance for Translarna from two third-party manufacturers and the bulk drug substance for our cancer stem cell program through another third-party manufacturer.

We engage two separate manufacturers to provide bulk drug product. We have a relationship with three manufacturers that are capable of providing fill and finish services for our finished commercial and clinical product, although we are still in the process of finalizing arrangements with one of these manufacturers with respect to commercial product services. We anticipate completing applicable validation procedures for this manufacturer in 2017 for both commercial and clinical product.

We do not currently have any agreements with third-party manufacturers for the long-term commercial supply of Translarna or any of our product candidates, although we may seek to establish such arrangements in the future. We may be unable to conclude agreements for commercial or clinical supply with third-party manufacturers, or may be unable to do so on acceptable terms.

We currently obtain our supplies of Translarna and our other product candidates from our third-party manufacturers pursuant to agreements that include specific supply timelines and volume expectations. If a manufacturer should become unavailable to us for any reason, we would seek to obtain supply from another manufacturer engaged by us for the applicable product or service. In the event that we were unable to procure the applicable supply from a validated manufacturer, we believe that there are a number of potential replacements for each of our outsourced services, however we likely would experience delays in our ability to supply Translarna to patients or in advancing our clinical trials while we identify and qualify replacement suppliers.

All of our drug candidates are organic compounds of low molecular weight, generally called small molecules. We have selected these compounds not only on the basis of their potential efficacy and safety, but also for their ease of synthesis and reasonable cost of their starting materials. Translarna is manufactured in reliable and reproducible synthetic processes. Our raw materials are not scarce and are readily available. We currently rely on a single source for the production of some raw materials and switching to an alternative source could, in some instances, take time and could lead to delays in manufacturing. No shortages or delays of raw materials were encountered in 2016, and none are currently expected in 2017. The chemistry is amenable to scale up and does not require unusual equipment in

the manufacturing process. We expect to continue to develop drug candidates that can be produced cost-effectively at contract manufacturing facilities.

Manufacturers and suppliers of product candidates are subject to the FDA's current Good Manufacturing Practices, or cGMP, requirements, and other rules and regulations prescribed by foreign regulatory authorities. We depend on our third-party suppliers and manufacturers for continued compliance with cGMP requirements and applicable foreign standards.

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We currently have a contract with a pharmacy and hospital distributor in the European Union that distributes Translarna for clinical programs and limited commercial and EAP programs. We have engaged with third party logistic providers, or 3PLs, which distribute Translarna for the majority of our commercial and EAP programs on our behalf.

Research and Development Expense and Other Financial Information

The research and development expenses in each of our last three fiscal years is provided in Item 7. “Management’s Discussion and Analysis of Financial Condition and Results of Operations.”

Financial information about our net product revenues, net loss per share attributable to our common stockholders and our total assets are provided in our consolidated financial statements included in this Annual Report on Form 10-K.

Commercial Matters

Sales and marketing team

To date all of our product revenue has been attributable to sales of Translarna for the treatment of nmDMD in territories outside of the United States. In addition to multiple European countries, we have employees in Latin America, Japan and Canada. As of December 31, 2016, our international team was comprised of approximately 87 employees and nine full-time contractors, including support personnel and members of our commercial team who work with physicians, patient advocacy groups and other stakeholders who are involved in the treatment of patients suffering from nmDMD.

In addition, in select territories, we have engaged full time consultants, marketing partners and distribution partners to assist us with our international commercialization efforts. We continue to evaluate new territories to determine in which geographies we might, if approved, choose to commercialize Translarna ourselves and in which geographies we might choose to collaborate with third parties. We expect that our internal team and partnership network will continue to grow, as needed, to maximize access to patients.

Customers

During 2016, all of our product revenue was attributable to Translarna for the treatment of nmDMD. Translarna for the treatment of nmDMD was available on a commercial basis or via reimbursed EAP programs in multiple territories outside of the United States. In some territories orders for Translarna are placed directly with us and in other territories we have engaged with third-party distributors. As a result, orders for Translarna are generally received from hospital and retail pharmacies and, in some cases, one of our third-party partner distributors. Our third-party distributors act as intermediaries between us and end-users and do not typically stock significant quantities of Translarna. The ultimate payor for Translarna is typically a government authority or institution or a third-party health insurer. The payment terms are generally 30 to 90 days after receipt of products.

During 2016, over 10% of our net product sales were attributable to orders from two of our distributors. Financial information about our net product revenues and other revenues generated in the principal geographic regions in which we operate and our long-lived assets is set forth in our financial statements and in Note 14, “Geographic Information” to our consolidated financial statements included in this Annual Report on Form 10-K.

Translarna can generally only be returned if agreed upon in writing by us and the product is not opened nor in receipt by the final user, except in the case of quality issues associated with the product. Product is generally shipped when a specific patient is approved by the applicable government or insurer and an individual prescription has been written. The right of return is eliminated as a matter of course when the product is dispensed to patients. Since the initial product sale of Translarna in the third quarter of 2014, we have had no requests for product returns.

In some countries, including Brazil, orders for named patient sales may be for multiple months of therapy, which can lead to an unevenness in orders which could result in significant fluctuations in quarterly net product sales.

Market Access Considerations

Translarna for the treatment of nmDMD is currently available on a commercial basis in Austria, Czech Republic, Denmark, Hungary, Israel, Italy, Norway, Slovakia, and the United Kingdom (including England, Scotland, Northern Ireland, and Wales). Commercial drug is also currently available in Germany, subject to the matters discussed below. We consider Translarna to be commercially available when a reference price for the drug is established in the applicable country and we are permitted to market treatment to patients.

Translarna for the treatment of nmDMD is also currently available through reimbursed early access programs, or EAP programs, in select countries where funded named patient or cohort programs exist, both within the EEA and in other territories. These programs generally reference the EMA's determinations with respect to our marketing authorization in the EEA. As of today, Translarna is available under EAP or similar styled programs in Argentina, Brazil, Canada, Colombia,

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Cyprus, France, Greece, Hong Kong, Kuwait, Portugal, Spain, Sweden, Switzerland, and Turkey. Generally, EAP programs allow for access to Translarna pursuant to a named patient program, under which a physician requests access to Translarna on behalf of the specific, or "named" patient or pursuant to a cohort program, which allows for a broader temporary authorization for use for nmDMD meeting the inclusion criteria. Our EAP programs are named patient or similar styled programs in all territories other than France, which is a cohort program.

Our ability to make Translarna available via commercial or EAP programs is dependent upon our ability to maintain our marketing authorization in the EEA for Translarna for the treatment of nmDMD in ambulatory patients aged five years and older. The marketing authorization is subject to annual review and renewal by the European Commission following reassessment by the EMA as well as the specific obligation to conduct and submit the results of Study 041. See "Item 1. Business—Marketing authorization matters for Translarna in nonsense mutation Duchenne muscular dystrophy—European Economic Area" and "Risk Factors"—Risks Related to Regulatory Approval of our Product and our Product Candidates" for further information regarding the marketing authorization in the EEA and related risks.

Our future revenues from Translarna, and any other product candidates we may develop, depends largely on our ability to obtain and maintain reimbursement from governments and third-party insurers. Each country in the EEA has its own pricing and reimbursement regulations and many countries in the EEA have other regulations related to the marketing and sale of pharmaceutical products in the applicable country. The pricing and reimbursement process varies from country to country and can take over 18 months from initiation to complete. As a result, our commercial launch in the EEA has been and is expected to continue to be on a country-by-country basis and we generally will not be able to commence commercial sales of Translarna for the treatment of nmDMD pursuant to our marketing authorization in the EEA in any particular member state of the EEA until we conclude the applicable pricing and reimbursement negotiations and comply with any licensing, employment or related regulatory requirements in that country.

We have submitted pricing and reimbursement dossiers with respect to Translarna for the treatment of nmDMD in key EEA countries and have received both pricing and reimbursement approval on terms that are acceptable to us in a number of countries. The price that is approved by local governmental authorities pursuant to commercial pricing and reimbursement processes may be lower than the price that can be realized for purchases of product in that country pursuant to a reimbursed early access program.

In some instances, reimbursement may be subject to challenge, reduction or denial by the government and other payers. For example, in France, EAP and commercial sales of a product can begin while pricing and reimbursement rates are under discussion with the applicable government health programs. In the event that the negotiated price of the product is lower than the amount reimbursed for sales made prior to the conclusion of price negotiations, we may become obligated to repay such excess amount to the applicable government health program. Such retroactive reimbursement would be made following the conclusion of price negotiations with the applicable government health authority.

We delisted Translarna from the German pharmacy ordering system, effective April 1, 2016, based on unsustainable pricing established by the arbitration board in Germany. However, patients and healthcare professionals in Germany have generally been able to access Translarna through a reimbursed importation pathway possible under German law. There can be no assurance that all such patients will continue to be successful in obtaining reimbursed access to Translarna.

In England, our pricing and reimbursement negotiations took place between mid-2014 to mid-2016, and culminated in a five-year managed access agreement between us, NHS England, NICE, and other interested parties. The managed access agreement establishes the clinical details surrounding the use of Translarna, including the confidential financial terms and the collection of further data on the efficacy of Translarna for the treatment of nmDMD with NICE guidance to be reviewed again at the end of the five-year period, before future funding decisions are taken.

We record revenue net of estimated third party discounts and rebates. Allowances are recorded as a reduction of revenue at the time revenues from product sales are recognized. These allowances are adjusted to reflect known changes in factors and may impact such allowances in the quarter those changes are known.

For important information regarding market access and pricing and reimbursement considerations see "Item 1. Business—Pharmaceutical Pricing and Reimbursement" and "Item 1A. Risk Factors—Risks Related to the Development and

Commercialization of our Product and our Product Candidates" and "—Risks Related to Regulatory Approval of our Product and our Product Candidates".

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our technologies, knowledge, experience and scientific resources provide us with competitive advantages, we face potential competition from many different sources, including

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commercial pharmaceutical and biotechnology enterprises, academic institutions, government agencies and private and public research institutions. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

Many of our competitors may have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel, as well as in acquiring technologies complementary to, or necessary for, our programs. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer side effects, are more convenient or are less expensive than any products that we may develop. In addition, our ability to compete may be affected because in some cases insurers or other third-party payors seek to encourage the use of generic products. This may have the effect of making branded products less attractive, from a cost perspective, to buyers.

The key competitive factors affecting the success of Translarna and our other product candidates are likely to be its efficacy, safety, convenience, price and the availability of coverage and reimbursement from government and other third-party payors.

The competition for Translarna and our other product candidates includes the following:

- Translarna for nmDMD. There is currently no marketed therapy, other than Translarna in the EEA, which has received approval for the treatment of the underlying cause of nmDMD. Sarepta Therapeutics recently received approval in the United States for a treatment addressing the underlying cause of disease for different mutations in the DMD gene. Other biopharmaceutical companies are developing treatments addressing the underlying cause of disease for different mutations in the DMD gene (Sarepta, Daiichi Sankyo, and Nippon Shinyaku).
- Translarna for Other Indications. Aldurazyme, which is manufactured by BioMarin Pharmaceutical Inc. and sold by Genzyme Corporation, is an enzyme replacement therapy for the treatment of mucopolysaccharidosis I. Furthermore, Diacomit is marketed in the European Union by Laboratoires Biocodex for the treatment of Dravet syndrome. Other companies are also pursuing product candidates for the treatment of Dravet syndrome, including GW Pharmaceuticals, Zogenix, and Insys Therapeutics. Aniridia therapeutic interventions, such as artificial iris implantation, are being developed by HumanOptics AG.
- Spinal Muscular Atrophy Collaboration. Our SMA collaboration with Roche and the SMA Foundation also faces competition. For example, in December 2016, the FDA approved nusinersen, a drug developed by Ionis Pharmaceuticals, Inc. and marketed by Biogen, to treat SMA. AveXis, Inc. is also evaluating a gene therapy product candidate for the treatment of SMA. Other companies are also pursuing product candidates for the treatment of SMA, including Trophos (also in collaboration with Roche), Kowa, Novartis Pharmaceuticals Corporation, and Cytokinetics.

Government Regulation

Government authorities in the United States, at the federal, state and local level, and in other countries extensively regulate, among other things, the research, development, testing, quality control, approval, manufacturing, labeling, post-approval monitoring and reporting, recordkeeping, packaging, promotion, storage, advertising, distribution, marketing and export and import of pharmaceutical products such as those we are developing. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources. See “Item 1A. Risk Factors—Risks Related to Regulatory Approval of our Product and our Product Candidates” for important information regarding some of the risks to our business arising as a result of government regulation.

U.S. government regulation

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or the FDCA, and implementing regulations. Failure to comply with the applicable FDA requirements at any time pre- or post-approval may result in a delay of approval or administrative or judicial sanctions. These sanctions could include the FDA’s imposition of a clinical hold on trials, refusal to approve pending applications, withdrawal of an approval, issuance of

warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties or criminal prosecution. Any agency or judicial enforcement action could have a material adverse effect on us.

The new drug approval process

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Failures to comply with the applicable FDA requirements at any time during the product development process or approval process may result in a delay of approval or administrative or judicial sanctions. These sanctions could include the FDA's imposition of a clinical hold on trials, refusal to approve pending applications, withdrawal of an approval, issuance of warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties or criminal prosecution. Any agency or judicial enforcement action could have a material adverse effect on us.

In the United States, the information that must be submitted to the FDA in order to obtain approval to market a new drug varies depending upon whether the drug is a new product whose safety and efficacy have not previously been demonstrated in humans or a drug whose active ingredients and certain other properties are the same as those of a previously approved drug. A New Drug Application, or NDA, is the vehicle through which the FDA approves a new pharmaceutical product for sale and marketing in the United States.

To market a new drug in the United States, a sponsor generally must undertake the following:

- completion of preclinical laboratory tests, animal studies and formulation studies under the FDA's good laboratory practices regulations and other applicable laws or regulations;
- submission to the FDA of an investigational new drug application, or IND, for clinical testing, which must become effective before clinical trials may begin;
- approval by an independent Institutional Review Board, or IRB, prior to initiation and subject to continuing review;
- completion of adequate and well-controlled clinical trials in accordance with Good Clinical Practices, or GCP, and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, or ICH, E6 GCP guidelines, to establish the safety and efficacy of the product for each of its proposed indications;
- submission and FDA acceptance of an NDA, or satisfactory completion of an FDA Advisory Committee meeting, if applicable;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with current good manufacturing practices, or cGMP, which require that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity; and
- FDA review and approval of the NDA.

Preclinical tests include laboratory evaluations of product chemistry, stability, toxicity and formulation, as well as animal studies. In order to begin clinical testing, a sponsor must submit an IND to the FDA, which includes, among other things, the results of the preclinical tests, manufacturing information, analytical data, proposed clinical protocols, and any available clinical data or literature on the drug product. Some preclinical testing may continue after the IND is submitted. The IND must become effective before human clinical trials may begin. An IND will automatically become effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions about issues such as the conduct of the trials as outlined in the IND. In that case, the IND sponsor and the FDA must resolve any outstanding FDA concerns or questions before clinical trials can proceed. In other words, submission of an IND may not result in the FDA allowing clinical trials to commence.

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators. Clinical trials are conducted in accordance with protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and subsequent protocol amendments must be submitted to the FDA as part of the IND. All research subjects or their legally authorized representatives must provide their informed consent in writing prior to their participation in a clinical trial. Each clinical trial must be reviewed and approved by an IRB and is subject to ongoing IRB monitoring. The IRB must approve the protocol, protocol amendments, and the informed consent form. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, to be publicly posted on the Clinicaltrials.gov website.

Clinical trials typically are conducted in three sequential phases, but the phases may overlap or be combined. Phase 1 clinical trials may be conducted in patients or healthy volunteers to evaluate the product's safety, dosage tolerance and pharmacokinetics and, if possible, seek to gain an early indication of its effectiveness. Phase 2 clinical trials usually involve controlled trials in a larger but still relatively small number of subjects from the relevant patient population to

evaluate dosage tolerance and appropriate dosage; identify possible short-term adverse effects and safety risks; and provide a preliminary evaluation of the efficacy of the drug for specific indications.

Phase 2 clinical trials are sometimes denoted by companies as Phase 2a or Phase 2b clinical trials. Phase 2a clinical trials typically represent the first human clinical trial of a drug candidate in a smaller patient population and are designed to provide

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earlier information on drug safety and efficacy. Phase 2b clinical trials typically involve larger numbers of patients or longer durations of therapy and may involve comparison with placebo, standard treatments or other active comparators.

Phase 3 clinical trials usually further evaluate clinical efficacy and test further for safety in an expanded patient population. Phase 3 clinical trials usually involve comparison with placebo, standard treatments or other active comparators. These trials are intended to establish the overall risk- benefit profile of the product or product candidate and provide an adequate basis for physician labeling. Phase 3 clinical trials are usually larger, more time consuming, more complex and more costly than Phase 1 and Phase 2 clinical trials.

Clinical trials may not be completed successfully within any specified period, if at all. The FDA, the sponsor, or a data safety monitoring board may suspend or terminate clinical trials at any time on various grounds, including a finding that the subjects are or would be exposed to an unreasonable and significant risk of illness or injury. Similarly, an IRB can suspend or terminate approval of a clinical trial if the trial is not being conducted in accordance with the IRB's requirements or if the research has been associated with unexpected serious harm to patients. The FDA typically requires that an NDA include data from two adequate and well-controlled clinical trials, but approval may be based upon a single adequate and well-controlled clinical trial plus confirmatory evidence. In some cases, the FDA may condition approval of an NDA on the applicant's agreement to conduct additional clinical trials to further assess the drug's safety and effectiveness after NDA approval. Such post-approval trials are typically referred to as Phase 4 studies.

The FDA's accelerated approval process allows for potentially faster development and approval of certain drugs intended to treat serious or life- threatening illnesses that provide meaningful therapeutic benefit to patients over existing treatments. Under the accelerated approval process, the adequate and well-controlled clinical trials conducted with the drug establish that the drug has an effect on a "surrogate" endpoint that is reasonably likely to predict clinical benefit or on the basis of an effect on a clinical benefit other than survival or irreversible morbidity. Drugs approved through the accelerated approval process are subject to certain post-approval requirements, including that the applicant complete Phase 4 clinical trials to demonstrate the drug's clinical benefit. If the trials fail to verify the clinical benefit of the drug, the FDA may withdraw approval of the application through a streamlined process.

The FDA has explained in guidance that some drugs are dependent upon the use of an in vitro diagnostic test, such as when the use of the drug is limited to a specific patient subpopulation that can be identified by using the test. The guidance refers to the diagnostic tests used with these types of drugs as in vitro companion diagnostic devices. According to the guidance, in vitro companion diagnostic devices may require the submission and approval of a premarket approval application before they are marketed. Some in vitro companion diagnostic devices, however, could potentially be cleared through a 510(k) premarket notification submission. The guidance states that the FDA generally will not approve a drug that is dependent upon the use of an in vitro companion diagnostic device if no such device is FDA- approved or -cleared for the relevant indication. According to the guidance, however, the FDA may approve such a drug without an approved or cleared in vitro companion diagnostic device when the drug is intended to treat a serious or life- threatening condition for which no satisfactory alternative treatment exists and the FDA determines that the benefits from the use of drug with an unapproved or uncleared in vitro companion diagnostic device are so pronounced as to outweigh the risks from the lack of an approved or cleared in vitro companion diagnostic device. The FDA guidance documents represent the FDA's current thinking on a topic but do not establish legally enforceable responsibilities.

Assuming successful completion of the required clinical testing, the results of the preclinical studies and of the clinical trials, together with other detailed information, including proposed labeling and information on the chemistry, manufacture and composition of the product, are submitted to the FDA in the form of an NDA requesting approval to market the product for one or more indications. In most cases, the NDA must be accompanied by a substantial user fee, though a waiver of such fees may be obtained under certain limited circumstances. The FDA has 60 days from its receipt of an NDA to determine whether the application will be accepted for filing based on the FDA's threshold determination that it is sufficiently complete to permit a substantive review.

If the FDA determines that the NDA is incomplete, the FDA may refuse to file the application. If the FDA refuses to file an NDA, the applicant may request an informal conference with the FDA about whether the application should be

filed. After the conference, the applicant may request that the application be filed over protest. When an application is filed over protest, the FDA is required to review the application as filed. Generally, the FDA does not favor the file over protest procedure and the FDA's policies explain that an application filed over protest does not receive a timeline for review and is designated a standard review.

In addition, an applicant that receives an RTF can, in some circumstances, appeal the decision using the FDA's dispute resolution procedures. After the NDA submission is accepted for filing, the FDA reviews the NDA to determine, among other things, whether a product is safe and effective for its intended use and whether the product is being manufactured in accordance with cGMP to assure and preserve the product's identity, strength, quality and purity. Under the goals and policies agreed to by

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the FDA under the Prescription Drug User Fee Act, or PDUFA, the FDA has 12 months after submission of an NDA in which to complete its initial review of a standard NDA and respond to the applicant, and eight months for a priority review NDA. The FDA does not always meet its PDUFA goal dates for review of NDAs. The review process and the PDUFA goal date may be extended by additional three month review periods whenever the FDA requests or the NDA sponsor otherwise provides additional information or clarification regarding information already provided in the submission at any time during the review cycle.

Under the Pediatric Research Equity Act of 2003, or PREA, NDAs or supplements to NDAs must contain data to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any drug for an indication for which orphan designation has been granted. As the FDA has not issued regulations applying PREA to orphan-designated indications, submission of a pediatric assessment is not presently required for an application to market a product for an orphan-designated indication. However, PREA compliance may be required if approval is sought for other indications for which the drug has not received orphan designation.

The FDA will typically inspect one or more clinical sites to assure compliance with GCP before approving an NDA. The FDA also will inspect the facility or the facilities at which the product is manufactured before the NDA is approved. The FDA will not approve the product unless current good manufacturing practice, or cGMP, compliance is satisfactory. The FDA may also take into account results of inspections performed by certain counterpart foreign regulatory agencies in assessing compliance with GCP or cGMP. The FDA has entered into international agreements with foreign agencies, including the EMA, in order to facilitate this type of information sharing. If the FDA determines the application, manufacturing process or manufacturing facilities are not acceptable, it will outline the deficiencies in the submission and often will request additional testing or information.

Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

The testing and approval process requires substantial time, effort and financial resources, and may take years to complete. Data obtained from clinical trials are not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. The FDA may not grant approval on a timely basis, or at all.

We may encounter difficulties or unanticipated costs in our efforts to secure necessary FDA approvals, which could delay or prevent us from marketing our products. The FDA may refer applications for novel drug products or drug products which present difficult questions of safety or efficacy to an advisory committee for review, evaluation and recommendation as to whether the application should be approved and under what conditions. The advisory committee process may cause delays in the approval timeline. The FDA is not bound by the recommendation of an advisory committee, but it considers such recommendations carefully, particularly any negative recommendations or limitations, when making drug approval decisions.

The FDA may limit the indications for use, approve narrow labeling relegating a drug to second- line or later-line use, add limitations of use to the labeling or place other conditions on approvals, which could restrict the marketing of the products. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling. After approval, some types of changes to the approved product, such as adding new indications, which may themselves require further clinical testing, or changing the manufacturing process are subject to further FDA review and approval.

Post-approval requirements.

After FDA approval of a product is obtained, we are required to comply with a number of post-approval requirements, including, among other things, establishment registration and product listing, record-keeping requirements, reporting certain adverse reactions and production problems to the FDA, providing updated safety and efficacy information, and complying with requirements concerning advertising and promotional labeling. As a condition of approval of an NDA, the FDA may require the applicant to conduct additional clinical trials or other post market testing and surveillance to further monitor and assess the drug’s safety and efficacy.

The FDA also has the authority to require a drug-specific risk evaluation and mitigation strategy, or REMS, to ensure the safe use of the drug. In determining whether a REMS is necessary, the FDA must consider the size of the population likely to use the drug, the seriousness of the disease or condition to be treated, the expected benefit of the drug, the duration of treatment, the seriousness of known or potential adverse events, and whether the drug is a new molecular entity. A REMS may be required to include various elements, such as a medication guide or patient package insert, a communication plan to educate health care providers of the drug's risks, limitations on who may prescribe or dispense the drug, or other measures that the FDA deems necessary to assure the safe use of the drug. The REMS strategy must be approved by the FDA. In addition, the REMS must include a timetable to assess the strategy at 18 months, three years, and seven years after the strategy's approval. The FDA may

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also impose a REMS requirement on an approved drug if the FDA determines, based on new safety information, that a REMS is necessary to ensure that the drug's benefits outweigh its risks.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Although physicians may prescribe a drug for off-label uses, manufacturers may only promote the drug for the approved indications and in accordance with the approved labeling. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. Failure to comply with the laws and regulations governing advertising and promotion can have negative consequences, including adverse publicity, warning and untitled letters from the FDA, requests for corrective advertising or communications with doctors, and civil penalties or criminal prosecution.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level and sets minimum standards for the registration and regulation of drug distributors by the states. Similarly, the Drug Supply Chain Security Act, or DSCSA, regulates the distribution of prescription pharmaceutical drugs, requiring passage of a pedigree to track and trace each prescription drug at the saleable unit level through the distribution system. The DSCSA also imposes obligations on drug manufacturers related to suspect product identification/removal, verification, dealing only with authorized trading partners, and other elements. The DSCSA will be effective incrementally over a 10-year period, with serialization of prescription drug products distributed in the U.S. effective November 27, 2017 for drug manufacturers. The PDMA, DSCSA, and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

Also, quality control and manufacturing procedures must continue to conform to cGMP after approval. The FDA periodically inspects manufacturing facilities to assess compliance with cGMP, which imposes certain procedural, substantive and recordkeeping requirements. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP and other aspects of regulatory compliance.

We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our product and product candidates. Future FDA inspections may identify compliance issues at our facilities or at the facilities of our contract manufacturers that may disrupt production or distribution, or require substantial resources to correct. In addition, discovery of problems with a product or the failure to comply with applicable requirements may result in restrictions on a product, manufacturer or holder of an approved NDA, including withdrawal or recall of the product from the market or other voluntary, FDA-initiated or judicial action that could delay or prohibit further marketing.

Once approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements is not maintained or if issues bearing on the product's safety or efficacy are discovered. Newly discovered or developed safety or effectiveness data or other information may also require changes to a product's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures. New government requirements, including those resulting from new legislation, may be established that could delay or prevent FDA approval of our products under development or negatively impact the marketing of any future approved products.

Orphan drug designation.

We have received orphan drug designation from the FDA for Translarna for the treatment of nmCF, nmDMD, nmMPS I, and nonsense mutation aniridia. The FDA may grant orphan drug designation to drugs intended to treat a "rare disease or condition," which is defined as a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for this type of disease or condition will be recovered from sales in the United States for that drug. Orphan drug designation must be requested before submitting an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. Orphan drug designation can provide opportunities for grant funding towards clinical trial costs, tax advantages and FDA user-fee benefits. In addition, if a product which has an orphan drug designation subsequently receives the first FDA approval for the indication for

which it has such designation, the product is entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. However, competitors may receive approval of different drugs or biologics for the indications for which the orphan product has exclusivity.

Hatch-Waxman exclusivity.

Market and data exclusivity provisions under the FDCA can delay the submission or the approval of certain applications for competing products. The FDCA provides a five-year period of non-patent data exclusivity within the United States to the first applicant to gain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety. During the exclusivity period, the FDA generally may not

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accept for review an abbreviated new drug application, or ANDA, or a 505(b)(2) NDA submitted by another company that references the previously approved drug. However, an ANDA or 505(b)(2) NDA may be submitted after four years if it contains a certification of patent invalidity or non-infringement.

For some applications that do not qualify for five-year exclusivity, the FDCA provides a shorter three-year period of market exclusivity. Three-year exclusivity applies to an NDA, 505(b)(2) NDA, or supplement to an existing NDA or 505(b)(2) NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example, for new indications, dosages, strengths or dosage forms of an existing drug. This three-year exclusivity covers only the conditions of use associated with the new clinical investigations and, as a general matter, does not prohibit the FDA from approving ANDAs or 505(b)(2) NDAs for generic versions of the original, unmodified drug product. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Pediatric exclusivity

Pediatric exclusivity is another type of non-patent market exclusivity in the United States and, if granted, provides for the attachment of an additional six months of market protection to the term of any existing Orange Book- listed patents or regulatory exclusivity, including the non-patent exclusivity periods described above. This six-month exclusivity may be granted based on the voluntary completion of a pediatric study or studies in accordance with an FDA-issued “Written Request” for such a study or studies.

Regulation outside the United States

In order to market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of our products. Whether or not we obtain FDA approval for a product, we would need to obtain the necessary approvals by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the product in those countries. The approval process varies from country to country and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others. And, even if regulatory approval is granted, it may be withdrawn or limited under certain circumstances or post-approval requirements may be imposed by the applicable regulatory authority.

Regulation in the European Union

We have obtained an orphan medicinal product designation from the European Commission, following an evaluation by the EMA’s Committee for Orphan Medicinal Products, for Translarna for the treatment of nmDMD, Becker muscular dystrophy, nmCF, aniridia and nmMPS I - but have only received conditional marketing authorization for Translarna for the treatment of nmDMD. The European Commission can grant orphan medicinal product designation to products for which the sponsor can establish that it is intended for the diagnosis, prevention, or treatment of (1) a life-threatening or chronically debilitating condition affecting not more than five in 10,000 people in the European Union, or (2) a life threatening, seriously debilitating or serious and chronic condition in the European Union and that without incentives it is unlikely that sales of the drug in the European Union would generate a sufficient return to justify the necessary investment. In addition, the sponsor must establish that there is no other satisfactory method approved in the European Union of diagnosing, preventing or treating the condition, or if such a method exists, the proposed orphan drug will be of significant benefit to patients. Orphan drug designation is not a marketing authorization. It is a designation that provides a number of benefits, including fee reductions, regulatory assistance, and the possibility to apply for a centralized E.U. marketing authorization, as well as 10 years of E.U. market exclusivity following a marketing authorization. During this market exclusivity period, neither the EMA, nor the European Commission nor any E.U. member states can accept an application or grant a marketing authorization for a “similar medicinal product.” A “similar medicinal product” is defined as a medicinal product containing a similar active substance or substances as contained in an authorized orphan medicinal product, and which is intended for the same

therapeutic indication. The market exclusivity period for the authorized therapeutic indication may be reduced to six years if, at the end of the fifth year, it is established that the orphan designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. In addition, a competing similar medicinal product may in limited circumstances be authorized prior to the expiration of the market exclusivity period, including if it is shown to be safer, more effective or otherwise clinically superior to our product. Our product and product candidates can lose orphan designation, and the related benefits, prior to us obtaining a marketing authorization if it is demonstrated that the orphan designation criteria are no longer met.

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Overview of application process. To obtain regulatory approval of a drug under the European Union's regulatory systems and authorization procedures, an applicant may submit marketing authorization applications under a centralized, decentralized, or national procedure. The centralized procedure is compulsory for certain medicinal products, including orphan medicinal products, like Translarna for the treatment of nmDMD, and medicinal products produced by certain biotechnological processes, and optional for certain other innovative products. The centralized procedure enables applicants to obtain a marketing authorization that is valid in all E.U. member states based on a single application. Under the centralized procedure, the EMA's Committee for Human Medicinal Products, or CHMP, is required to adopt an opinion on a valid application within 210 days, excluding clock stops, when additional written or oral information is to be provided by the applicant in response to questions. More specifically, on day 120 of the procedure, once the CHMP has received the preliminary assessment reports and opinions from the rapporteur and co-rapporteur, it prepares a list of potential outstanding issues, referred to as "other concerns" or "major objections". These are sent to the applicant together with CHMP's recommendation. The CHMP can make one of two recommendations: (1) the marketing authorization could be granted provided that satisfactory answers are given to the "other concerns" and/or "major objections" identified and that all conditions outlined in the list of outstanding issues are implemented and complied with; or (2) the product is not approvable since there are "major objections".

Applicants have three months from the date of receiving the potential outstanding issues to respond to the CHMP, and can request a three-month extension if necessary. The granting of a marketing authorization will depend on the recommendations and potential major objections identified by the CHMP as well as the ability of the applicant to adequately respond to these findings. An accelerated assessment can be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest, in particular from the viewpoint of therapeutic innovation. In this circumstance, the EMA ensures that the opinion of the CHMP is given within 150 days. After the adoption of the CHMP opinion, a decision on the marketing authorization application must be adopted by the European Commission, after consulting the European Union member states, which in total can take more than 60 days.

An applicant for a marketing authorization application may request a re-examination in the event of a negative opinion, in connection with which CHMP appoints new rapporteurs. Within 60 days of receipt of the negative opinion, the applicant must submit a document explaining the basis for its request for re-examination. The CHMP has 60 days to consider the applicant's request for re-examination. The applicant may request an oral explanation before the CHMP, which is routinely granted, following which CHMP will adopt a final opinion. The final opinion, whether positive or negative, is published by the CHMP shortly following the CHMP meeting at which the oral explanation takes place.

Conditional marketing authorizations. In specific circumstances, as with Translarna for the treatment of nmDMD, E.U. legislation enables applicants to obtain a marketing authorization on a conditional basis prior to obtaining the comprehensive clinical data required for an application for a full marketing authorization. Such conditional approvals may be granted for products designated as orphan medicinal products, if (1) the benefit-risk balance of the product is positive, (2) it is likely that the applicant will be in a position to provide the required comprehensive clinical trial data, (3) the product fulfills unmet medical needs, and (4) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required. A conditional marketing authorization may contain specific obligations to be fulfilled by the marketing authorization holder, including obligations with respect to the completion of ongoing or new studies, and with respect to the collection of pharmacovigilance data. Conditional marketing authorizations are valid for one year, and may be renewed annually, if the benefit-risk balance remains positive, and after an assessment of the need for additional or modified conditions and/or specific obligations. The timelines for the centralized procedure described above also apply with respect to the review by the CHMP of applications for a conditional marketing authorization. The granting of a conditional marketing authorization will depend on the applicant's ability to fulfill the conditions imposed within the agreed upon deadline.

For important information about matters that may adversely affect our ability to renew our conditional marketing authorization for Translarna, see "Item 1A. Risk Factors—Risks Related to the Development and Commercialization of our Product and our Product Candidates" and "Risks Related to Regulatory Approval of our Product and our Product

Candidates."

Variations to conditional marketing authorizations. After the granting of a conditional marketing authorization, the marketing authorization holder may submit an application to vary the conditional marketing authorization under a variation procedure. In the case of the introduction of an additional therapeutic indication, the timeframe for the variation procedure for the initial assessment of the dossier is generally 90 days (plus up to 20 days for validation). However, in the framework of a variation application assessment procedure, the EMA may send one or more requests for supplementary information to the marketing authorization holder, requiring that additional information be provided by the marketing authorization holder to support its variation application. Such supplementary requests will be sent together with a timetable stating the date by when the marketing authorization holder must submit the requested data and, where appropriate, the extended evaluation period to be applied to such variation procedure. The 90 day variation procedure may be suspended for up to three months for the marketing authorization holder to submit its responses to such supplementary requests. The

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marketing authorization holder will be notified of the outcome of the CHMP's assessment of the variation procedure within 15 days from the adoption of the CHMP opinion. If unfavorable, the CHMP opinion may be subject to a re-examination procedure upon the marketing authorization holder's request. This may imply an additional minimum two month procedure. If the CHMP opinion is favorable, the European Commission will usually vary the marketing authorization to introduce the additional therapeutic indication within approximately two months from the receipt of the final CHMP opinion.

Additional requirements and considerations. Prior to obtaining a marketing authorization in the European Union, applicants have to demonstrate compliance with all measures included in an EMA-approved Pediatric Investigation Plan, or PIP, covering all subsets of the pediatric population, unless the EMA has granted (1) a product-specific waiver, (2) a class waiver, or (3) a deferral for one or more of the measures included in the PIP. In the case of orphan medicinal products, completion of an approved PIP can result in an extension of the aforementioned market exclusivity period from ten to twelve years.

In the European Union, independently generated data submitted as part of a full marketing authorization application dossier are protected by regulatory data protection ('data exclusivity') for a period of eight years from the granting of a marketing authorization for a 'reference product'. This means that for a period of eight years, competent authorities may not accept marketing authorization applications that rely on the independently generated data in the marketing authorization dossier of the reference product. Generic medicinal products that rely on the independently generated data of the reference product may not be placed on the market for 10 years from the granting of the initial marketing authorization for the reference medicinal product. These periods of data exclusivity and market exclusivity do not prevent other companies from obtaining a marketing authorization based on their own independently generated data.

If a marketing authorization is granted by the EEA for a medicinal product, such as the marketing authorization granted for Translarna for the treatment of nmDMD by the EMA, the marketing authorization holder is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of the medicinal products that are in addition to the other conditions of the marketing authorization described above. The marketing authorization holder must, for example, comply with the E.U.'s stringent pharmacovigilance or safety reporting rules, pursuant to which post- authorization studies and additional monitoring obligations can be imposed. Other requirements relate to, for example, the manufacturing of products and active pharmaceutical ingredients in accordance with good manufacturing practice standards. Competent authorities of E.U. member states may conduct inspections to verify compliance with applicable requirements, and the marketing authorization holder will have to continue to expend time, money and effort to remain compliant. Non-compliance with E.U. requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties in the E.U. Similarly, failure to comply with the E.U.'s requirements regarding the protection of individual personal data can also lead to significant penalties and sanctions. Individual E.U. member states may also impose various sanctions and penalties in case we do not comply with locally applicable requirements.

Off-label promotion of medicinal products is prohibited in the European Union. The applicable laws at European Union level and in the individual European Union member states also prohibit the direct-to-consumer advertising of prescription-only medicinal products. Violations of the rules governing the promotion of medicinal products in the European Union could be penalized by administrative measures, fines and imprisonment. These laws may further limit or restrict our promotional activities with health care professionals. In addition, legislation adopted at the European Union level and by individual European Union member states require that promotional materials and advertising in relation to medicinal products comply with the product's Summary of Product Characteristics, or SmPC, as approved by the competent authorities. The SmPC is the document that provides information to physicians concerning the safe and effective use of the medicinal product. Promotion of indications not covered by the SmPC is specifically prohibited.

The EMA is responsible for coordinating inspections to verify compliance with the principles of good clinical practice, or GCP, good manufacturing practice, or GMP, good laboratory practice, or GLP, and good pharmacovigilance practice, or GVP. These inspections are also intended to verify compliance with other aspects of the supervision of authorized medicinal products in use in the European Union. The EMA coordinates any inspection

requested by the CHMP in connection with the assessment of marketing authorization applications or matters referred to these committees. Inspections may be routine or triggered by issues arising during the assessment of the dossier or by other information, such as previous inspection experience. Inspections usually are requested during the initial review of a marketing authorization application, but could arise post-authorization.

Inspectors are drawn from member states of the European Union and the European Economic Area. Following an inspection, the inspectors provide a written inspection report to the inspected site or applicant and provide an opportunity for response. Some inspection reports require follow-up and may result in additional adverse consequences due to critical or major findings. The inspectors and the CHMP will comment on any response from an inspected site or applicant and may monitor future compliance with any proposed corrective action plan.

In the GCP area, inspectors grade their findings according to the following scale:

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- Critical: Conditions, practices or processes that adversely affect the rights, safety or well-being of the subjects or the quality and integrity of data. Observations classified as critical may include a pattern of deviations classified as major.
- Major: Conditions, practices or processes that might adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data. Observations classified as major may include a pattern of deviations or numerous minor observations.
- Minor: Conditions, practices or processes that would not be expected to adversely affect the rights, safety or wellbeing of the subjects or the quality and integrity of data. Minor observations indicate the need for improvement of conditions, practices and processes.
- Comments: Suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

Possible consequences of critical and major findings include rejection of clinical trial data, causing significant delays in obtaining final marketing authorization, or other direct action by national regulatory authorities.

Early access programs

Many jurisdictions allow the supply of unauthorized medicinal products in the context of strictly regulated and exceptional early access programs, and some countries may provide reimbursement for drugs provided in the context of such programs. In the European Union, the legal basis for early access programs, also referred to as named-patient and compassionate use programs, is set out in the E.U. legislation regulating the authorization, manufacture, distribution and marketing of medicinal products. Detailed regulatory requirements applicable to early access programs have been adopted and implemented by E.U. member states in their national laws. The promotion, advertising and marketing of unauthorized medicinal products is generally prohibited, and authorization for early access programs must generally be obtained from national competent authorities, which might not grant such authorization. Obtaining authorization for an early access program in one country does not ensure that authorization will be obtained in another country. U.S. law permits “expanded access” (also known as compassionate use and treatment use) for certain patients with serious diseases who have no comparable alternative treatment options. To provide expanded access, sponsors must submit detailed regulatory information to the FDA. FDA authorization depends on several different factors, including whether expanded access will interfere with related clinical trials or drug development. Sponsors may not promote products as safe or effective for expanded-access uses.

Pharmaceutical Pricing and Reimbursement

The containment of healthcare costs has become a priority of federal, state and foreign governments, and the prices of pharmaceuticals have been a focus of this effort. Foreign governments, the U.S. government, and state legislatures have shown significant interest in implementing cost-containment programs to limit the growth of government-paid healthcare costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs.

In some countries, particularly the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing and reimbursement negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. In some countries, governments can set conditions that must be satisfied for prices to be set at a certain value. Political, economic and regulatory developments may further complicate pricing and reimbursement negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various E.U. member states, and parallel distribution (arbitrage between low-priced and high- priced member states), can further reduce prices. In some countries we may be required to conduct a clinical trial or other studies that compare the cost-effectiveness of our product or product candidate to other available therapies in order to obtain reimbursement or pricing approval.

Coverage policies, third-party reimbursement rates and drug pricing regulation may change at any time. For example in the United States, healthcare reform measures under the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, referred to together as the Affordable Care Act, contain provisions that may reduce the profitability of drug products. However, the new Presidential administration and Congress have expressed a desire to repeal the Affordable Care Act, which has contributed to the uncertainty of the ongoing implementation and impact of the Affordable Care Act and also underscores the potential

for additional reform going forward. Certain provisions of enacted or proposed legislative changes may negatively impact coverage and reimbursement of healthcare items and services. We cannot assure that the Affordable Care Act, as currently enacted or as amended in the future, will not adversely affect our business and financial results and we cannot predict how future federal or state legislative or administrative changes relating to healthcare reform will affect our business.

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Any regulatory approval of a product is limited to specific diseases and indications for which such product has been deemed safe and effective by the FDA. Coverage by federal healthcare programs, however, may be more limited than the purposes for which the drug is approved by the FDA or comparable foreign regulatory authorities' coverage of the same products. Sales of any products for which we may receive regulatory approval for commercial sale will depend in part on the extent to which the costs of the products will be covered and reimbursed by third-party payors, including government healthcare programs (such as, in the United States, Medicare and Medicaid), private health insurers and other organizations. Obtaining reimbursement for orphan drugs may be particularly difficult because of the significant research and development challenges and costs and resulting pricing considerations typically associated with drugs developed to treat conditions that affect a small population of patients. In addition, third-party payors are likely to impose strict requirements for reimbursement in connection with drugs that are perceived as having high costs. Net prices for products may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors.

The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third- party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the approved products for a particular indication. Third-party payors are increasingly challenging the price and examining the cost-effectiveness of medical products and services. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the cost-effectiveness of our product or product candidates or conduct direct head-to-head studies to demonstrate clinical superiority and cost- effectiveness. Our products and product candidates may not be considered clinically superior and cost- effective to competitor products.

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and other third-party payors fail to provide adequate coverage and reimbursement.

For important information regarding certain pricing and reimbursement matters see "Item 1. Business-Market Access Considerations" and "Item 1A. Risk Factors," including the risk factor titled "Our initial commercial launch of Translarna has begun in, and is expected to continue to take place in, countries that tend to impose strict price controls, which may adversely affect our revenues. Failure to obtain and maintain acceptable pricing and reimbursement terms for Translarna for the treatment of nmDMD in the EEA and other countries where Translarna is available would delay or prevent us from marketing our product in such regions, which would adversely affect our anticipated revenue, growth and business."

Freedom of Information Requests

We are also subject, in the U.S. and many other countries, to various regulatory schemes that require disclosure of clinical trial data or allow access to our data via freedom of information requests. We have been and may, from time to time, be notified by regulators, such as the EMA or the competent authorities of EU member states that they have received a freedom of information request for documents that they hold relating to our company, including information related to our product or our product candidates. For example, in 2015, we were notified by the EMA that it had received from another pharmaceutical company a request under Regulation (EC) No 1049/2001 seeking access to aspects of our marketing authorization application for Translarna for the treatment of nmDMD. Following the decision of the EMA to release such documentation with only minimal redactions we initiated litigation before the General Court of the European Union to prevent disclosure of this information, and in July 2016, the Court took the interim measure of ordering the EMA not to release our documents until the substantive case has been decided (by the General Court and/or in possible appeal proceedings). The EMA appealed the interim measure to the Court of Justice of the European Union but the Court of Justice dismissed the appeal in the first quarter of 2017. While we expect to continue to object to the disclosure of any information that we consider commercially confidential, there can be no assurance that we will be successful in the aforementioned litigation or in any future challenge that may be raised and we may not ultimately be successful in preventing disclosure of the data in our marketing authorization application for Translarna for the treatment of nmDMD.

Fraud and Abuse Laws

Any present or future arrangements with third-party payors, healthcare providers and professionals and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may restrict certain

marketing and contracting practices. These laws include, and are not limited to, anti-kickback and false claims statutes.

Both the federal Foreign Corrupt Practices Act, or FCPA, and the UK Bribery Act of 2010, or Bribery Act are broad in scope and will require companies to make and keep books and records that accurately and fairly reflect the transactions of the company and to devise and maintain an adequate system of internal accounting controls. The FCPA prohibits the offering, promising, giving, or authorizing others to give anything of value, either directly or indirectly, to a non-U.S. government official in order to improperly influence any act or decision, secure any other improper advantage, or obtain or retain business. Under the UK Bribery Act, companies which carry on a business or part of a business in the United Kingdom may be held

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liable for bribes given, offered or promised to any person, including non-UK government officials and private persons, by employees and persons associated with the company in order to obtain or retain business or a business advantage for the company. Similar statutes have been adopted, or may be adopted in the future, by other countries in which we operate and with which we are or may be required to comply.

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration, directly or indirectly, in cash or kind, to induce or reward either the referral of an individual for, or the purchase, or order or recommendation of, any good or service, for which payment may be made under federal and state healthcare programs such as Medicare and Medicaid. This statute imposes criminal penalties and has been broadly interpreted to apply to manufacturer arrangements with prescribers, purchasers and formulary managers, among others. Although a number of statutory exemptions and regulatory safe harbors exist to protect certain common activities from prosecution, the exemptions and safe harbors for this statute are narrow, and practices that involve compensation intended to induce prescriptions, purchases, or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor. Our practices may not always meet all of the criteria for safe harbor protection. Further, the Affordable Care Act amended the intent requirement of the federal anti-kickback and criminal health care fraud statutes. This amendment provides that a person or entity no longer needs to have knowledge of these statutes or specific intent to violate them. In addition, 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 federal False Claims Act. Several other countries, including the United Kingdom, have enacted similar anti-kickback, fraud and abuse laws and regulations.

The federal False Claims Act, which may permit civil whistleblower or qui tam actions, imposes civil liability and criminal penalties on individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government. Several pharmaceutical and health care companies have been prosecuted under this law for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the free product. Other companies have been prosecuted for causing false claims to be submitted because of these companies' marketing of a product for unapproved, and thus non reimbursable, uses. Potential liability under the federal False Claims Act includes mandatory treble damages and significant per claim penalties, currently set at $10,781 to $21,563 (as adjusted for inflation) per false claim. The majority of states also have statutes or regulations similar to the federal anti-kickback statute and False Claims Act, which apply to items and services reimbursed under Medicaid and other state programs; furthermore, in several states, these statutes and regulations apply regardless of the payor. Sanctions under these federal and state laws may include civil monetary penalties, exclusion of a manufacturer's product from reimbursement under government programs, debarment, criminal fines, and imprisonment.

The Affordable Care Act included a provision requiring certain providers and suppliers of items and services to Federal Health Care Programs to report and return overpayments within sixty days after they are "identified" (the "Overpayment Statute"). In 2014 and 2016, the Centers for Medicare and Medicaid Services ("CMS") released regulatory guidance (in the form of a final rule) to Medicare providers, suppliers and managed care and prescription drug plans regarding how to comply with the Overpayment Statute. Although these Medicare providers, suppliers and plans have faced federal False Claims Act liability since 2010 for failures to comply with the Overpayment Statute, these final rules interpreting the Overpayment Statute provide guidance regarding how to comply with applicable obligations, and guidance to government regulators and enforcement authorities regarding monitoring and prosecuting suspected violations. These final rules are not directly applicable to manufacturers, but may impact their customers and potential customers who are Medicare providers, suppliers, and plans.

The federal Physician Payments Sunshine Act, enacted as part of the Affordable Care Act, and its implementing regulations, require manufacturers of drugs, devices, biologics and medical supplies to report to the Department of Health and Human Services information related to payments and other transfers of value made to covered recipients, such as physicians and teaching hospitals, as well as physician ownership and investment interests. Payments made to physicians and certain research institutions for clinical trials are included within the ambit of this law. Pharmaceutical manufacturers are required annually to report and disclose payments and ownership and investment interests held by

physicians and their immediate family members during the preceding calendar year. Such information is publicly available from the Secretary of Health and Human Services in a searchable format, with data collected in each calendar year published the following June. Failure to submit required information may result in civil monetary penalties, with increased penalties for “knowing failures,” for all payments, transfers of value or ownership or investment interests not reported in an annual submission. If not preempted by this federal law, several states currently 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 those states. Depending on the state, legislation may prohibit various other marketing related activities, or require the posting of information relating to clinical studies and their outcomes. In addition, certain states, such as California, Nevada, Connecticut and Massachusetts, require pharmaceutical companies to implement compliance programs or marketing codes and several other states are considering similar proposals. Manufacturers that fail to comply with these state laws can face civil penalties.

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Statutory requirements to disclose publicly payments made to healthcare professionals and healthcare organizations have also been enacted in certain European Union member states. In addition, self-regulatory bodies of the pharmaceuticals industry, such as the European Federation of Pharmaceutical Industries and Associations ("EFPIA"), have published codes of conduct to which its members have agreed to abide to, that require the public disclosure of payments made to healthcare professionals and healthcare organizations.

The Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, imposes criminal liability for executing a scheme to defraud any healthcare benefit program and for knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statements in connection with the delivery of or payment for healthcare benefits, items or services. HIPAA, and similar state laws, also impose obligations, including mandatory contractual terms under HIPAA, with respect to safeguarding the privacy, security and transmission of individually identifiable health information, and imposes criminal and civil liability for violations of these obligations. Recently, the U.S. federal government criminally prosecuted an employee of a pharmaceutical company for an alleged violation of the privacy requirements under HIPAA. Furthermore, certain privacy laws and genetic testing laws may apply directly to our operations and/or those of our collaborators and may impose restrictions on our use and dissemination of individuals' health information.

We expect that the new Presidential Administration and U.S. Congress may seek to modify, repeal, or otherwise invalidate all, or certain provisions of, the Affordable Care Act, which could have an impact on fraud and abuse provisions and other requirements that were authorized and enacted under the Affordable Care Act.

The foregoing discussion should be read in conjunction with the information appearing under "Item 1A. Risk Factors—Our relationships with customers, healthcare providers and professionals, patients, patient organizations, and third-party payors are or will be subject to applicable anti-kickback, fraud and abuse, transparency and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings." which contains important information regarding some of the risks to our business arising as a result fraud and abuse laws.

Employees

As of December 31, 2016, we had 304 employees, of whom 298 were employed on a full-time basis, and 23 full-time consultants and contractors. None of our U.S. based employees are represented by labor unions or covered by collective bargaining agreements, although certain international employees are covered by collective labor agreements established under local law. We consider our relationship with our employees to be good.

Our Corporate Information

We were incorporated under the laws of the State of Delaware on March 31, 1998, under the name PTC Therapeutics, Inc. Our principal executive offices are located at 100 Corporate Court, South Plainfield, New Jersey 07080. Our telephone number is (908) 222-7000. We maintain a website at www.ptcbio.com.

Additional Information

We make available, free of charge on our website, www.ptcbio.com, our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and all amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, as soon as reasonably practicable after we electronically file those reports with, or furnish them to, the Securities and Exchange Commission, or SEC. We also make available, free of charge on our website, the reports filed with the SEC by our executive officers, directors and 10% stockholders pursuant to Section 16 under the Exchange Act as soon as reasonably practicable after copies of those filings are provided to us by those persons. Such reports, proxy statements and other information may be obtained through the SEC's website (www.sec.gov) or by visiting the Public Reference Room of the SEC at 100 F Street, N.E., Washington D.C. 20549 or calling the SEC at 1-800-SEC-0330. The information contained on, or that can be accessed through, our website is not a part of or incorporated by reference in this Annual Report on Form 10-K.

Item 1A. Risk Factors

The following risk factors and other information included in this Annual Report on Form 10-K should be carefully considered. The risks and uncertainties described below are not the only ones we face. Additional risks and

uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. Please see page 1 of this Annual Report on Form 10-K for a discussion of some of the forward looking statements that are qualified by these risk factors. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected.

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Risks Related to Our Planned Acquisition of Emflaza™ (deflazacort)

Consummation of our planned acquisition of Emflaza™ (deflazacort) from Marathon Pharmaceuticals, LLC, or Marathon, is subject to satisfaction of closing conditions, including antitrust approval, which, if delayed or not granted or granted with unacceptable conditions, may prevent, delay or impair the consummation of the transaction, result in additional expenditures of money and resources, subject us to business uncertainties that could adversely affect our business and operations, and/or reduce the anticipated benefits of the transaction.

On March 16, 2017, we announced that we have entered into an asset purchase agreement with Marathon under which we have agreed to acquire all rights to Emflaza. Completion of the planned acquisition is subject to certain closing conditions, including, among others, the clearance of the transaction by certain governmental and regulatory authorities, including the expiration or termination of applicable waiting periods under the Hart-Scott-Rodino Antitrust Improvements Act. The governmental and regulatory agencies with which we and Marathon will make these filings and seek certain of these approvals and consents have broad discretion in administering applicable governing regulations. We can provide no assurance that all required approvals and consents will be obtained. Moreover, as a condition to their approval of the transaction, certain governmental agencies may impose requirements, limitations or costs or place restrictions on the conduct of our business after the closing of the transaction. Any one of these requirements, limitations, costs or restrictions could jeopardize or delay the effective time of the transaction or reduce the anticipated benefits of the transaction. Further, no assurance can be given that the required closing conditions will be satisfied and, if all required consents and approvals are obtained and the closing conditions are satisfied, no assurance can be given as to the terms, conditions and timing of the approvals or clearances. The occurrence of any of the foregoing could result in a failure to close the transaction or have a material adverse effect on our business, financial condition and results of operations.

In addition, while the transaction is pending, we will be subject to business uncertainties that could adversely affect our business and operations. These uncertainties may impair our ability to attract, retain and motivate key personnel until the transaction is consummated and for a period of time thereafter. We may also experience negative reactions from our stockholders, patients, the medical community, vendors, payors, and employees, among others. Further, if the transaction is not completed for any reason, the price of our common stock may decline to the extent that current market prices reflect a market assumption that the transaction will be completed and the perception of the effectiveness of our management and our company may suffer in the marketplace. In addition, some costs related to the transaction must be paid whether or not it is completed.

Even if we successfully consummate our planned acquisition of Emflaza, we may fail to realize all of the anticipated benefits of the transaction, those benefits may take longer to realize than expected, or we may encounter significant integration difficulties.

Our ability to realize the anticipated benefits of the planned acquisition will depend, to a large extent, on our ability to integrate Emflaza into our business and realize anticipated growth opportunities and synergies. We have no history of commercializing pharmaceutical products in the United States and we expect the process will be complex, costly and time-consuming. As a result, we will be required to devote significant management attention and resources to integrating this product into our business. The process may be disruptive to our business and the expected benefits may not be achieved within the anticipated time frame, or at all. The failure to meet the challenges involved and to realize the anticipated benefits of the transaction could cause an interruption of, or a loss of momentum in, our commercialization efforts and could adversely affect our business, financial condition and results of operations.

Our ability to realize the anticipated benefits of the transaction is expected to entail numerous material potential difficulties, including, among others:

- the diversion of management attention to integration matters;
- difficulties in achieving anticipated business opportunities and growth prospects from the acquisition;
- challenges related to public and market perception of Emflaza and/or our acquisition of the product;
- increased scrutiny from third parties, including regulators, legislative bodies and enforcement agencies, with respect to product pricing and commercialization matters;
- difficulties in managing the expanded operations of a significantly larger and more complex company following the acquisition;

- difficulties in assimilating employees and in attracting and retaining key personnel; and
- potential unknown liabilities, adverse consequences, unforeseen increased expenses or other unanticipated problems associated with the transaction.

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Many of these factors are outside of our control, and any one of them could result in increased costs, decreased expected revenues and further diversion of management time and energy, which could materially impact our business, financial condition and results of operations.

In addition, following the completion of the acquisition, we will possess not only the rights to Emflaza, but also certain corresponding liabilities and obligations, including the contractual liabilities and regulatory obligations that will be assumed by us upon closing of the transaction, including certain post-marketing commitments. These obligations are expected to result in additional investment in Emflaza by us, and failure to satisfy any such requirements could delay our realization of, or prevent us from ever realizing, the anticipated benefits from the transaction. Further, it is possible that undisclosed, contingent, or other liabilities or problems may arise in the future of which we were previously unaware. These undisclosed liabilities could have an adverse effect on our business, financial condition and results of operations.

All of these factors could decrease or delay the expected accretive effect of the transaction and negatively impact our stock price. As a result, it cannot be assured that the pending transaction with Marathon will result in the full realization of the benefits anticipated from the transaction within the anticipated time frames or at all.

In addition, upfront consideration for the planned acquisition is comprised of approximately $75 million in cash and approximately $65 million in our common stock, subject to a maximum 6.9 million share limit (with any shortfall to be made whole with additional cash consideration). Marathon is also entitled to receive payments from PTC based on annual net sales of Emflaza beginning in 2018 and has the opportunity to receive a single $50 million sales-based milestone. The issuance of our common stock to complete this transaction will be dilutive to our existing stockholders and because we have limited financial resources, by investing in this transaction, we may forego or delay pursuit of other opportunities that may have proven to have greater commercial potential.

Risks Related to Our Financial Position and Need for Additional Capital

We have incurred significant losses since our inception. We may never generate profits from operations or maintain profitability and expect to continue to incur significant operating losses and expenses for at least the next several years.

Since inception, we have incurred significant operating losses. As of December 31, 2016, we had an accumulated deficit of $735.1 million. We have historically financed our operations primarily through the issuance and sale of our common stock in public offerings, the private placements of our preferred stock, collaborations, bank debt, convertible debt financings, and grants and clinical trial support from governmental and philanthropic organizations and patient advocacy groups in the disease areas addressed by our product and product candidates. We expect to continue to incur significant expenses and operating losses for at least the next several years. The net losses we incur may fluctuate significantly from quarter to quarter.

On March 2, 2017, we announced that the primary and secondary endpoints were not achieved in ACT CF, our Phase 3 clinical for Translarna in nonsense mutation cystic fibrosis, or nmCF, and that, as a result, we plan to discontinue our current clinical development of Translarna for nmCF. We have withdrawn our type II variation submission with the European Medicines Agency, or EMA, which sought approval of Translarna for the treatment of nmCF in the European Economic Area, or EEA.

In October 2015, we announced that the primary efficacy endpoint in the intent to treat, or ITT, population did not achieve statistical significance in ACT DMD, our Phase 3 clinical trial for Translarna™ (ataluren) for the treatment of nonsense mutation Duchenne muscular dystrophy, or nmDMD. Please review the risk factor under “Risks Related to the Development and Commercialization of our Product and our Product Candidates” titled, “ACT DMD did not meet its primary efficacy endpoint, and there is substantial risk that regulators will not agree with our interpretation of the results of ACT DMD and the totality of clinical data from our trials in Translarna for the treatment of nmDMD, which would have a material adverse effect on our business, financial performance and results of operations” for additional information on recent developments that have had, and may continue to have, a material adverse effect on our ability to obtain or maintain marketing authorizations necessary to commercialize Translarna for the treatment of nmDMD in the United States, Europe and other territories.

Our current ability to generate revenue from sales of Translarna is dependent upon our ability to maintain our marketing authorization in the EEA of Translarna for the treatment of nmDMD in ambulatory patients aged five years

and older. The marketing authorization in the EEA is subject to annual review and renewal by the European Commission following reassessment by the EMA of the benefit-risk balance of the authorization and is further subject to a specific obligation to conduct and report the results of Study 041, a multi-center, randomized, double-blind, 18-month, placebo-controlled trial, followed by an 18-month open-label extension, according to an agreed protocol, in order to confirm the efficacy and safety of Translarna in the approved patient population. Enrolling, conducting and reporting a clinical trial is a time-consuming, expensive and uncertain process that takes years to complete, and we expect that we will incur material costs related to the implementation and conduct of Study 041. In addition, it is likely that we will enroll patients in Study 041 in countries where Translarna for the treatment of nmDMD is currently available on a reimbursed basis, which could negatively impact growth in

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our net product sales. We may experience unknown complications with Study 041 and may not achieve the pre-specified endpoint with statistical significance, which would have a material adverse effect on our ability to maintain our marketing authorization in the EEA.

If, in any annual renewal cycle, the EMA determines that the balance of benefits and risks of using Translarna for the treatment of nmDMD has changed materially or that we have not or are unable to comply with the specific obligation to complete Study 041 or any other requirement that has been or may be placed on the marketing authorization, the European Commission could, at the EMA's recommendation, vary, suspend, withdraw or refuse to renew the marketing authorization for Translarna or impose other specific obligations or restrictions, which would have a materially adverse effect on our business. We expect to incur significant costs in connection with our efforts to maintain our marketing authorization in the EEA. If our marketing authorization in the EEA is not renewed, or our product label is materially restricted, we would lose all, or a significant portion of, our ability to generate revenue from product sales, whether pursuant to a commercial or a reimbursed early access program, or EAP program, and throughout all territories. For additional information, see the risk factor under "Risks Related to Regulatory Approval of our Product and our Product Candidates" titled, "Our marketing authorization in the EEA is a "conditional marketing authorization" that requires annual review and renewal by the European Commission following reassessment by the EMA of the benefit-risk balance of the authorization and is further conditioned upon our ability to satisfy the specific obligation to conduct and report the results of Study 041 by September 2021, and, as such, there is ongoing risk that we may be unable to maintain such authorization. If we are unable to obtain renewal of our marketing authorization in any future renewal cycle, we would lose all, or a significant portion of, our ability to generate revenue from product sales, whether pursuant to a commercial or an EAP program and throughout all territories, which would have a material adverse effect on our business, financial performance and results of operations."

We also expect that our efforts to advance Translarna for the treatment of nmDMD in the United States, whether pursuant to the recently initiated file over protest process with the FDA, or otherwise, will be time-consuming and may be expensive. For additional information, see the risk factor under "Risks Related to Regulatory Approval of our Product and our Product Candidates" titled, "There is substantial risk that the FDA will continue to disagree with our interpretation of the results of ACT DMD and the totality of clinical data from our trials in Translarna for the treatment of nmDMD and we will be unable to advance Translarna for the treatment of nmDMD in the United States in a timely manner, or at all, whether pursuant to the file over protest process or otherwise, and by determining to file our NDA over protest, we have postponed other available strategic pathways which may have proven to be more effective. If there are delays in obtaining regulatory approval in the United States, we will not be able to commercialize Translarna for nmDMD in that territory and our ability to generate revenue will be materially impaired. In the event that the FDA requires us to conduct a new clinical trial in nmDMD which, if successful, may enable FDA review of an NDA submission by us, we would expect to incur significant costs, which may have a material adverse effect on our business and results of operations."

We anticipate that our expenses will further increase in connection with the expansion of our global infrastructure as we continue to establish an international presence and commercialize Translarna for the treatment of nmDMD, including sales and marketing, legal and regulatory, distribution and manufacturing and administrative and employee-based expenses. In addition, the clinical and regulatory developments noted in this risk factor may exacerbate the risks related to our commercialization efforts set forth under the heading "Risks Related to the Development and Commercialization of our Product and our Product Candidates," which could increase the costs associated with our commercial activities or have a negative impact on our revenues. For additional information, see also, the risk factor under the heading "Risks Related to the Regulation of our Product and our Product Candidates" titled "Our initial commercial launch of Translarna has begun in, and is expected to continue to take place in, countries that tend to impose strict price controls, which may adversely affect our revenues. Failure to obtain and maintain acceptable pricing and reimbursement terms for Translarna for the treatment of nmDMD in the EEA and other countries where Translarna is available would delay or prevent us from marketing our product in such regions, which would adversely affect our anticipated revenue, growth and business."

We may seek to expand and diversify our product pipeline through opportunistically in-licensing or acquiring the rights to products, product candidates or technologies and we may incur expenses, including with respect to

transaction costs, subsequent development costs or any upfront, milestone or other payments or other financial obligations associated with any such transaction, which would increase our future capital requirements.

In addition to the foregoing, we expect to continue to incur significant costs in connection with our open label extension clinical trials of Translarna for the treatment of nmDMD as well as our Phase 2 studies for nmMPS I, nonsense mutation aniridia and nonsense mutation Dravet syndrome/CDKL5. We also expect to incur ongoing research and development expenses for our other product candidates, including our cancer stem cell program. We have begun seeking and intend to continue to seek marketing authorization for Translarna for the treatment of nmDMD in territories outside of the EEA. These efforts may significantly impact the timing and extent of our commercialization expenses. With respect to our outstanding 3.00%

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convertible senior notes due August 15, 2022, or the Convertible Notes, cash interest payments are payable on a semi-annual basis in arrears, which will require total funding of $4.5 million annually.

In addition, our expenses will increase if and as we:

- are required to complete any additional clinical and non-clinical trials or analyses in order to advance Translarna for the treatment of nmDMD in the United States or elsewhere;
- are required to take other steps, in addition to Study 041, to maintain our current marketing authorization in the EEA for Translarna for the treatment of nmDMD or to obtain further marketing authorizations for Translarna for the treatment of nmDMD or other indications;
- initiate or continue the research and development of Translarna for additional indications and of our other product candidates;
- seek to discover and develop additional product candidates;
- seek to expand and diversify our product pipeline through strategic transactions;
- maintain, expand and protect our intellectual property portfolio;
- add operational, financial and management information systems and personnel, including personnel to support our product development and commercialization efforts; and
- complete our planned acquisition of Emflaza, subject to satisfying closing conditions and obtaining applicable regulatory approvals, integrate the acquired assets into our business, and seek to satisfy contractual and regulatory obligations that will be assumed by us following closing of the planned acquisition.

We also could be forced to expend significant resources in the defense of the pending securities class action lawsuits brought against us and certain of our executives, as described under Part I, Item 3. Legal Proceedings in this Form 10-K.

Our ability to generate profits from operations and become and remain profitable depends on our ability to successfully develop and commercialize drugs that generate significant revenue. This will require us to be successful in a range of challenging activities, including:

- maintaining the marketing authorization of Translarna for the treatment of nmDMD in the EEA, including successfully obtaining annual renewals of the marketing authorization, fulfilling the specific obligation to conduct and report the results of Study 041 to the EMA, and meeting any ongoing requirements related to the marketing authorization;
- advancing Translarna for the treatment of nmDMD in the United States in a timely manner, or at all, whether pursuant to the file over protest process with the FDA or otherwise, and including, if required, performing additional clinical and non-clinical trials or analyses at significant cost which, if successful, may enable FDA review of an NDA submission by us and, ultimately, may support approval of Translarna for nmDMD in the U.S.;
- expanding the territories in which we are approved to market Translarna for the treatment of nmDMD;
- minimizing the enrollment impact of Study 041 on commercialization efforts for Translarna for nmDMD;
- developing Translarna for the treatment of additional indications, including nmMPS I, nonsense mutation aniridia, and nonsense mutation Dravet syndrome/CDKL5 and successfully advancing our other programs and collaborations, including our cancer stem cell and SMA programs;
- establishing a global commercial infrastructure, including the sales, marketing and distribution capabilities to effectively market and sell Translarna for the treatment of nmDMD in the EEA and other parts of the world;
- implementing marketing and distribution relationships with third parties in territories where we do not pursue direct commercialization;
- negotiating and securing adequate pricing and reimbursement terms for Translarna for the treatment of nmDMD on a timely basis, or at all, in the countries in which we have obtained, and may obtain, regulatory approval;
- negotiating and securing adequate reimbursement from other third-party payors for Translarna for the treatment of nmDMD;
- launching commercial sales of Translarna for the treatment of nmDMD in accordance with our estimated timeline

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- identifying patients eligible for treatment with Translarna for nmDMD;
- obtaining approval to market Translarna for the treatment of other indications;
- expanding the approved product label of Translarna for the treatment of nmDMD;
- successfully developing or commercializing any product candidate or product that we may in-license or acquire, including Emflaza;
- protecting our rights to our intellectual property portfolio related to Translarna; and
- contracting for the manufacture and distribution of commercial quantities of Translarna.

We may never succeed in these activities and, even if we do, may never generate revenues that are significant enough to generate profits from operations. Even if we do generate profits from operations, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to generate profits from operations and remain profitable would decrease the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product offerings or continue our operations. A decline in the value of our company could also cause our stockholders to lose all or part of their investment in our company.

We will need substantial additional funding. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts.

As noted in the prior risk factor, we expect to incur significant expenses related to our clinical, regulatory, commercial, legal, research and development, and other business efforts. We believe that our cash flows from product sales, together with existing cash and cash equivalents, including the net proceeds from our Convertible Note offering, public offerings of common stock, marketable securities and research funding that we expect to receive under our collaborations, will be sufficient to fund our operating expenses and capital expenditure requirements for at least the next twelve months. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we currently expect.

Our future capital requirements will depend on many factors, including:

- our ability to maintain the marketing authorization in the EEA for Translarna for the treatment of nmDMD, including whether the EMA determines on an annual basis that the benefit-risk balance of Translarna supports renewal of our marketing authorization in the EEA, on the current approved label, or at all;
- the costs, timing and outcome of Study 041;
- the costs, timing and outcome of our efforts to advance Translarna for the treatment of nmDMD in the United States, whether pursuant to the file over protest process with the FDA, or otherwise, and including, whether we will be required to perform additional clinical and non-clinical trials or complete additional analyses at significant cost which, if successful, may enable FDA review of an NDA submission by us and, ultimately, may support approval of Translarna for nmDMD in the U.S.;
- the progress and results of our pediatric study of Translarna for the treatment of nmDMD, our open label extension clinical trials of Translarna for the treatment of nmDMD as well as our studies for nmMPS I and nonsense mutation aniridia and nonsense mutation Dravet syndrome/CDKL5 and activities under our cancer stem cell program;
- the scope, costs and timing of our commercialization activities, including product sales, marketing, legal, regulatory, distribution and manufacturing, for nmDMD and any of our other product candidates that may receive marketing authorization or any additional indications or territories in which we receive authorization to market Translarna;
- the costs, timing and outcome of regulatory review of our other product candidates and Translarna in other territories or for indications other than nmDMD;
- the timing and scope of growth in our employee base;
- the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials for Translarna for additional indications and for our other product candidates;
- revenue received from commercial sales of Translarna or any of our other product candidates;
- our ability to successfully negotiate adequate pricing and reimbursement processes on a timely basis, or at all, in the countries in which we may obtain regulatory approval, including the countries in the EEA;

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- our ability to obtain additional and maintain existing reimbursed named patient and cohort EAP programs for Translarna for the treatment of nmDMD on adequate terms, or at all;
- the costs of preparing, filing and prosecuting patent applications, maintaining, and protecting our intellectual property rights and defending against intellectual property-related claims;
- the extent to which we acquire or invest in other businesses, products, product candidates, and technologies, including the success of any acquisition, in-licensing or other strategic transaction we may pursue, including our planned acquisition of Emflaza, and the costs of subsequent development requirements and commercialization efforts; and
- our ability to establish and maintain collaborations, including our collaborations with Roche and the SMA Foundation, and our ability to obtain research funding and achieve milestones under these agreements.

Conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain regulatory approval and achieve product sales for certain product candidates or indications. In addition, our product candidates, if approved, may not achieve commercial success, including Translarna for the treatment of nmDMD.

To date all of our product revenue has been attributable to sales of Translarna for the treatment of nmDMD in territories outside of the United States. We are continuing to engage in significant commercialization efforts for this product. In order to continue sales and our commercial launch of Translarna, we must maintain our marketing authorization in the EEA and secure market access through commercial programs following the conclusion of pricing and reimbursement terms at sustainable levels in the member states of the EEA or through EAP programs in the EEA and other territories. Other commercial revenue, if any, would be derived from product acquisitions or, if none, from sales of products that we are not planning to have commercially available for several years, if at all. If our marketing authorization in the EEA is not renewed, or our product label is materially restricted, we would lose all, or a significant portion of, our ability to generate revenue from sales of Translarna for the treatment of nmDMD, whether pursuant to a commercial or an EAP program and throughout all territories.

Accordingly, we will need to continue to rely on additional financing in connection with our continuing operations and to achieve our business objectives. In addition, we may seek additional capital due to favorable market conditions or based on strategic considerations, even if we believe that we have sufficient funds for our current or future operating plans. Additional financing may not be available to us on acceptable terms or at all. If we are unable to raise capital when needed or on attractive terms, we could be forced to delay, reduce or eliminate our research and development programs or our commercialization efforts.

We may engage in strategic transactions to acquire assets, businesses, or rights to products, product candidates or technologies or form collaborations or make investments in other companies or technologies that could harm our operating results, dilute our stockholders' ownership, increase our debt, or cause us to incur significant expense.

As part of our business strategy, we may engage in strategic transactions to expand and diversify our product pipeline, including through the acquisition of assets, businesses, or rights to products, product candidates or technologies or through strategic alliances or collaborations. We may not identify suitable strategic transactions, or complete such transactions in a timely manner, on a cost-effective basis, or at all. Moreover, we may devote resources to potential opportunities that are never completed or we may incorrectly judge the value or worth of such opportunities. Even if we successfully execute a strategic transaction, we may not be able to realize the anticipated benefits of such transaction, may incur additional debt or assume unknown or contingent liabilities in connection therewith, and may experience losses related to our investments in such transactions. Integration of an acquired company or assets into our existing business may not be successful and may disrupt ongoing operations, require the hiring of additional personnel and the implementation of additional internal systems and infrastructure, and require management resources that would otherwise focus on developing our existing business. Even if we are able to achieve the long-term benefits of a strategic transaction, our expenses and short-term costs may increase materially and adversely affect our liquidity. Any of the foregoing could have a detrimental effect on our business, results of operations and financial condition.

In addition, future strategic transactions may entail numerous operational, financial and legal risks, including:

- incurrence of substantial debt, dilutive issuances of securities or depletion of cash to pay for acquisitions;
- exposure to known and unknown liabilities, including possible intellectual property infringement claims, violations of laws, tax liabilities and commercial disputes;

- higher than expected acquisition and integration costs;
- difficulty in integrating operations and personnel of any acquired business;
- increased amortization expenses or, in the event that we write-down the value of acquired assets, impairment losses;

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- impairment of relationships with key suppliers or customers of any acquired business due to changes in management and ownership;
- inability to retain personnel, customers, distributors, vendors and other business partners integral to an in-licensed or acquired product, product candidate or technology;
- potential failure of the due diligence processes to identify significant problems, liabilities or other shortcomings or challenges;
- entry into indications or markets in which we have no or limited direct prior development or commercial experience and where competitors in such markets have stronger market positions; and
- other challenges associated with managing an increasingly diversified business.

If we are unable to successfully manage any strategic transaction in which we may engage, our ability to develop new products and continue to expand and diversify our product pipeline may be limited.

Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings; debt financings; collaborations; strategic alliances; grants and clinical trial support from governmental and philanthropic organizations and patient advocacy groups in the disease areas addressed by our product candidates; and marketing, distribution or licensing arrangements.

To the extent that we raise additional capital through the sale of equity or convertible debt securities, our shareholders' ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates; or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Our limited operating history may make it difficult for our stockholders to evaluate the success of our business to date and to assess our future viability.

Since mid-2014, we have been transitioning from a company with a research and development focus to a company capable of supporting global commercial activities. We may not be successful in completing this transition. Our ability to develop product candidates, manufacture a commercial scale product or arrange for a third party to do so on our behalf, and conduct sales and marketing activities necessary for a successful full scale product commercialization is largely limited to our activities with respect to the marketing authorization in the EEA for Translarna for the treatment of nmDMD, which is subject to annual review and renewal following reassessment of the benefit-risk balance of the authorization by the EMA and satisfaction of the specific obligation to conduct and report to the EMA Study 041. In addition, other than our marketing authorization in the EEA and the marketing authorizations granted in Israel and South Korea (which are largely contingent upon continued EMA approval), we have not proven our ability to successfully obtain marketing authorizations to sell our product or product candidates. Further, we recently announced that we are discontinuing our current clinical development of Translarna for nmCF based on the results of ACT CF, and we may not successfully complete development of other product candidates. Consequently, any predictions our stockholders make about our future success or viability may not be as accurate as they could be if we had a longer operating history. In addition, as a new business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors.

Our ability to use our net operating losses and certain other tax attributes may be subject to annual limitations under federal and state tax law that could materially affect our ability to utilize such losses and attributes.

If a corporation undergoes an "ownership change" within the meaning of Section 382 of the Internal Revenue Code, or Section 382, the corporation's ability to utilize any net operating losses, or NOLs, and certain tax credits and other

attributes generated before such an ownership change, is limited. We believe that we have in the past experienced ownership changes within the meaning of Section 382 that have resulted in limitations under Section 382 (and similar state provisions) on the use of our NOLs and other tax attributes.

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Future changes in ownership could result in additional ownership changes within the meaning of Section 382 that could further limit our ability to utilize our NOLs and certain other tax attributes.

Changes in our effective income tax rates could adversely affect our results of operations.

We are subject to income taxes in the Unites States and various foreign jurisdictions. Taxes will be incurred as income is earned among these different jurisdictions. Various factors may have favorable or unfavorable effects on our effective income tax rate. These factors include, but are not limited to, interpretations of existing tax laws, changes in tax laws and rates, the accounting for stock options and other share-based compensation, changes in accounting standards, future levels of research and development spending, changes in the mix and level of pre-tax earnings by taxing jurisdiction, the outcome of examinations by the U.S. Internal Revenue Service and other jurisdictions, the accuracy of our estimates for unrecognized tax benefits, the realization of deferred tax assets, or by changes to our ownership or capital structure. The impact on our income tax provision resulting from the above-mentioned factors and others may be significant and could adversely affect our results of operations.

In addition, there is growing pressure in many jurisdictions (including the United States) and from multinational organizations such as the Organization for Economic Co-operation and Development, or OECD, and the EU, to amend existing international tax rules in order to render them more responsive to current global business practices. For example, the OECD has released guidance relating to various international tax related topics in an initiative referred to as Base Erosion and Profit Shifting, or BEPS, that aims to standardize and modernize global tax policy. Depending on the final form of the BEPS guidance and the legislation ultimately enacted by the OECD members, BEPS could have material adverse consequences on our effective tax rate, the amount of tax we pay and on our financial position and results of operations.

In addition, some members of the U.S. Congress have recently begun publicly considering potential tax reform, including the possibility of replacing large parts of the existing federal income tax with a so-called “destination-based cash flow tax” in addition to other potential tax reforms that the recently elected President and members of his administration may be considering.

Although we monitor these developments, it is very difficult to assess to what extent these changes may be implemented in the United States and other jurisdictions in which we conduct our business or may impact the way in which we conduct our business or our effective tax rate due to the unpredictability and interdependency of these potential changes. Changes in tax laws and related regulations and practices could have a material adverse effect on our business operations, effective tax rate and financial position and results of operations.

Risks Related to the Development and Commercialization of our Product and our Product Candidates

ACT DMD did not meet its primary efficacy endpoint, and there is substantial risk that regulators will not agree with our interpretation of the results of ACT DMD and the totality of clinical data from our trials in Translarna for the treatment of nmDMD, which would have a material adverse effect on our business, financial performance and results of operations.

In October 2015, we announced that the primary efficacy endpoint in the ITT population did not achieve statistical significance in ACT DMD. On the basis of our position that the totality of clinical data from ACT DMD and our prior Phase 2b trial support the clinical benefit of Translarna for the treatment of nmDMD, we submitted our analyses of the ACT DMD data and meta-analysis of the combined ACT DMD and Phase 2b subgroup data to the FDA, as part of our NDA.

On February 22, 2016, we received a Refuse to File letter from the FDA stating that, in the view of the FDA, both our Phase 2b and Phase 3 ACT DMD trials were negative and do not provide substantial evidence of effectiveness. Additionally, the FDA stated that we had proposed a post-hoc adjustment of ACT DMD that eliminates data from a majority of enrolled patients. In addition, the FDA noted that our NDA does not contain adequate information regarding the abuse potential of Translarna. In October 2016, the FDA denied our first appeal of the Refuse to File letter. In the first quarter of 2017, we filed our Translarna NDA for nmDMD with the FDA via the “file over protest” process that allows a company to have its NDA filed and reviewed when there is a disagreement with regulators over the acceptability of the NDA submission. When an application is filed over protest, the FDA is required to review the application as filed. Generally, the FDA does not favor the file over protest procedure and the agency’s policies explain that an application filed over protest does not receive a timeline for review and is designated as a standard review. The

FDA has granted a standard review for the NDA and has set a target review date under the Prescription Drug User Fee Act, or PDUFA, of October 24, 2017. The PDUFA date is the goal date for the FDA to complete its review of the NDA, however, such date is not binding on the agency and there can be no assurance that the FDA will complete its review of our NDA by the PDUFA goal date.

There is substantial risk that, notwithstanding any dialogue we have had or any further dialogue we may be able to initiate with the agency, pursuant to the file over protest process or otherwise, the FDA will continue to disagree with our interpretation of the results of ACT DMD and the totality of clinical data from our trials. Even if we are successful in resolving some or all of

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the matters raised by the FDA in the Refuse to File letter, there is significant risk that we will be unable to obtain FDA approval of Translarna for nmDMD, on a timely basis or at all, and we may be required to perform additional clinical and non-clinical trials or complete additional analyses at significant cost. Even if we are able to enroll and fund any such additional trials or complete such analyses, there is substantial risk that the results would not ultimately support the approval of the NDA filed over protest or a new NDA submission in the United States for Translarna for nmDMD. In addition, any such requirement for additional trials would most likely result in our inability to sell Translarna in the United States for a significant period of time, which would have a material adverse effect on our ability to generate revenue from the sales of Translarna for the treatment of nmDMD. Due to these uncertainties, we are unable to estimate the timing or potential for a launch of Translarna for the treatment of nmDMD in the United States.

We also submitted our analyses of the ACT DMD data and meta-analyses of the combined ACT DMD and Phase 2b subgroup data to the EMA to support continuation of our marketing authorization in the EEA, which is subject to annual review and renewal by the European Commission following reassessment by the EMA of the benefit-risk balance of the authorization. The EMA and European Commission did not approve our request for full marketing authorization of Translarna for the treatment of nmDMD and, instead, approved the annual renewal of our conditional marketing authorization with the specific obligation to confirm the efficacy and safety of Translarna for the treatment of nmDMD in ambulatory patients aged 5 years or older via Study 041.

Enrolling, conducting and reporting a clinical trial is a time-consuming, expensive and uncertain process that takes years to complete, and we expect that we will incur material costs related to the implementation and conduct of Study 041. We expect that conducting a placebo-controlled trial in nmDMD of this size will be challenging and it is probable that we will enroll patients in territories where Translarna has already become available on a reimbursed basis, which could negatively impact growth in our product sales. We may enroll patients in countries with a different standard of care for nmDMD patients or at clinical trial sites that are inexperienced with clinical trials in general, or specifically with nmDMD trials. In addition, we may experience unknown complications with Study 041 and may not achieve the pre-specified endpoint with statistical significance, which would have a material adverse effect on our ability to maintain our marketing authorization in the EEA.

The marketing authorization renewal approved in January 2017 is effective through August 5, 2017, unless extended. If the EMA determines in any annual renewal cycle that the balance of benefits and risks of using Translarna for the treatment of nmDMD has changed materially or that we have not or are unable to comply with any conditions that have been or may be placed on the marketing authorization, the European Commission could, at the EMA's recommendation, vary, suspend, withdraw or refuse to renew the marketing authorization for Translarna or require the imposition of other conditions or restrictions. As such, there is ongoing risk to our ability to maintain our marketing authorization in the EEA.

Our current ability to generate revenue from sales of Translarna is dependent upon our ability to maintain our marketing authorization in the EEA of Translarna for the treatment of nmDMD in ambulatory patients aged five years and older. If we are unable to renew our EEA marketing authorization during any annual renewal cycle, or if our product label is materially restricted, we would lose all, or a significant portion of, our ability to generate revenue from product sales, whether pursuant to a commercial or an EAP program, which would have a material adverse effect on our business, results of operations and financial condition.

There is substantial risk that other regulators where we have not yet sought or are currently seeking marketing authorization will not agree with our interpretation of the results of ACT DMD and the totality of clinical data from our trials in Translarna for the treatment of nmDMD, which would have a material adverse effect on our ability to generate revenue from the sales of Translarna for the treatment of nmDMD in those applicable territories. In addition, we may not be able to maintain or obtain marketing authorizations in areas where such authorizations are contingent upon decisions of the EMA with respect to our marketing authorization in the EEA.

For additional information, see "Risks Related to Regulatory Approval of our Product and our Product Candidates" below.

We depend heavily on the success of our lead product, Translarna, which we are developing for nmDMD and other indications. All of our other product candidates, including those under our collaboration with Roche and the SMA Foundation, are still in early clinical or preclinical development. If we are unable to execute our commercial strategy

for Translarna for the treatment of nmDMD in the EEA, fail to receive regulatory approval in the United States and other territories, fail to obtain renewal of, or satisfy the conditions of our marketing authorization in the EEA, or if we experience significant delays in accomplishing such goals, our business will be materially harmed.

We have invested a significant portion of our efforts and financial resources in the development of Translarna for nmDMD and nmCF. Our ability to generate product revenues will depend heavily on the successful development and commercialization of Translarna.

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On March 2, 2017, we announced that the primary and secondary endpoints were not achieved in ACT CF and that, as a result, we plan to discontinue our current clinical development of Translarna for nmCF. We have withdrawn our type II variation submission with the EMA, which sought approval of Translarna for the treatment of nmCF in the EEA, and do not currently expect to pursue other marketing authorizations for this indication.

While we have obtained marketing authorization for Translarna for the treatment of nmDMD in the EEA, such authorization is subject to annual review and renewal by the European Commission following the annual EMA reassessment as well as the specific obligation to conduct and submit the results of Study 041. For a review of recent developments that have had, and may continue to have, a material adverse effect on our ability to commercialize Translarna for the treatment of nmDMD, please review the risk factor titled, "ACT DMD did not meet its primary efficacy endpoint, and there is substantial risk that regulators will not agree with our interpretation of the results of ACT DMD and the totality of clinical data from our trials in Translarna for the treatment of nmDMD, which would have a material adverse effect on our business, financial performance and results of operations"

We are currently pursuing further clinical development efforts for Translarna for the treatment of nmDMD, nonsense mutation aniridia, nonsense mutation MPS I, and nonsense mutation CDKL5/Dravet syndrome. Each genetic disorder has unique genetic and pathophysiological characteristics and we believe that regulators, including the FDA and the EMA, will evaluate the effectiveness of Translarna for any given indication based on the merits of the clinical efficacy evidence available for such indication. However, because we are developing Translarna for the treatment of multiple indications associated with genetic disorders that arise as a result of a nonsense mutation, there is a risk that negative results in a clinical trial evaluating the efficacy of Translarna for one indication, such as ACT CF, could adversely affect the perception of the efficacy of Translarna in a different indication. There can be no assurance that regulators, including the FDA and the EMA, will not consider such results when making determinations with respect to our ongoing or future regulatory submissions for marketing authorization of Translarna for any indication, including in connection with the FDA's review of our NDA (which was filed over protest with the FDA in the first quarter of 2017) for Translarna for the treatment of nmDMD and the EMA's annual reassessment of our marketing authorization for Translarna for the treatment of nmDMD, which could have an adverse effect on the outcome of the applicable regulatory review. We intend to submit the safety results of ACT CF to regulators with any applicable safety updates and submissions, including the EMA. While the safety profile of Translarna in the ACT CF study was consistent with previous studies and no new safety signals were identified, there can be no assurance that the EMA or other regulators will agree with our interpretation of the safety data from the trial.

If we do not successfully renew and maintain our marketing authorization and commercialize Translarna in the EEA, or receive regulatory approval in the United States for Translarna for the treatment of nmDMD and subsequently successfully commercialize Translarna in the United States, our ability to generate additional revenue will be jeopardized and, consequently, our business will be materially harmed.

The success of Translarna will depend on a number of additional factors, including the following:

- whether we are able to continue to satisfy our obligations under, and maintain, the marketing authorization in the EEA for Translarna for the treatment of nmDMD, including whether the EMA determines on an annual basis that the benefit-risk balance of Translarna supports renewal of our marketing authorization in the EEA, on the current approved label;
- the costs, timing and outcome of Study 041;
- whether, and within what timeframe, we are able to advance Translarna for the treatment of nmDMD in the United States, pursuant to the file over protest process with the FDA or otherwise, and including, whether we will be required to perform additional clinical and non-clinical trials or complete additional analyses at significant cost which, if successful, may enable FDA review of an NDA submission by us and, ultimately, may support approval of Translarna for nmDMD in the U.S.;
- the successful advancement of Translarna in additional indications, in particular, nmMPS I, nonsense mutation aniridia, and nonsense mutation Dravet syndrome/CDKL5;
- the maintenance and expansion of an international commercial infrastructure capable of supporting product sales, marketing, and distribution of Translarna;
-

the implementation and maintenance of marketing and distribution relationships with third parties in territories where we do not pursue direct commercialization;

- our ability to obtain additional and maintain existing reimbursed named patient and cohort EAP programs for Translarna for the treatment of nmDMD on adequate terms;

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- our ability to successfully prepare and advance regulatory submissions for marketing authorizations for Translarna in additional territories and for additional or expanded indications and whether and in what timeframe we may obtain such authorizations;
- successful negotiation of adequate pricing and reimbursement terms for Translarna on a timely basis, or at all, in the countries which require such negotiation and in which we obtain regulatory approval;
- the ability and willingness of patients and healthcare professionals to access Translarna through alternative means if pricing and reimbursement negotiations in the applicable territory do not have a positive outcome;
- the timing and scope of commercial launches of Translarna in nmDMD;
- our ability to establish and maintain commercial manufacturing arrangements with third party manufacturers;
- the ability of our third-party manufacturers to successfully produce commercial and clinical supplies of Translarna on a timely basis sufficient to meet the needs of our commercial and clinical activities;
- successful identification of eligible patients;
- acceptance of Translarna for the treatment of nmDMD by patients, the medical community and third-party payors, including any impact the results of ACT CF may have on the perception of the effectiveness of Translarna;
- effectively competing with other therapies;
- a continued acceptable safety profile of Translarna;
- obtaining and maintaining patent and trade secret protection and regulatory exclusivity; and
- protecting our rights in our intellectual property portfolio.

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to continue to commercialize Translarna, which would have a material adverse effect on our business, results of operations and financial condition.

The marketing authorization granted by the European Commission for Translarna for the treatment of nmDMD is limited to ambulatory patients aged five years and older located in the EEA, which significantly limits an already small treatable patient population, which reduces our commercial opportunity and is also subject to annual reassessment of the benefit-risk balance by the EMA as well as the specific obligation to conduct Study 041, and may be varied, suspended or withdrawn by the European Commission if we fail to satisfy those requirements.

We have obtained orphan drug designations from the EMA and from the FDA for Translarna for the treatment of nmDMD because the number of patients who could benefit from treatment with Translarna is small. The marketing label approved by the European Commission further limits the currently treatable patient population to ambulatory nmDMD patients aged five years and older who have been identified through genetic testing as having a nonsense mutation. Prevalence estimates for rare diseases are uncertain due to the uncertainties associated with the methodologies used to derive estimates, such as epidemiology assumptions. It can take many years of experience in rare disease market places before prevalence becomes well characterized. We are launching the first therapy specifically aimed at nmDMD patients. Our experience to date suggests that there may be up to 7,000 nmDMD patients globally and that approximately 35 to 40% of such patients satisfy the conditions for treatment under our current product label in the EEA, however, we expect that country specific epidemiology will continue to be refined and characterized over the coming years. Our estimates of both the number of people who have DMD caused by a nonsense mutation, as well as the subset of people with nmDMD who are ambulatory and at least five years old (and, therefore, satisfy the conditions for treatment under our current product label in the EEA), are based on our beliefs and estimates derived from a variety of sources and may prove to be incorrect. Prevalence estimates vary given some degree of variation in the incidence of live male births, the incidence of DMD, the incidence of nonsense mutations and other factors. Information concerning the eligible patient population is generally limited to certain geographies and may not employ definitive measures capable of establishing with precision the actual number of nmDMD patients in such geography. If the market opportunities for Translarna for the treatment of nmDMD are smaller than we believe they are, our business and anticipated revenues will be negatively impacted. Although we intend to seek to expand the approved product label of Translarna for the treatment of nmDMD in the future, the timing of, and our ability to generate, the necessary data or results required to obtain expanded regulatory approval is currently uncertain. Given the small number of patients who have nmDMD, and the smaller number of patients who meet the criteria for treatment under our current marketing authorization, our commercial opportunity is limited. It is critical to the

commercial success of Translarna for nmDMD that we successfully identify and treat these patients.

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Translarna is not approved, and is an investigational new drug, in the United States. In order to continue to generate revenue from Translarna, we must maintain our marketing authorization in the EEA for Translarna for the treatment of nmDMD in ambulatory patients aged five years and older. The marketing authorization in the EEA is subject to annual review and renewal by the European Commission following reassessment by the EMA of the benefit-risk balance of the authorization, which we refer to as the annual EMA reassessment, as well as the specific obligation to complete and report the results of Study 041 to the EMA. The marketing authorization was last renewed in January 2017 and is effective, unless extended, through August 5, 2017. Enrolling Study 041 may further reduce the number of patients available for reimbursed treatment.

If the EMA determines in any annual renewal cycle that the balance of benefits and risks of using Translarna for the treatment of nmDMD has changed materially or that we have not or are unable to comply with any conditions that have been or may be placed on the marketing authorization, the European Commission could, at the EMA's recommendation, vary, suspend, withdraw or refuse to renew the marketing authorization for Translarna or require the imposition of other conditions or restrictions. As such, there is ongoing risk to our ability to maintain our marketing authorization in the EEA. If we are unable to renew our marketing authorization in the EEA during any annual renewal cycle, or if our product label is materially restricted, we would lose all, or a significant portion of, our ability to generate revenue from product sales, whether pursuant to a commercial or an EAP program, and in all territories, which would have a material adverse effect on our business, results of operations and financial condition. See "Risks Related to Regulatory Approval of our Product and our Product Candidates" below for further detail regarding conditional marketing authorizations in the EEA.

If clinical trials of our product or product candidates fail to demonstrate safety and efficacy to the satisfaction of the EMA, the FDA or other regulators, or do not otherwise produce favorable results, we may experience delays in completing, or ultimately be unable to complete, the development and commercialization of Translarna or any other product candidate.

In connection with seeking marketing authorization from regulatory authorities for the sale of any product candidate, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of testing. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing authorization of their products.

On March 2, 2017, we announced that the primary and secondary endpoints were not achieved in ACT CF and that, as a result, we plan to discontinue our current clinical development of Translarna for nmCF. We have withdrawn our type II variation submission with the EMA, which sought approval of Translarna for the treatment of nmCF in the EEA, and do not currently expect to pursue other marketing authorizations for this indication.

In addition, the primary efficacy endpoint in the ITT population did not achieve statistical significance in the Phase 2b (completed in 2009) or Phase 3 ACT DMD (completed in 2015) clinical trials of Translarna for the treatment of nmDMD. For a review of recent developments that have had, and may continue to have, a material adverse effect on our ability to commercialize Translarna for the treatment of nmDMD, please review the risk factor titled, "ACT DMD did not meet its primary efficacy endpoint, and there is substantial risk that regulators will not agree with our interpretation of the results of ACT DMD and the totality of clinical data from our trials in Translarna for the treatment of nmDMD, which would have a material adverse effect on our business, financial performance and results of operations."

If the FDA, the EMA and other regulators do not agree with our interpretation of the results of the clinical data from our trials, including ACT DMD and, when and if completed, Study 041 and related analyses, or otherwise do not view the results of these trials as favorable; if we are required to conduct additional clinical trials or other testing of Translarna or any other product candidate that we develop beyond those that we contemplate; if we are unable to successfully complete our clinical trials or other testing; if the results of these trials or tests are not positive or are only

modestly positive; or if there are safety concerns, we may, among other things:

- be unable to successfully maintain our marketing authorization in the EEA for Translarna for the treatment of nmDMD, which is subject to annual review and renewal following reassessment of the benefit-risk balance of the authorization by the EMA;
- be delayed in obtaining additional marketing authorizations, or not obtain additional marketing authorizations at all, for Translarna for the treatment of nmDMD;
- be delayed in obtaining marketing authorizations, or not obtain marketing authorizations at all, for Translarna for other indications, or for our other product candidates;

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- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings, including boxed warnings;
- be subject to additional post-marketing testing requirements or restrictions;
- have the product removed from markets after obtaining applicable marketing authorizations; or
- not be permitted to sell Translarna under some or any reimbursed EAP programs.

If we or our collaborators experience any of a number of possible unforeseen events in connection with clinical trials related to our product or product candidates, including Study 041 and those under our collaboration with Roche and the SMA Foundation, maintenance of our existing marketing authorization in the EEA and any additional potential marketing authorization or commercialization of our product or product candidates could be delayed or prevented.

We or our collaborators may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing authorization or commercialize our product or product candidates, including:

- clinical trials of our product or product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- the number of patients required for clinical trials of our product and product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate;
- we may be unable to enroll a sufficient number of patients in our clinical trials to ensure adequate statistical power to detect any statistically significant treatment effects;
- we may enroll patients at clinical trial sites in countries that are inexperienced with clinical trials in general, or with the indication that is the subject of the trial;
- we may enroll patients at clinical trial sites in countries that have a different standard of care for patients in general, or with respect to the indication that is the subject of the trial;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- regulators, institutional review boards or independent ethics committees may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site or may require us to submit additional data, conduct additional studies or amend our investigational new drug application, or IND, or comparable application prior to commencing a clinical trial;
- we may have delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- we may have to suspend or terminate clinical trials of our product or product candidates for various reasons, including a finding that the participants are being exposed to unacceptable health risks;
- regulators, institutional review boards or independent ethics committees may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;
- the cost of clinical trials of our product or product candidates may be greater than we anticipate;
- the supply or quality of our product or product candidates or other materials necessary to conduct clinical trials of our product or product candidates may be insufficient or inadequate; or
- our product or product candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators, institutional review boards or independent ethics committees to suspend or terminate the trials.

For example, the Phase 2 Moonfish study, which was evaluating the safety and efficacy of RG7800 under our SMA collaboration, was terminated in December 2016 following a suspension and clinical hold in the first half of 2015 to investigate

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an eye finding in a 39-week study in cynomolgus monkeys. The suspension and termination of Moonfish resulted in unanticipated delays in the advancement of the SMA program.

In addition, based on pre-clinical safety signals observed during the third quarter of 2015, we are no longer advancing PTC672 under our antibacterial program. Our product development costs will increase if we experience delays in testing or marketing authorizations. We do not know whether any preclinical tests or clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant preclinical or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product or product candidates, allow our competitors to bring products to market before we do, or impair our ability to successfully commercialize our product or product candidates, and so may harm our business, results of operations and financial condition.

Our conclusions regarding the activity and potential efficacy of Translarna in nmDMD are primarily based on retrospective, subgroup and meta-analyses of the results of our Phase 2b and ACT DMD clinical trials of Translarna for the treatment of nmDMD. Other than with respect to certain of our meta-analyses, results of our analyses are expressed as nominal p-values, which are generally considered less reliable indicators of efficacy than adjusted p-values. In addition, retrospective analyses are generally considered less reliable than pre-specified analyses.

After determining that we did not achieve the primary efficacy endpoint with the pre-specified level of statistical significance in our completed ACT DMD and Phase 2b clinical trials of Translarna for the treatment of nmDMD, we performed subgroup, retrospective, and meta-analyses. On the basis of our position that the totality of clinical data from these trials support the clinical benefit of Translarna for the treatment of nmDMD, we submitted these analyses to the FDA, as part of our NDA. In addition, after determining that the primary efficacy endpoint did not achieve statistical significance in ACT DMD or our Phase 2b clinical trial of Translarna for the treatment of nmDMD, we performed retrospective and subgroup analyses that we believe provide strong support for concluding that Translarna was active and showed clinically meaningful improvements over placebo in these trials.

Although we believe that these additional analyses of the results of these trials were warranted, a retrospective analysis performed after unblinding trial results can result in the introduction of bias if the analysis is inappropriately tailored or influenced by knowledge of the data and actual results.

Some of our favorable statistical data from these trials also are based on nominal p-values that reflect only one particular comparison when more than one comparison is possible. A p-value is called nominal if it is the result of one particular comparison prior to any pre-specified multiplicity adjustment, such as when two active treatments are compared to placebo or when two or more subgroups are analyzed. For example, while the p-values for change from baseline at week 48 in the 6-minute walk test, or 6MWT, which we also refer to as 6-minute walk distance, or 6MWD, and each secondary end point timed function test in the pre-specified subgroup of ACT DMD patients with a baseline 300-400 meter 6MWD had p-values of less than 0.05, due to the sequential testing method, these p-values are considered nominal.

Typically, a trial result is statistically significant if the chance of it occurring when the treatment is like placebo is less than one in 20, resulting in a p-value of less than 0.05. Nominal p-values cannot be compared to the typical significance level (p-value less than 0.05) to determine statistical significance without being adjusted for the testing of multiple dose groups, end points or analyses of subgroups.

Because of these limitations, regulatory authorities typically give greater weight to results from pre-specified analyses and adjusted p-values and less weight to results from post-hoc, retrospective analyses and nominal p-values.

On February 22, 2016, we received a Refuse to File letter from the FDA stating that, in the view of the FDA, both the Phase 2b and Phase 3 ACT DMD trials were negative and do not provide substantial evidence of effectiveness and that our NDA does not contain adequate information regarding the abuse potential of Translarna. Additionally, the FDA stated that we had proposed a post-hoc adjustment of ACT DMD that eliminates data from a majority of enrolled patients. Our reliance on nominal p-values for some of our statistical data and our use of retrospective analyses had a negative impact on the FDA’s view of our interpretation of the results of our Phase 2b trial, ACT DMD and the totality of data from our clinical trials.

Although we recently filed our NDA over protest with the FDA, there is substantial risk that, notwithstanding any dialogue we have had or any further dialogue we may be able to initiate with the agency, pursuant to the file over

protest process or otherwise, the FDA will continue to disagree with our interpretation of the results of ACT DMD and the totality of clinical data from our trials. Even if we are successful in resolving some or all of the matters raised by the FDA in the Refuse to File letter, there is significant risk that we will be unable to obtain FDA approval of Translarna for nmDMD, on a timely basis or at all, and we may be required to perform additional clinical and non-clinical trials or complete additional analyses at significant cost. Even if we are able to enroll and fund any such additional trials or complete such analyses, there is substantial risk that the results would not ultimately support the approval of the NDA filed over protest or a new NDA submission in the United States for Translarna for nmDMD. In addition, any such requirement for additional trials would most likely result in our inability to

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sell Translarna in the United States for a significant period of time, which would have a material adverse effect on our ability to generate revenue from the sales of Translarna for the treatment of nmDMD.

Our reliance on nominal p-values for some of our statistical data and our use of retrospective analyses has also had a negative impact on the EMA's evaluation of our last application for continued marketing authorization for Translarna for the treatment of nmDMD, including delays in timing of the CHMP's opinion with respect to the annual renewal of our marketing authorization, and could negatively impact regulatory determinations by regulators in other territories. An unfavorable view of our data and analyses by the FDA and EMA for Translarna has and could continue to negatively impact our ability to obtain or maintain authorizations to market Translarna for the treatment of nmDMD. An inability to obtain new marketing authorizations or maintain our current marketing authorization in the EEA would have a material adverse effect on our revenue from Translarna and would materially harm our business, financial results and results of operations.

Because we are developing our product and our product candidates for the treatment of diseases in which there is little clinical experience and, in some cases, using new endpoints or methodologies, there is increased risk that the outcome of our clinical trials will not be favorable.

There are no marketed therapies approved to treat the underlying cause of nmDMD. In addition, there has been limited historical clinical trial experience generally for the development of drugs to treat nmDMD and other diseases that we are studying or have studied, including, nmCF, nmMPS I, nonsense mutation aniridia, and nonsense mutation Dravet syndrome/CDKL5. As a result, the design and conduct of clinical trials for these diseases, particularly for drugs to address the underlying nonsense mutations causing these diseases in some subsets of patients, is subject to increased risk.

For example, on March 2, 2017, we announced that the primary and secondary endpoints were not achieved in ACT CF, our Phase 3 clinical for Translarna in nmCF and that, as a result, we plan to discontinue our current clinical development of Translarna for nmCF.

Prior to the Phase 2b clinical trial of Translarna for nmDMD, there was no precedent of an established trial design to evaluate the efficacy of Translarna in nmDMD over a 48 week duration. In addition, clinical understanding of the methodologies used to analyze the resulting data were also limited. The study design and enrollment criteria for ACT DMD were based on available natural history data of the disease, including third party data and results from our Phase 2b clinical trial. An evolving understanding in the DMD community has led to a greater appreciation of the optimal window for the 6MWT in assessing physical function. We believe that this factor may have led to the primary efficacy endpoint in the intent to treat population not achieving statistical significance in ACT DMD.

We are faced with similar challenges in connection with the design of our studies of Translarna in nmMPS I, nonsense mutation aniridia, and nonsense mutation Dravet syndrome/CDKL5 because there is also limited historical clinical trial experience for the development of drugs to treat the underlying cause of these disorders.

For example, with respect to nmMPS I, while clinical trials of enzyme replacement therapies conducted by third party sponsors have provided some insight into the disorder, enzyme replacement therapies do not sufficiently address the central nervous system, skeletal or cardiac symptoms associated with the disorder. In addition, our own pre-clinical and early stage clinical trials targeting nmMPS I have been limited in duration and, as a result, it is substantially uncertain whether our clinical design will optimize the duration or level of dosing or that we will be able to demonstrate a statistically significant biochemical or clinical effect in the primary or secondary pre-specified endpoints selected for the study.

If we experience delays or difficulties in the enrollment of patients in our clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.

We may not be able to initiate or continue clinical trials for our product candidates, including Study 041 or our Phase 2 studies of Translarna in nmMPS I, nonsense mutation aniridia, or nonsense mutation Dravet syndrome/CDKL5, if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials. The studies under our SMA collaboration face similar risks.

Each of the indications we are currently pursuing are characterized by relatively small patient populations, which could result in slow enrollment of clinical trial participants. The feasibility of patient enrollment was a critical factor discussed with the EMA in connection with the specific obligation to conduct Study 041, in particular due to factors

that increase the challenges of enrollment, such as the small nmDMD patient population, the patient eligibility criteria for the mITT for Study 041, and the fact that Translarna is available to patients in the EEA and other limited territories pursuant to commercial and EAP programs.

In addition, our competitors have ongoing clinical trials for product candidates that could be competitive with our product candidates. As a result, potential clinical trial sites may elect to dedicate their limited resources to participation in our

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competitors' clinical trials and not ours, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' product candidates.

Patient enrollment is affected by other factors including:

- severity of the disease under investigation;
- eligibility criteria for the study in question;
- perceived benefits and risks of the product candidate under study;
- efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment; and
- proximity and availability of clinical trial sites for prospective patients.

Enrollment delays in our clinical trials may result in increased development costs for our product candidates. Our inability to enroll a sufficient number of patients in Study 041 or our Phase 2 studies of Translarna in nmMPS I, nonsense mutation aniridia, and nonsense mutation Dravet syndrome/CDKL5 or any of our, or our collaboration partners', other clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether. As the conduct of Study 041 is a specific obligation to our marketing authorization in the EEA for Translarna for the treatment of nmDMD, any such delay or inability to enroll sufficient patients could have a material adverse effect on our ability to maintain our authorization in the EEA and, failure to maintain such authorization would have a material adverse effect on our business, results of operations and financial performance.

In addition, during the first quarter of 2015, we amended the study design for our proof-of-concept study for Translarna for the treatment of nmMPS I to include patients currently on enzyme replacement therapy, which contributed to delays in site initiation and patient accrual. Despite the protocol amendment, we have continued to encounter difficulties identifying qualified patients for this study.

If serious adverse or inappropriate side effects are identified during the development of Translarna or any other product candidate, we may need to abandon or limit our development of that product or product candidate.

Our product and our product candidates are in clinical or preclinical development and their risk of failure is high. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive regulatory approval. If our product or product candidates are associated with undesirable side effects or have characteristics that are unexpected, we may need to abandon their development or limit development to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a benefit-risk perspective. Many compounds that initially showed promise in clinical or earlier stage testing have later been found to cause side effects that prevented further development of the compound.

For example, although we did not observe a pattern of liver enzyme elevations in our Phase 2 or Phase 3 clinical trials of Translarna, we did observe modest elevations of liver enzymes in some subjects in one of our Phase 1 clinical trials. These elevated enzyme levels did not require cessation of Translarna administration, and enzyme levels typically normalized after completion of the treatment phase. We did not observe any increases in bilirubin, which can be associated with serious harm to the liver, in the Phase 1 clinical trial.

In addition, in Study 009, our first Phase 3 clinical trial of Translarna for the treatment of nmCF, five adverse events in the Translarna arm of the trial that involved the renal system led to discontinuation. As compared to the placebo group, the Translarna treatment arm also had a higher incidence of adverse events of creatinine elevations, which can be an indication of impaired kidney function. In the Translarna treatment arm, more severe clinically meaningful creatinine elevations were reported in conjunction with cystic fibrosis pulmonary exacerbations. These creatinine elevations were associated with concomitant treatment with antibiotics associated with impaired kidney functions, such as aminoglycosides or vancomycin. This led to the subsequent prohibition of concomitant use of Translarna and these antibiotics, which was successful in addressing this issue in the clinical trial.

Our focus on the discovery and development of product candidates that target post-transcriptional control processes is unproven, and we do not know whether we will be able to develop products of any, or sustained, commercial value.

Our scientific approach focuses on the discovery and development of product candidates that target post-transcriptional control processes. While a number of commonly used drugs and a growing body of research validate the importance of post-

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transcriptional control processes in the origin and progression of a number of diseases, no existing drugs have been specifically designed to alter post-transcriptional control processes in the same manner as Translarna or our other product candidates. As a result, our focus on targeting these processes may not result in the discovery and development of commercially viable drugs that safely and effectively treat genetic disorders or other diseases.

For example, on March 2, 2017, we announced that the primary and secondary endpoints were not achieved in ACT CF and that, as a result, we plan to discontinue our current clinical development of Translarna for nmCF. We have withdrawn our type II variation submission with the EMA, which sought approval of Translarna for the treatment of nmCF in the EEA.

In addition, although we have received marketing authorization by the European Commission for Translarna for the treatment of nmDMD, such marketing authorization is subject to the specific obligation to conduct and submit the results of Study 041 to the EMA and is also subject to annual review and renewal by the European Commission following reassessment of the benefit-risk balance of the authorization by the EMA. In 2016, the FDA refused to file our NDA for Translarna for the treatment of nmDMD, noting that both the Phase 2b and Phase 3 ACT DMD trials of Translarna for the treatment of nmDMD were negative and do not provide substantial evidence of effectiveness.

We may not be successful in renewing our marketing authorization for Translarna for the treatment of nmDMD in the EEA or in obtaining full regulatory approval for Translarna for the treatment of nmDMD or any indication or for any other potentially commercially viable drug that treats an approved indication by targeting a particular post-transcriptional control process. Furthermore, we may not receive regulatory approval for product candidates that target different post-transcriptional control processes. If we fail to develop and commercialize viable drugs, we will not achieve commercial success.

Translarna for the treatment of nmDMD, or any other product candidate that receives marketing authorization, if any, may fail to achieve the degree of market acceptance by physicians, patients, third party payors and others in the medical community necessary for commercial success.

Although Translarna is currently authorized by the EMA for marketing for the treatment of nmDMD such marketing authorization is subject to the specific obligation to conduct and submit the results of Study 041 to the EMA and is also subject to annual review and renewal by the European Commission following reassessment of the benefit-risk balance of the authorization by the EMA. Even if our marketing authorization in the EEA for Translarna for the treatment of nmDMD is maintained, or we are successful in obtaining marketing authorization for Translarna for other indications or territories or marketing authorization for any of our other product candidates, such product may nonetheless fail to gain sufficient market acceptance by physicians, patients, third party payors and others in the medical community. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenues or any profits from operations.

The degree of market acceptance of our product or product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy and potential advantages compared to alternative treatments;
- the prevalence and severity of any side effects;
- the ability to offer our product or product candidates for sale at competitive prices;
- convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support;
- sufficient third-party coverage or reimbursement; and
- any restrictions on concomitant use of other medications.

In addition, because we are developing Translarna for the treatment of different indications, negative results in a clinical trial evaluating the efficacy of Translarna for one indication, such as our recent ACT CF trial results, could have a negative impact on the perception of the efficacy of Translarna in a different indication, which could have an adverse effect on our commercialization efforts and financial results.

Our ability to negotiate, secure and maintain third-party coverage and reimbursement may be affected by political, economic and regulatory developments in the United States, the European Union and other jurisdictions, including Latin America. Governments continue to impose cost containment measures, and third-party payors are increasingly

challenging prices charged for medicines and examining their cost effectiveness, in addition to their safety and efficacy. These and other similar

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developments could significantly limit the degree of market acceptance of Translarna for the treatment of nmDMD or any of our other product candidates that receive marketing authorization.

If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell our product or product candidates, we may not be successful in our continuing efforts to commercialize Translarna or commercializing any other product candidate if and when they are approved.

Our experience in the sale and marketing of pharmaceutical products is limited to our activities under the marketing authorization in the EEA for Translarna for the treatment of nmDMD, which is subject to annual review and renewal following reassessment of the benefit-risk balance of the authorization by the EMA and satisfaction of the specific obligation to conduct Study 041. We may be unable to successfully execute our commercial strategy for Translarna for the treatment of nmDMD in other territories, including, if approved, in the United States, or for other indications or product candidates that may receive marketing authorization, if any.

Our ongoing commercial strategy for Translarna involves the development of a commercial infrastructure that spans multiple jurisdictions and is heavily dependent upon our ability to continue to build an infrastructure that is capable of implementing our global commercial strategy. International operations are subject to inherent risks. The establishment and development of our commercial infrastructure will continue to be expensive and time consuming, and we may not be able to develop our commercial organizations in all intended territories in a timely manner or at all. Doing so will require a high degree of coordination and compliance with laws and regulations in numerous jurisdictions, including restrictions on advertising practices, enforcement of intellectual property rights, restrictions on pricing or discounts, and unexpected changes in international regulatory requirements and tariffs. If we are unable to effectively coordinate such activities or comply with such laws and regulations, our ability to commercialize Translarna in those jurisdictions in which it is or may be approved will be adversely affected. If we are unable to establish and maintain adequate sales, marketing and distribution capabilities, whether independently or with third parties, we may not be able to generate product revenue consistent with our expectations and may not become profitable.

We have evaluated markets outside of the EEA to determine in which geographies we might, if approved, choose to commercialize Translarna ourselves and in which geographies we might choose to collaborate with third parties. We intend to continue to promote Translarna for the treatment of nmDMD in permitted territories using both internal and external resources.

There are risks involved with establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training an internal commercial team is expensive and time consuming and could delay our commercialization efforts for Translarna for the treatment of nmDMD or any other product launch. If the commercial launch of Translarna or any other product candidate for which we recruit a commercial team and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition such personnel.

The arrangements that we have entered into, or may enter into, with third parties to perform sales and marketing services will generate lower product revenues or profitability of product revenues to us than if we were to market and sell any products that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell and market our product candidates or may be unable to do so on terms that are favorable to us. We have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively.

If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

Factors that may materially affect our efforts to commercialize our products on our own include:

- our ability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- our ability to implement third party marketing and distribution relationships on favorable terms, or at all, in territories where we do not pursue direct commercialization;
- the ability of our commercial team to obtain access to or persuade adequate numbers of physicians to prescribe Translarna or any future products;
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the lack of complementary products to be offered by our commercial team, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and

- unforeseen costs and expenses associated with creating an independent commercial organization.

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Any of these factors, individually or as a group, if not resolved in a favorable manner may have a material adverse effect on our business and results of operations. Similar risks apply in those territories where Translarna is available on a reimbursed basis under an EAP program.

All of our sales of Translarna for the treatment of nmDMD currently occur in territories outside of the United States, which subjects us to additional business risks that could adversely affect our revenue and results of operations.

All of our revenue from sales of Translarna to date has been generated from countries other than the United States. We have operations in multiple European countries and other territories, including Latin America. We expect that we will continue to expand our international operations in the future, including in emerging growth markets, pending successful completion of the applicable regulatory processes. International operations inherently subject us to a number of risks and uncertainties, including:

- political, regulatory, compliance and economic developments that could restrict our ability to manufacture, market and sell our products;
- financial risks such as longer payment cycles, difficulty collecting accounts receivable and exposure to fluctuations in foreign currency exchange rates;
- difficulty in staffing and managing international operations;
- potentially negative consequences from changes in or interpretations of tax laws;
- changes in international medical reimbursement policies and programs;
- trade protection measures, including import or export licensing requirements and tariffs;
- our ability to develop relationships with qualified local distributors and trading companies;
- political and economic instability in particular foreign economies and markets, in particular in emerging markets;
- diminished protection of intellectual property in some countries outside of the United States;
- differing labor regulations and business practices; and
- 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, UK Bribery Act or similar local regulation.

For example, we face risks arising out of the potential uncertainty caused by the recent vote in the United Kingdom in favor of exiting the European Union, commonly referred to as Brexit. Brexit could adversely affect European or worldwide political, regulatory, economic or market conditions and could contribute to instability in global political institutions, regulatory agencies and financial markets. Currency exchange rates in the pound sterling and the euro with respect to each other and the U.S. dollar have already been adversely affected by Brexit and, in the event that such foreign exchange volatility were to continue, it could cause volatility in our quarterly financial results. In addition, if the United Kingdom were to significantly alter its regulations affecting the pharmaceutical industry, we could face significant new regulatory costs and challenges.

In addition, some of the countries in which Translarna for the treatment of nmDMD is available for sale are in emerging markets and we anticipate that Translarna will become available to new emerging markets during 2017. Some countries within emerging markets may be especially vulnerable to periods of global or regional financial instability or may have very limited resources to spend on health care, including Brazil. We also may be required to increase our reliance on third-party agents within less developed markets. In addition, many emerging market countries have currencies that fluctuate substantially and if such currencies devalue and we cannot offset the devaluations, our financial performance within such countries could be adversely affected.

In addition, in some countries, including Brazil, orders for named patient sales may be for multiple months of therapy, which can lead to an unevenness in orders which could result in significant fluctuations in quarterly net product sales. Other factors may also contribute to fluctuations in quarterly net product sales including Tranlarna's availability in any particular territory, government actions, economic pressures, political unrest and other factors. Net product sales are impacted by factors, such as the timing of decisions by regulatory authorities, in particular the FDA and the EMA with respect to our ability to market or sell Translarna for the treatment of nmDMD, and our ability to successfully negotiate favorable pricing and reimbursement processes on a timely basis in the countries in which we have or may obtain regulatory approval, including the United States, EEA and other territories.

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

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As we continue to expand our existing international operations, we may encounter new risks.

We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do.

The development and commercialization of new drug products is highly competitive. We face competition with respect to our current product candidates and any products we may seek to develop or commercialize in the future from major pharmaceutical companies, specialty pharmaceutical companies, and biotechnology companies worldwide.

There is currently no marketed therapy, other than Translarna in the EEA, which has received approval for the treatment of the underlying cause of nmDMD. Sarepta Therapeutics recently received approval in the United States for a treatment addressing the underlying cause of disease for different mutations in the DMD gene. Other biopharmaceutical companies are developing treatments for the underlying cause of disease for different mutations in the DMD gene (Sarepta, Daiichi Sankyo, and Nippon Shinyaku).

Aldurazyme, which is manufactured by BioMarin Pharmaceutical Inc. and sold by Genzyme Corporation, is an enzyme replacement therapy for the treatment of mucopolysaccharidosis I. Furthermore, Diacomit is marketed in the European Union by Laboratoires Biocodex for the treatment of Dravet syndrome. Other companies are also pursuing product candidates for the treatment of Dravet syndrome, including GW Pharmaceuticals, Zogenix, and Insys Therapeutics. Aniridia therapeutic interventions, such as artificial iris implantation, are being developed by HumanOptics AG. Our SMA collaboration with Roche and the SMA Foundation also faces competition. For example, in December 2016, the FDA approved nusinersen, a drug developed by Ionis Pharmaceuticals, Inc. and marketed by Biogen, to treat SMA. AveXis, Inc. is also evaluating a gene therapy product candidate for the treatment of SMA. Other companies are also pursuing product candidates for the treatment of SMA, including Trophos (also in collaboration with Roche), Kowa, Novartis Pharmaceuticals Corporation, and Cytokinetics.

Our competitors may develop products that are more effective, safer, more convenient or less costly than any that we are developing or that would render our product candidates obsolete or non-competitive. Our competitors may also obtain marketing authorization for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market.

We believe that many competitors are attempting to develop therapeutics for the target indications of our product candidates, including academic institutions, government agencies, public and private research organizations, large pharmaceutical companies and smaller more focused companies.

Many of our competitors may have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to or necessary for our programs.

Even if we are able to commercialize Translarna for the treatment of nmDMD on a broad scale or commercialize Translarna for other indications or any other product candidate that we develop, the product may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, which would harm our business.

We believe that Translarna for the treatment of nmDMD has been and will continue to be priced at levels consistent with the pricing for other therapies for the treatment of rare disorders where high unmet medical need exists, although, for the reasons discussed below, there can be no assurance in this regard.

The regulations and practices that govern marketing authorizations, pricing, coverage and reimbursement for new drug products vary widely from country to country. Current and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries, including almost all of the member states of the EEA, require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is

granted. In some foreign markets, including the European market, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing authorization for a product in a particular country, but then be subject to price regulations that delay our commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if our product candidates obtain marketing authorization.

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Our ability to successfully commercialize Translarna or any other product candidate that receives marketing authorization also will depend in part on the extent to which coverage and reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers and other organizations. Government authorities and other third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. A primary trend in the EU and U.S. healthcare industries and elsewhere is cost containment. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Prices at which our products are reimbursed can be subject to challenge, reduction or denial by the government and other payers. Increasingly, third-party payors are requiring that drug companies provide them with discounts off the products' list prices and are challenging the prices manufacturers charge for medical products. We cannot be sure that coverage will be available for Translarna or any other product that we may commercialize and, if coverage is available, the level of reimbursement is also uncertain. Reimbursement may impact the demand for, or the price of, any product or product candidate for which we obtain marketing authorization. Obtaining reimbursement for Translarna has been and is expected to be particularly difficult because of the significant research and development challenges and costs and resulting price considerations typically associated with drugs that are developed to treat conditions that affect a small population of patients. In addition, third-party payors are likely to impose strict requirements for reimbursement of a higher priced drug, such as prior authorization requirements. If reimbursement is not available or is available only on a limited basis, we may not be able to successfully commercialize any product or product candidate for which we have obtained or may obtain marketing authorization.

There may be significant delays in obtaining reimbursement for newly approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the applicable regulatory authority. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs, and may be incorporated into existing payments for other services. Further, 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 receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. In the United States, third-party payors include federal health care programs, such as Medicare Medicaid, TRICARE, and Veterans Health Administration programs; managed care providers, private health insurers and other organizations. Several of the U.S. federal health care programs require that drug manufacturers extend discounts or pay rebates to certain programs in order for their products to be covered and reimbursed. For example, the Medicaid Drug Rebate Program requires pharmaceutical manufacturers of covered outpatient drugs to enter into and have in effect a national rebate agreement with the federal government as a condition for coverage of the manufacturer's covered outpatient drug(s) by state Medicaid programs. Similarly, in order for a covered outpatient drug to receive federal reimbursement under the Medicare Part B and Medicaid programs or to be sold directly to U.S. government agencies, the manufacturer must extend discounts on the covered outpatient drug to entities that are enrolled and participating in the 340B drug pricing program. In addition, U.S. private health insurers often rely upon Medicare coverage policies and payment limitations in setting their own coverage and reimbursement policies. Payment by private payors is subject to payor-determined coverage and reimbursement policies that vary considerably and are subject to change without notice.

In addition, there has been recent negative publicity and increasing legislative and public scrutiny around pharmaceutical drug pricing in the U.S. Moreover, U.S. government authorities and third-party payors are increasingly attempting to limit or regulate drug prices and reimbursement, often with particular focus on new and innovative therapies. These dynamics may give rise to heightened attention and potential negative reactions to pricing decisions for products for which we may receive regulatory approval in the future, possibly limiting our ability to generate

revenue and attain profitability. Moreover, we expect that the new Presidential Administration and U.S. Congress may seek to modify, repeal, or otherwise invalidate all, or certain provisions of, the 2010 U.S. healthcare reform legislation (the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, known collectively as the Affordable Care Act), which could have an impact on coverage and reimbursement for healthcare items and services covered by the federal and state healthcare programs as well as plans in the private health insurance market.

In the European Union, reference pricing systems and other measures may lead to cost containment and reduced prices. Our inability to promptly obtain coverage and profitable payment rates from both government-funded and private payors for our product or any of our product candidates that may receive marketing authorization, or a reduction in coverage for payment rates for our product or any such product candidates, could have a material adverse effect on our business, results of operations and financial condition. In addition, in the European Union, for medicines authorized by the centralized authorization procedure, an

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authorized trader, such as a wholesaler, can purchase a medicine in one EU member state and import the product into another EU member state. This process is called “parallel distribution”. As a result, a purchaser in one EU member state may seek to import Translarna from another EU member state where Translarna is sold at a lower price. This could have a negative impact on our business, financial condition, results of operations and growth.

Product liability lawsuits against us could cause us to incur substantial liabilities and to limit commercialization of any products that we may develop.

We face an inherent risk of product liability exposure related to the commercialization of Translarna, any other product that we may commercialize, and in connection with the human clinical trials testing of our product candidates and the sales of our products, including Translarna and any other product that we may develop. If we cannot successfully defend ourselves against claims that our product candidates or products caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- reduced resources of our management to pursue our business strategy;
- decreased demand for any product candidates or products that we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend the related litigation;
- increased insurance costs, or an inability to maintain appropriate insurance coverage;
- substantial monetary awards to trial participants or patients;
- loss of revenue; and
- the inability to commercialize any products that we may develop.

We have product liability insurance that covers our commercial sales, sales pursuant to reimbursed EAP programs and clinical trials up to a $25.0 million annual aggregate limit, and subject to a per claim deductible. The amount of insurance we currently hold may not be adequate to cover all liabilities and defense costs that we may incur. We may need to further increase our insurance coverage as we continue commercializing Translarna or as and when we begin commercializing any other product candidate that receives marketing authorization. The cost of insurance coverage is highly variable, based on a wide range of factors, and is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability or defense costs that may arise.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations currently, and may in the future, involve the use of hazardous and flammable materials, including chemicals and medical and biological materials, and produce hazardous waste products. Even if we contract with third parties for the disposal of these materials and wastes, we cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials or disposal of hazardous wastes, we could be held liable for any resulting damages, and any liability could exceed our resources. Although we maintain workers’ compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We also maintain liability insurance for some of these risks, but our liability policy excludes pollution and has an aggregate coverage limit of $11.0 million.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success. Because we have limited financial and managerial resources, we focus on research programs and product candidates for specific indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or

for other

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indications that later prove to have greater commercial potential. For example, we initiated separate Phase 2 clinical trials of Translarna for the treatment of hemophilia in 2009 and the metabolic disorder methylmalomic acidemia in 2010, but then suspended these clinical trials to focus on the development of Translarna for nmDMD and nmCF when we found variability in the assays used in these trials and preliminary data from these trials did not indicate definitive evidence of activity. In March 2017, we discontinued our current clinical development of Translarna for nmCF based on the negative outcome of a Phase 3 clinical trial. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products.

We have based our research and development efforts on small-molecule drugs that target post-transcriptional control processes. Notwithstanding our large investment to date and anticipated future expenditures in proprietary technologies, including our GEMS, nonsense mutation and alternative splicing technologies, which we use in the discovery of these molecules, to date we have only been granted marketing authorization in the EEA to treat nmDMD under a restricted label that is subject to the specific obligation to conduct Study 041 as well as annual renewal and reassessment requirements. We may not be able to successfully renew or satisfy the ongoing requirements of our current marketing authorization for nmDMD in the EEA and we may never successfully develop any other marketable drugs or indications using our scientific approach. As a result of pursuing the development of product candidates using our proprietary technologies, we may fail to develop product candidates or address indications based on other scientific approaches that may offer greater commercial potential or for which there is a greater likelihood of success.

Research programs to identify new product candidates require substantial technical, financial and human resources. These research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development

If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

Risks Related to Regulatory Approval of our Product and our Product Candidates

Our marketing authorization in the EEA is a “conditional marketing authorization” that requires annual review and renewal by the European Commission following reassessment by the EMA of the benefit-risk balance of the authorization and is further conditioned upon our ability to satisfy the specific obligation to conduct and report the results of Study 041 by September 2021, and, as such, there is ongoing risk that we may be unable to maintain such authorization. If we are unable to obtain renewal of our marketing authorization in any future renewal cycle, we would lose all, or a significant portion of, our ability to generate revenue from product sales, whether pursuant to a commercial or an EAP program and throughout all territories, which would have a material adverse effect on our business, financial performance and results of operations.

Conditional marketing authorizations based on incomplete clinical data, including our marketing authorization for Translarna for the treatment of nmDMD, may be granted in the EEA for a limited number of listed medicinal products for human use, including products designated as orphan medicinal products under EU law, if (1) the EMA determines that the benefit-risk balance of the product is positive, (2) it is likely that the applicant will be in a position to provide the required comprehensive clinical trial data, (3) unmet medical needs will be fulfilled and (4) the benefit to public health of the immediate availability on the market of the medicinal product outweighs the risk inherent in the fact that additional data are still required. Specific obligations or conditions, including with respect to the completion of ongoing or new studies, and with respect to the collection of pharmacovigilance data, may be specified in the conditional marketing authorization. Marketing authorizations subject to conditions are only valid for one year, and must be renewed annually by the European Commission after an assessment by the EMA of the ongoing positive benefit-risk balance in favor of continued authorization and the need for additional or modified conditions.

We received initial marketing authorization for Translarna for the treatment of nmDMD in ambulatory patients aged five years and older from the European Commission in August 2014 as a “conditional marketing authorization.” The marketing authorization is subject to annual review and renewal by the European Commission following reassessment

by the EMA of the benefit-risk balance of the authorization and is further conditioned upon our satisfaction of the specific obligation to conduct and submit the results of Study 041 by September 2021to the EEA. We are also required to implement measures, including pharmacovigilance plans, which are detailed in the risk management plan. Our marketing authorization was previously conditioned upon our submission to the EMA of the final efficacy and safety report from ACT DMD during 2015. Although we have fulfilled the condition to submit the ACT DMD report to the EMA, that trial did not meet the primary efficacy endpoint of change from baseline at week 48 in distance walked in the 6-minute walk test. The EMA and European Commission did not approve our request for full marketing authorization of Translarna for the treatment of nmDMD and, instead, approved the renewal of our conditional marketing authorization with the specific

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obligation to confirm the efficacy and safety of Translarna for the treatment of nmDMD in ambulatory patients aged 5 years or older via Study 041.

Enrolling, conducting and reporting a clinical trial is a time-consuming, expensive and uncertain process that takes years to complete, and we expect that we will incur material costs related to the implementation and conduct of Study 041. We expect that conducting a placebo-controlled trial in nmDMD of this size will be challenging and it is probable that we will enroll patients in territories where Translarna has already become available on a reimbursed basis. We may enroll patients in countries with a different standard of care for nmDMD patients or at clinical trial sites that are inexperienced with clinical trials in general, or specifically with nmDMD trials. In addition, we may experience unknown complications with Study 041 and may not achieve the pre-specified endpoint with statistical significance, which would have a materially adverse effect on our ability to maintain our marketing authorization in the EEA.

If we fail to satisfy our obligations under the marketing authorization, or if it is determined in any annual renewal cycle that the balance of benefits and risks of using Translarna has changed materially, the European Commission could, at the EMA's recommendation, vary, suspend, withdraw or refuse to renew the marketing authorization for Translarna. The EMA may also impose other new conditions to our marketing authorization (in addition to Study 041), and may make other recommendations, including new label restrictions. In the event that we do secure annual renewal of the marketing authorization for any given annual renewal cycle, the EMA could nevertheless later determine that we have not complied, or are unable to comply, with any conditions that have been or may be placed on the marketing authorization, including those related to Study 041, which could result in the withdrawal of our marketing authorization or other outcome that would have a materially adverse effect on our business, results of operations and financial condition.

If our marketing authorization in the EEA is not renewed, or our product label is materially restricted, we would lose all, or a significant portion of, our ability to generate revenue from product sales, whether pursuant to a commercial or an EAP program and throughout all territories, which would have a material adverse effect on our business,results of operations and financial condition.

There is substantial risk that the FDA will continue to disagree with our interpretation of the results of ACT DMD and the totality of clinical data from our trials in Translarna for the treatment of nmDMD and we will be unable to advance Translarna for the treatment of nmDMD in the United States in a timely manner, or at all, whether pursuant to the file over protest process or otherwise, and by determining to file our NDA over protest, we have postponed other available strategic pathways which may have proven to be more effective. If there are delays in obtaining regulatory approval in the United States, we will not be able to commercialize Translarna for nmDMD in that territory and our ability to generate revenue will be materially impaired. In the event that the FDA requires us to conduct a new clinical trial in nmDMD which, if successful, may enable FDA review of an NDA submission by us, we would expect to incur significant costs, which may have a material adverse effect on our business and results of operations.

In December 2015, we completed our rolling new drug application, or NDA, for Translarna for the treatment of nmDMD with the FDA. In February 2016, we received a Refuse to File letter from the FDA regarding this NDA. The FDA stated in the Refuse to File letter that our NDA was not sufficiently complete to permit a substantive review. Specifically, we were notified in the letter that, in the view of the FDA, both of our Phase 2b and Phase 3 ACT DMD trials of Translarna for the treatment of nmDMD were negative and do not provide substantial evidence of effectiveness. Additionally, the FDA stated that we had proposed a post-hoc adjustment of ACT DMD that eliminates data from a majority of enrolled patients. During the third quarter of 2016, we filed an appeal of the FDA's decision refuse to file the NDA, which was denied in the fourth quarter of 2016.

Rather than continue our appeal under the formal dispute resolution process, we recently filed the NDA over protest with the FDA and the agency granted a standard review for the NDA and has set a PDUFA target review date of October 24, 2017, which is not binding on the agency. There can be no assurance that the FDA will complete its review of our NDA by the PDUFA goal date.

Filing over protest is a procedural path permitted by FDA regulations that allows a company to have its NDA filed and reviewed when there is a disagreement with regulators over the acceptability of the NDA submission. When an application is filed over protest, the FDA is required to review the application as filed. Generally, the FDA does not

favor the file over protest procedure and the agency's policies explain that an application filed over protest does not receive a timeline for review and is designated as a standard review.

There is substantial risk that, notwithstanding any dialogue we have had or any further dialogue we may be able to initiate with the agency, pursuant to the file over protest process or otherwise, that we will continue to be unable to resolve the matters raised by the FDA in its Refuse to File letter in a timely manner, or at all. Even if we are successful in resolving some or all of those matters, there is significant risk that the FDA will continue to disagree with our interpretation of the results of ACT DMD and the totality of clinical data from our trials and we will be unable to obtain FDA approval of Translarna for nmDMD, on a

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timely basis or at all. We may be required to perform additional clinical and non-clinical trials or analyses at significant cost. Even if we are able to enroll and fund any such additional trials or analyses, there is substantial risk that the results would not ultimately support the approval of the NDA filed over protest or a new NDA submission with the FDA for Translarna for the treatment of nmDMD in the U.S. In addition, any such requirement for additional trials would most likely result in our inability to sell Translarna in the United States for a significant period of time, if ever, which would have a material adverse effect on our ability to generate revenue from the sales of Translarna for the treatment of nmDMD.

For example, we filed a formal dispute resolution request with the FDA in connection with the agency's refuse to file our NDA submitted for approval of Translarna for the treatment of nmDMD that was based on our Phase 2b data. In January 2012, the FDA reaffirmed the appropriateness of its earlier decision to refuse to file the 2011 NDA. In February 2012, we discussed the design of a proposed Phase 3 clinical trial with the FDA. In that meeting, although the FDA indicated that the adequacy of data for filing and approval of an NDA would remain review issues, the FDA had no objections to key elements of our proposed trial design. We ultimately submitted the safety and efficacy data of that Phase 3 trial, ACT DMD, as part of the NDA that is the subject of the current file over protest procedure. In its 2016 Refuse to File letter, the FDA referenced its prior refusal to file relative to the Phase 2b data and our discussions with the FDA, reiterating the views previously disclosed.

Furthermore, we expect that our efforts to advance our regulatory strategy in the United States will be time-consuming and may be expensive. In addition, by determining to discontinue our strategy of appealing the FDA's refusal to file our NDA and pursue the file over protest strategy, we have postponed other strategic pathways, such as escalating our appeal to the next supervisory level of the FDA, commencing direct litigation, or discussing the design of a new clinical trial with the FDA. Such alternative strategies may be more effective than the file over protest procedure in achieving our ultimate goal of approval for Translarna for the treatment of nmDMD in the United States. We will not be able to commercialize Translarna for nmDMD in the United States until we have obtained regulatory approval from the FDA. Delays in obtaining such approval will materially impair our ability to generate revenue from Translarna for the treatment of nmDMD.

For additional information concerning recent developments that have had, and may continue to have, a material adverse effect on our ability to advance our regulatory strategy for Translarna for the treatment of nmDMD, please review the risk factor under "Risks Related to the Development and Commercialization of our Product and our Product Candidates" titled, "ACT DMD did not meet its primary efficacy endpoint, and there is substantial risk that regulators will not agree with our interpretation of the results of ACT DMD and the totality of clinical data from our trials in Translarna for the treatment of nmDMD, which would have a material adverse effect on our business, financial performance and results of operations."

If we are not able to comply with local regulations for our product or product candidates, we will not be able to obtain or maintain product approvals and commercialize our product or product candidates, and our ability to generate revenue will be materially impaired.

Translarna and our product candidates, and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and EMA and by comparable authorities in other countries. Failure to obtain or renew marketing authorization for Translarna or any product candidate will prevent us from commercializing such product or product candidate.

As noted in the foregoing risk factors, we may not receive necessary approvals from the FDA, the EMA, or other regulators to further commercialize Translarna for nmDMD or to commercialize Translarna for any other indication or commercialize any product candidate in any market. For example, in March 2017, we discontinued our current clinical development of Translarna for nmCF based on the outcome of our Phase 3 clinical trial, ACT CF, and have withdrawn our type II variation submission with the EMA, which we had commenced in the third quarter of 2015 to seek approval of Translarna for the treatment of nmCF in the EEA. We do not currently expect to pursue other marketing authorizations for this indication.

We have not proven our ability to successfully obtain marketing authorizations to sell our product or product candidates, other than with respect to the marketing authorization granted by the European Commission in August

2014 for Translarna for the treatment of nmDMD, which is subject to annual review and renewal following reassessment of the benefit-risk balance of the authorization by the EMA and satisfaction of any conditions that may be imposed by the EMA, including the specific obligation to conduct and report the results of Study 041 and our marketing authorizations in Israel and South Korea (which are largely contingent upon continued EMA approval). We have begun seeking and intend to continue to seek marketing authorization for Translarna for the treatment of nmDMD in territories outside of the EEA. There is substantial risk that regulators in other territories will not agree with our interpretation of the results of ACT DMD and the totality of clinical data from our trials, which would have a material adverse effect on our ability to generate revenue, or may prevent us from generating any revenue, from the sales of Translarna for the treatment of nmDMD in those territories.

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We have only limited experience in filing and supporting the applications necessary to obtain marketing authorizations for product candidates and expect to continue to rely on third-party contract research organizations to assist us in this process. Securing marketing authorization requires the timely preparation and submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. In response to changes in the regulatory environment or requests from regulators, we may elect, or be obliged, to postpone a regulatory submission to include additional analyses, including those intended to strengthen our submission or facilitate regulator review, which could cause delays in getting our products to market and substantially increase our costs. Securing marketing authorization also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. Regulatory authorities may determine that Translarna or any of our other product candidates are not effective or only moderately effective, or have undesirable or unintended side effects, toxicities, safety profiles or other characteristics that preclude us from obtaining marketing authorization or that prevent or limit commercial use.

The process of obtaining marketing authorizations is expensive, may take many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Changes in marketing authorization policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing authorization of a product candidate. Any marketing authorization we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable. For example, the marketing authorization granted on a conditional basis by the EMA in the EEA for Translarna is limited to ambulatory nmDMD patients aged five years and older who have been identified through genetic testing and is subject to the specific obligation to conduct Study 041 and annual reassessment by the EMA of the benefit-risk analysis.

In addition, marketing authorizations in countries outside the United States do not ensure pricing approvals in those countries or in any other countries, and marketing authorizations and pricing approvals do not ensure that reimbursement will be obtained.

We may not be able to obtain orphan drug exclusivity for our product candidates. If our competitors are able to obtain orphan drug exclusivity for their products and those products are determined by the FDA to be the "same drug" as our product candidate(s) under applicable FDA standards, or if those products can be classified as a "similar medicinal product" within the meaning of EU law, we may not be able to have competing products approved by the applicable regulatory authority for a significant period of time.

Regulatory authorities in some jurisdictions, including the European Union and the United States, may designate drugs for relatively small patient populations as orphan drugs. We have obtained orphan drug designations from the EMA and from the FDA for Translarna for the treatment of nmDMD, nmCF, nmMPS I, and nonsense mutation aniridia. The FDA has also granted orphan drug designation to RG7916, a compound under development in our SMA collaboration with Roche and the SMA Foundation. Generally, if a product with an orphan drug designation subsequently receives the first marketing authorization for the indication for which it has such designation, the product is entitled to a period of market exclusivity, which, subject to certain exceptions, precludes the EMA from accepting another marketing application for a similar medicinal product or the FDA from approving another marketing application for the same drug for the same indication for that time period. The applicable market exclusivity period is currently ten years in the European Union and seven years in the United States. The EU exclusivity period can be reduced to six years if a drug no longer meets the criteria for orphan drug designation, including if the drug is sufficiently profitable so that market exclusivity is no longer justified. However, in the European Union, generic medicinal products that rely on the independently generated data submitted as part of a full marketing authorization application dossier of an authorized medicinal product, a "reference product", may not be placed on the market for 10 years from the granting of the initial marketing authorization for the reference product. In addition, the respective

orphan designation and exclusivity frameworks in the United States and in the European Union are subject to change, and any such changes may affect our ability to obtain, or the impact of obtaining, EU or U.S. orphan designations in the future.

In the European Union, a “similar medicinal product” is a medicinal product containing a similar active substance or substances as contained in a currently authorized orphan medicinal product, and which is intended for the same therapeutic indication. For a drug such as Translarna, which is composed of small molecules, the FDA defines “same drug” as a drug that contains the same active moiety and is intended for the same use. Obtaining orphan drug exclusivity for Translarna for these indications, both in the European Union and in the United States, may be important to the product candidate’s success. If a competitor obtains orphan drug exclusivity for and approval of a product with the same indication as Translarna before we do and if the competitor’s product is the same drug or a similar medicinal product as ours, we could be excluded from the market for a

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period of time. Even if we obtain orphan drug exclusivity for Translarna for these indications, we may not be able to maintain it. For example, if a competitive product that is the same drug or a similar medicinal product as Translarna is shown to be "clinically superior" to our product candidate as determined by the FDA, any orphan drug exclusivity we have obtained will not block the approval of such competitive product. In addition, orphan drug exclusivity will not prevent the approval of a product that is the same drug as Translarna if the FDA finds that we cannot assure the availability of sufficient quantities of the drug to meet the needs of the persons with the disease or condition for which the drug was designated. The same considerations would apply to any of our orphan product candidates.

All pharmaceutical products for which marketing authorization has been granted, including Translarna for the treatment of nmDMD in the EEA, are subject to extensive and rigorous governmental regulation and could be subject to restrictions or withdrawal from the market and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our products, when and if any of them are approved.

We, Translarna, our product candidates, our operations, our facilities, our suppliers, and our contract manufacturers, distributors, and contract testing laboratories are subject to extensive regulation by governmental authorities in the EEA, the United States, and other territories, with regulations differing from country to country.

We are not permitted to market our product candidates in the EEA, the United States, or other territories until we have received requisite regulatory approvals. In order to receive and maintain such approvals, we and our third-party service providers must comply on a continuous basis with a broad array of regulations related to establishment registration and product listing, manufacturing processes, risk management measures, quality and pharmacovigilance systems, pre- and post-approval clinical data, labeling, advertising and promotional activities, record keeping, distribution, and import and export of pharmaceutical products for any product for which we obtain marketing authorization. Any regulatory approval of any of our products or product candidates, once obtained, may be withdrawn. For example, our marketing authorization for Translarna for the treatment of nmDMD in the EEA is subject to annual review and renewal by the European Commission following reassessment by the EMA of the benefit-risk balance of the authorization, as well as the specific obligation to conduct and report the results of Study 041. Accordingly, we and others with whom we work must continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing and distribution. For additional information with respect to the risks related to renewal of our marketing authorization in the EEA, see the foregoing risk factor titled "Our marketing authorization in the EEA is a "conditional marketing authorization" that requires annual review and renewal by the European Commission following reassessment by the EMA of the benefit-risk balance of the authorization and is further conditioned upon our ability to satisfy the specific obligation to conduct and report the results of Study 041 by September 2021, and, as such, there is ongoing risk that we may be unable to maintain such authorization. If we are unable to obtain renewal of our marketing authorization in any future renewal cycle, we would lose all, or a significant portion of, our ability to generate revenue from product sales, whether pursuant to a commercial or an EAP program and throughout all territories, which would have a material adverse effect on our business, financial performance and results of operations."

We are required to submit safety and other post-market information and reports, implement pharmacovigilance plans, and comply with current good manufacturing practice, or cGMP, requirements related to manufacturing including, quality control, quality assurance and complaints and corresponding maintenance of records and documents, requirements regarding the distribution of samples to healthcare professionals and recordkeeping, among other things, in connection with the marketing authorization for Translarna for the treatment of nmDMD described above. Regulatory authorities, including the EMA and local regulatory authorities in EEA member states, subject a marketed product, its manufacturer and the manufacturing facilities to ongoing review and periodic inspections and the EMA is responsible for coordinating inspections, undertaken by the competent authorities of applicable member states, of our manufacturing facilities to assess whether our manufacturing, and other procedures, comply with cGMP. Similar regulatory and inspection requirements apply in other jurisdictions including those imposed by the FDA in the United States. The FDA will typically inspect a manufacturer, including its contract manufacturer organizations and clinical research organizations, following acceptance of an NDA, which can delay FDA approval, especially if unsatisfactory inspection results are observed. If an FDA inspection were to occur and compliance issues at our facilities or at the facilities of our contract manufacturers or research organizations were identified, it could also result in disruption of

production or distribution of a product or product candidate, or require substantial resources to correct.

Even if marketing authorization of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or may be subject to significant conditions of approval, including the requirement of risk evaluation and mitigation strategy, or REMS. A regulatory authority also may impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product. In addition, the competent authorities of each EU member state and the FDA closely regulate the post-approval marketing and promotion of drugs to ensure drugs are marketed only for the approved indications and in accordance with the provisions of the approved labeling and regulatory requirements. Such regulatory authorities can impose stringent restrictions on our communications regarding off-label use and if we do not comply with the laws governing promotion of approved drugs, we may be subject to enforcement

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action for off-label promotion. For example, violations of the Federal Food, Drug, and Cosmetic Act relating to the promotion of prescription drugs may lead to civil and criminal penalties, investigations alleging violations of federal and state health care fraud and abuse laws, as well as state consumer protection laws.

In addition, later discovery of previously unknown adverse events or other problems with our products, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may yield various results which could negatively affect our business, including:

- restrictions on such products, manufacturers or manufacturing processes;
- changes to or restrictions on the labeling or marketing of a product;
- restrictions on product distribution or use;
- requirements to implement a REMS;
- requirements to conduct post-marketing studies or clinical trials;
- warning or untitled letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing authorizations;
- refusal to permit the import or export of our products;
- product seizure;
- injunctions;
- the imposition of civil or criminal penalties; or
- debarment.

Non-compliance with regulatory requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with regulatory requirements regarding the protection of personal information can also lead to significant penalties and sanctions.

We are also subject to laws and license and registration requirements covering the distribution of marketed products. If we fail to comply with any of these requirements, we may be subject to action by regulatory agencies, which could negatively affect our business. Regulatory agencies may also change existing requirements or adopt new requirements or policies. We may be slow to adapt or may not be able to adapt to these changes or new requirements.

Our initial commercial launch of Translarna has begun in, and is expected to continue to take place in, countries that tend to impose strict price controls, which may adversely affect our revenues. Failure to obtain and maintain acceptable pricing and reimbursement terms for Translarna for the treatment of nmDMD in the EEA and other countries where Translarna is available would delay or prevent us from marketing our product in such regions, which would adversely affect our business, results of operations, and financial condition.

In some countries, particularly the member states of the EEA, the pricing of prescription pharmaceuticals is subject to strict governmental control. Each country in the EEA has its own pricing and reimbursement regulations and may have other regulations related to the marketing and sale of pharmaceutical products in the country. We generally will not be able to commence commercial sales of Translarna for the treatment of nmDMD pursuant to the conditional marketing authorization granted by the European Commission in any particular member state of the EEA until we conclude the applicable pricing and reimbursement negotiations and comply with any licensing, employment or related regulatory requirements in that country. In some countries we may be required to conduct additional clinical trials or other studies of our product, including trials that compare the cost-effectiveness of our product to other available therapies in order to obtain reimbursement or pricing approval. We may not be able to conclude pricing and reimbursement negotiations or comply with additional regulatory requirements in the countries in which we seek to commercialize Translarna on a timely basis, or at all.

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The pricing and reimbursement process varies from country to country and can take over 18 months to complete. Pricing negotiations may continue after reimbursement has been obtained. We cannot predict the timing of Translarna's commercial launch in countries where we are awaiting pricing and reimbursement guidelines. While we have submitted pricing and reimbursement dossiers with respect to Translarna for the treatment of nmDMD in many EEA countries, we have only received both pricing and reimbursement approval on terms that are acceptable to us in a limited number of countries.

The price that is approved by governmental authorities in any country pursuant to commercial pricing and reimbursement processes may be significantly lower than the price we are able to charge for sales under our reimbursed EAP programs. In some instances, reimbursement may be subject to challenge, reduction or denial by the government and other payors.

For example, in France, EAP and commercial sales of a product can begin while pricing and reimbursement rates are under discussion with the applicable government health programs. In the event that the negotiated price of the product is lower than the amount reimbursed for sales made prior to the conclusion of price negotiations, we may become obligated to repay such excess amount to the applicable government health program. We will make such retroactive reimbursement, if any, following the conclusion of price negotiations with the applicable government health authority. Further, based on unsustainable economics imposed by the arbitration board in Germany upon the recent conclusion of an arbitration process with us and the German Federal Association of the Statutory Health Insurances, we delisted Translarna from the German pharmacy ordering system, effective April 1, 2016. While some patients and healthcare professionals in Germany have been able to access Translarna through a reimbursed importation pathway possible under German law, there can be no assurance that other patients or healthcare professionals in Germany will be successful doing so or, if initially successful, that any or all will continue to be successful. We were required to reimburse payors in Germany the difference between the commercial price of Translarna and the price established by the arbitration board in Germany for sales made in Germany after December 2015, other than sales made pursuant to the reimbursed importation pathway.

Political, economic and regulatory developments may further complicate pricing and reimbursement negotiations and there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. For example, these factors influenced the length of our pricing and reimbursement negotiations in England, which took place between mid-2014 to mid-2016, and culminated in a five-year managed access agreement between us, National Health Services England, the National Institute for Health and Care Excellence, or NICE, NorthStar clinical network and the patient organisations Muscular Dystrophy UK and Action Duchenne. The managed access agreement establishes the clinical details surrounding the use of Translarna, including the terms and conditions of a confidential financial arrangement and the collection of further data on the efficacy of Translarna for the treatment of nmDMD with NICE guidance to be reviewed again at the end of the five-year period, before future funding decisions are taken.

In addition, adverse clinical and regulatory developments may exacerbate these risks, including the developments noted in the foregoing risk factor titled, "ACT DMD did not meet its primary efficacy endpoint, and there is substantial risk that regulators will not agree with our interpretation of the results of ACT DMD and the totality of clinical data from our trials in Translarna for the treatment of nmDMD, which would have a material adverse effect on our business, financial performance and results of operations."

Reference pricing used by various EU member states and parallel distribution, or arbitrage between low-priced and high-priced member states, can further reduce prices and revenues. Publication of discounts by third-party payors or authorities may lead to further pressure on prices or reimbursement levels within the country of publication and other countries.

If we fail to successfully secure and maintain pricing and reimbursement coverage for Translarna or are significantly delayed in doing so or if burdensome conditions are imposed by private payers, government authorities or other third-party payers on such reimbursement, planned launches in the affected countries will be delayed and our business, results of operations and financial condition could be adversely affected.

Our relationships with customers, healthcare providers and professionals, patients, patient organizations, and third-party payors are or will be subject to applicable anti-kickback, fraud and abuse, transparency and other

healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of any products or product candidates, including Translarna, for which we have obtained or may obtain marketing approval. Our arrangements with customers, healthcare providers and professionals and third-party payors may expose us to broadly applicable fraud and abuse, transparency and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute our products for which we obtain marketing authorization.

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Failure to maintain a comprehensive and effective compliance program, and to integrate the operations of any acquired businesses into a combined comprehensive and effective compliance program on a timely basis, could subject us to a range of regulatory actions that could adversely affect our ability to commercialize our products and could harm or prevent sales of the affected products, or could substantially increase the costs and expenses of commercializing and marketing our products.

Restrictions and reporting requirements under applicable U.S. federal and state healthcare laws and regulations, and equivalent laws and regulations in the European Union and other countries in which we operate, include, and are not limited to, the following:

- Anti-corruption and anti-bribery laws and regulations, such as the U.S. Foreign Corrupt Practices Act, or FCPA, the UK Bribery Act of 2010, or Bribery Act, and similar statutes which have been adopted, or may be adopted in the future, by other countries in which we operate and with which we are or may be required to comply.
- Anti-kickback laws and regulations, including those applicable in the United States, the United Kingdom and other countries where we operate, which generally prohibit, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under government funded healthcare programs. The U.S. federal statute imposes criminal penalties and has been broadly interpreted to apply to manufacturer arrangements with prescribers, purchasers and formulary managers, among others and many states have enacted equivalent state laws that apply not only to government payors but to commercial payors as well.
- False claim laws and regulations, including the U.S. False Claims Act and similar state laws, which may permit civil whistleblower or qui tam actions and may impose civil liability and criminal penalties on individuals and entities who submit, or cause to be submitted, false or fraudulent claims for payment to the government.
- Laws and regulations related to the privacy, security and transmission of individually identifiable health information, including the U.S. Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, and similar state laws, which impose obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information, and may impose criminal and civil liability for violations of these obligations. In addition, international data protection laws including the European Union Data Protection Directive and member state implementing legislation may apply to some or all of the clinical data obtained, transmitted, or stored outside of the United States. Furthermore, certain privacy laws and genetic testing laws may apply directly to our operations and/or those of our collaborators and may impose restrictions on our use and dissemination of individuals' health information.

HIPAA also imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program and criminal liability for knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services.

- Laws and regulations governing the advertising and promotion of medicinal products, interactions with physicians and patients, misleading and comparative advertising and unfair commercial practices. For example, legislation adopted by individual EU member states that may apply to the advertising and promotion of medicinal products require that promotional materials and advertising in relation to medicinal products comply with the product's Summary of Product Characteristics, or SmPC, as approved by the competent authorities. The SmPC is the document that provides information to physicians concerning the safe and effective use of the medicinal product. Promotion of indications not covered by the SmPC is specifically prohibited.
- Laws and regulations regulating off-label promotion of medicinal products, which is prohibited in the European Union. The applicable laws at European Union level and in the individual EU member states also prohibit the direct-to-consumer advertising of prescription-only medicinal products. Violations of the rules governing the promotion of medicinal products in the European Union could be penalized by administrative measures, fines and imprisonment. These laws may further limit or restrict the advertising and promotion of our products to the general public and may also impose limitations on our promotional activities with health care professionals. Under the Federal Food, Drug and Cosmetic Act and other laws, if any of our product candidates are approved, we would be prohibited

from promoting our products for off-label uses. This means, for example, that we would not be able to make claims about the use of our marketed products outside of their approved indications, and we would not be able to proactively discuss or provide information on off-label uses of such products, with very specific and limited exceptions. Should the FDA determine that our activities constituted the promotion of off-label use, the FDA could bring action to prevent us from distributing those products for the off-label use and could impose fines and penalties on us and our executives.

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- Laws and regulations requiring that we disclose publicly payments made to physicians, including in certain EU member states and the United States. For example, in the U.S., under the federal Physician Payments Sunshine Act requirements, manufacturers of drugs, devices, biologics and medical supplies must report information related to payments and other transfers of value made to or at the request of covered recipients, such as physicians and teaching hospitals, as well as physician ownership and investment interests in such manufacturers. A number of U.S. states and other countries have enacted their own transparency requirements that obligate manufacturers to report different types of spending related to physicians, certain hospitals, and other covered recipients.

In addition, interactions between pharmaceutical companies and physicians are also governed by industry self-regulation codes of conduct and physicians' codes of professional conduct. In the U.S., some state laws require pharmaceutical companies to comply with these industry and physician codes and the relevant compliance guidance promulgated by the federal government. The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is prohibited in the European Union. The provision of benefits or advantages to physicians is also governed by the national laws of the EU member states, as well as codes of conduct issued by self-regulatory industry bodies. Moreover, agreements with physicians must often be the subject of prior notification and approval by the physician's employer, their competent professional organization, and the competent authorities of the individual EU member states. These requirements are provided in the national laws, industry codes, or professional codes of conduct, applicable in the EU member states.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws, regulations, transparency requirements and self-regulatory codes have and will continue to involve substantial costs. We cannot guarantee that we, our employees, our consultants, our third-party contractors, or the physicians or other providers or entities with whom we expect to do business, are or will be in compliance with all federal, state and foreign regulations and codes. It is possible that governmental authorities could conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, exclusion from government funded healthcare programs, such as Medicare and Medicaid, reputational harm, and the curtailment or restructuring of our operations. Exclusion, suspension and debarment from government funded healthcare programs would adversely affect, perhaps materially, our ability to commercialize, sell or distribute any drug. Even if we were not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could also have an adverse effect on our business, financial condition and results of operations.

Legislative and regulatory changes affecting the pharmaceutical industry or the healthcare system more broadly may increase the difficulty and cost for us to obtain or maintain marketing authorization of and commercialize our product and product candidates and affect the coverage and reimbursement we may obtain.

Our industry is highly regulated and changes in law may adversely impact our business, operations, or financial results. In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing authorization of Translarna or any of our other product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product candidates, including Translarna, for which we obtain marketing authorization.

Certain provisions of enacted or proposed legislative changes may negatively impact coverage and reimbursement of healthcare items and services. For example, in the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or Medicare Modernization Act, changed the way Medicare covers and pays for pharmaceutical products. Cost reduction initiatives and other provisions of this legislation could decrease the coverage and reimbursement that we receive for any approved products. While the Medicare Modernization Act applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own policies. Therefore, any restrictions to coverage or reductions in reimbursement that result from the Medicare Modernization Act may result in a similar coverage restriction or reimbursement reduction from private payors. In addition, private payors may implement coverage restrictions or payment reductions independently from federal programs such as Medicare.

Similarly, in the United States, the Affordable Care Act contains provisions that may reduce the profitability of drug products. However, the new Presidential Administration and U.S. Congress have expressed a desire to modify, repeal or otherwise invalidate all, or certain provisions of, the Affordable Care Act, which has contributed to the uncertainty of the ongoing implementation and impact of the Affordable Care Act and also underscores the potential for additional reform going forward. We cannot assure that the Affordable Care Act, as currently enacted or as amended in the future, will not adversely affect our business and financial results.

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In the European Union, similar political, economic and regulatory developments may affect our ability to profitably commercialize Translarna and our product candidates. In addition to continuing pressure on prices and cost containment measures, legislative developments at the European Union or member state level may result in significant additional requirements or obstacles that may increase our operating costs. We cannot predict how future changes relating to healthcare reform in the European Union, the United States, or other territories, will affect our business. Legislative and regulatory proposals have also been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative or regulatory changes will be enacted in any territory in which we are authorized, or become authorized, to market Translarna or any of our other product candidates, or whether applicable regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing authorizations of our product or product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process or by comparable foreign bodies overseeing regulatory authorities in other territories may significantly delay or prevent marketing authorization, as well as subject us to more stringent product labeling and post-marketing testing and other requirements. We cannot predict how future changes relating to pre- and post-marketing approval and requirements will affect our business.

Risks Related to our Dependence on Third Parties

We contract with third parties for the manufacture and distribution of our product and our product candidates, which may increase the risk that we will not have sufficient quantities of our products or product candidates or such quantities at an acceptable cost, which could delay, prevent or impair our commercialization or development efforts.

We do not own or operate manufacturing or distribution facilities for the production or distribution of clinical or commercial supplies of our product candidates. We have limited personnel with experience in drug manufacturing and lack the resources and the capabilities to manufacture any of our product candidates on a clinical or commercial scale. We currently rely on third parties for supply of the active pharmaceutical ingredients in Translarna and all of our product candidates. We outsource all manufacturing, packaging, labeling and distribution of our products and product candidates to third parties, including our commercial supply of Translarna.

We currently rely on a single source for the production of some of our raw materials and we obtain our supply of the bulk drug substance for Translarna from two third-party manufacturers and the bulk drug substance for our cancer stem cell program through another third-party manufacturer. We engage two separate manufacturers to provide bulk drug product. We have a relationship with three manufacturers that are capable of providing fill and finish services for our finished commercial and clinical product, although we are still in the process of finalizing arrangements with one of these manufacturers with respect to commercial product services. We anticipate completing applicable validation procedures for this manufacturer in 2017 for both commercial and clinical product.

We do not currently have any agreements with third-party manufacturers for the long-term commercial supply of Translarna or any of our product candidates, although we may seek to establish such arrangements in the future. In the event that we are unable to procure supply from a validated manufacturer, we would seek to identify and qualify replacement suppliers, however this process would likely result in delays in our ability to supply Translarna to patients or in advance our clinical trials. We may be unable to conclude agreements for commercial or clinical supply with third-party manufacturers, or may be unable to do so on acceptable terms.

We currently have a contract with a pharmacy and hospital distributor in the European Union that distributes Translarna for clinical programs and limited commercial and EAP programs. We have engaged with third party logistic providers, or 3PLs, which distribute Translarna for the majority of our commercial and EAP programs on our behalf. We intend to engage additional distributors if and when, if ever, we become authorized to make Translarna available for purchase in such additional geographies.

Even if we are able to establish and maintain arrangements with third-party manufacturers and distributors, reliance on such service providers entails additional risks, including:

- reliance on the third party for regulatory compliance and quality assurance;
- the possible breach of the manufacturing agreement by the third party;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how;
- the possibility of commercial supplies of Translarna not being distributed to commercial vendors or end users in a timely manner, resulting in lost sales;

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- the possibility of clinical supplies not being delivered to clinical sites on time, leading to clinical trial interruptions; and
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

Many additional factors could cause production or distribution interruptions with the manufacture and distribution of Translarna and any of our product candidates, including human error, natural disasters, labor disputes, acts of terrorism or war, equipment malfunctions, contamination, or raw material shortages.

In addition, third-party manufacturers or distributors may not be able to comply with current good manufacturing practice, or cGMP, or good distribution practice, or GDP, or similar regulatory requirements outside the European Union and the United States. Our failure, or the failure of our third-party manufacturers or distributors, to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or product, operating restrictions, criminal prosecutions or debarment, any of which could significantly and adversely affect supplies of Translarna or our product candidates.

Our product and our product candidates and any other products that we may develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us.

If the third parties that we engage to manufacture product for our commercial sales, preclinical tests and clinical trials should, prior to the time that we have validated alternative providers, cease to continue to do so for any reason, we likely would experience delays in our ability to supply Translarna to patients or in advancing our clinical trials while we identify and qualify replacement suppliers and we may be unable to obtain replacement supplies on terms that are favorable to us. In addition, if we are not able to obtain adequate supplies of Translarna or our product candidates or the drug substances used to manufacture them, we will lose commercial sales revenue and it will be more difficult for us to develop our product candidates and compete effectively.

Our current and anticipated future dependence upon others for the manufacture and distribution of Translarna and our product candidates may adversely affect our business, financial condition, results of operations and limit our ability to grow including our ability to develop product candidates and commercialize our products that receive regulatory approval on a timely and competitive basis.

We rely on third parties to conduct our clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials.

We do not independently conduct clinical trials for our product or product candidates. We rely on third parties, such as contract research organizations, clinical data management organizations, medical institutions and clinical investigators, to perform this function. Any of these third parties may terminate their engagements with us at any time. If we need to enter into alternative arrangements, it would delay our product development activities.

Our reliance on these third parties for clinical development activities reduces our control over these activities but does not relieve us of our responsibilities. For example, we remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with standards, commonly referred to as Good Clinical Practices, or GCP, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions. Similar GCP and transparency requirements apply in the European Union. Failure to comply with such requirements, including with respect to clinical trials conducted outside the European Union and United States, can also lead regulatory authorities to refuse to take into account clinical trial data submitted as part of a marketing application.

For example, in the first half of 2013 inspectors acting at the request of the EMA conducted GCP inspections of selected clinical sites from our completed Phase 2b clinical trial of Translarna for the treatment of nmDMD and our clinical trial site relating to our then pending marketing authorization application for approval of Translarna for the treatment of nmDMD. Following these inspections, we received inspection reports containing a combination of

critical and major findings. These findings related to waivers we granted to admit patients to our Phase 2b clinical trial of Translarna for the treatment of nmDMD in advance of formal approval of protocol amendments that would have established their eligibility for the trial, as well as our oversight of our trial sites and the completeness or sufficiency of clinical trial documentation. In response to these findings, we described to the EMA the enhanced internal procedures and controls we have implemented, and the internal quality assurance

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department we have established, since the conclusion of our Phase 2b clinical trial of Translarna for the treatment of nmDMD. In addition, we proposed corrective action plans to address the inspectors' specific findings. If we do not meet our commitment to the corrective actions we proposed to the EMA, we may face additional consequences, including rejection of data or other direct action by national regulatory authorities, which could require us to conduct additional clinical trials or other supportive studies to maintain our marketing authorization in the EEA for Translarna for the treatment of nmDMD or to obtain full approval from the EMA.

Furthermore, third parties that we rely on for our clinical development activities may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing authorizations for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates. Our product development costs will increase if we experience delays in testing or obtaining marketing authorizations.

We also rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing authorizations of our product or product candidates or commercialization of our products, producing additional losses and depriving us of potential product revenue.

We currently depend, and expect to continue to depend, on collaborations with third parties for the development and commercialization of some of our product candidates. If those collaborations are not successful, we may not be able to capitalize on the market potential of these product candidates.

For each of our product candidates, we plan to evaluate the merits of retaining commercialization rights for ourselves or entering into selective collaboration arrangements with leading pharmaceutical or biotechnology companies, such as our collaborations with Roche and the SMA Foundation, for our spinal muscular atrophy program. We have entered into arrangements with certain third parties to market or distribute Translarna for the treatment of nmDMD in certain countries and, as we continue to implement our commercialization plans for Translarna, we anticipate that we will engage additional third parties to perform these functions for us in other countries. We generally plan to seek collaborators for the development and commercialization of product candidates that have high anticipated development costs, are directed at indications for which a potential collaborator has a particular expertise, or involve markets that require a large sales and marketing organization to serve effectively. Our likely collaborators for any marketing, distribution, development, licensing or broader collaboration arrangements may include: large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and/or biotechnology companies.

We will have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenues from these arrangements will depend on our collaborators' desire and ability to successfully perform the functions assigned to them in these arrangements. In particular, the successful development of a product candidate from our spinal muscular atrophy program will initially depend on the success of our collaborations with the SMA Foundation and Roche, including whether Roche continues clinical development of the current clinical candidate or pursues clinical development of any other compounds identified under the collaborations.

Collaborations involving our product candidates, including our collaborations with the SMA Foundation and Roche, pose the following risks to us:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs, based on clinical trial results, changes in the collaborators' strategic focus or available funding, or external factors such as an acquisition that diverts resources or creates competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate

for clinical testing;

- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;

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- a collaborator with marketing and distribution rights to one or more products may not commit sufficient resources to the marketing and distribution of such product or products;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability;
- disputes may arise between the collaborator and us as to the ownership of intellectual property arising during the collaboration;
- we may grant exclusive rights to our collaborators, which would prevent us from collaborating with others;
- disputes may arise between the collaborators and us that result in the delay or termination of the research, development or commercialization of our products or product candidates or that result in costly litigation or arbitration that diverts management attention and resources; and
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates.

Collaborators have terminated collaborations with us in the past. For example, in 2008, we entered into a collaboration with Genzyme Corporation for the development and commercialization of Translarna under which we granted to Genzyme rights to commercialize Translarna in all countries other than the United States and Canada. In 2011, we restructured the collaboration and regained worldwide rights to Translarna, with Genzyme obtaining an option to commercialize Translarna in indications other than nmDMD outside the United States and Canada. In 2012, this option expired without being exercised by Genzyme and the collaboration terminated.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. If a collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program could be delayed, diminished or terminated.

If we are not able to establish additional collaborations, we may have to alter our development and commercialization plans.

Our product development programs and the potential commercialization of our product candidates will require substantial additional cash to fund expenses. For some of our product candidates, we may decide to collaborate further with pharmaceutical and biotechnology companies for the development and potential commercialization of those product candidates.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborators' resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborators' evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by regulatory authorities, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge; and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us for our product candidate. We may also be restricted under future license agreements from entering into agreements on certain terms with potential collaborators. Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our

own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

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If we fail to comply with our obligations in our intellectual property licenses and funding arrangements with third parties, we could lose rights that are important to our business.

We are a party to a number of license agreements and expect to enter into additional licenses in the future. Our existing licenses impose, and we expect that future licenses will impose, various diligence, milestone payment, royalty, insurance and other obligations on us. If we fail to comply with these obligations, the licensor may have the right to terminate the license, in which event we might not be able to market any product that is covered by these agreements, which could materially adversely affect the value of the product candidate being developed under such license agreement. Termination of these license agreements or reduction or elimination of our licensed rights may result in our having to negotiate new or reinstated licenses with less favorable terms, or cause us to lose rights in important intellectual property or technology.

We have also received grant funding for some of our development programs from philanthropic organizations and patient advocacy groups pursuant to agreements that impose development and commercialization diligence obligations on us. If we fail to comply with these obligations, the applicable organization could require us to grant to the organization exclusive rights under certain of our intellectual property, which could materially adversely affect the value to us of product candidates covered by that intellectual property even if we are entitled to a share of any consideration received by such organization in connection with any subsequent development or commercialization of the product candidates.

Some of our patented technology was developed with U.S. federal government funding. When new technologies are developed with U.S. government funding, the government obtains certain rights in any resulting patents, including a nonexclusive license authorizing the government to use the invention for non-commercial purposes. These rights may permit the government to disclose our confidential information to third parties and to exercise “march-in” rights to use or allow third parties to use our patented technology. The government can exercise its march-in rights if it determines that action is necessary because we fail to achieve practical application of the U.S. government-funded technology, because action is necessary to alleviate health or safety needs, to meet requirements of federal regulations or to give preference to U.S. industry. In addition, U.S. government-funded inventions must be reported to the government and U.S. government funding must be disclosed in any resulting patent applications. Furthermore, our rights in such inventions are subject to government license rights and certain restrictions on manufacturing products outside the United States.

Risks Related to our Intellectual Property

If we are unable to obtain and maintain patent protection for our technology and products, or if the scope of the patent protection is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully commercialize our technology and products may be adversely affected.

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary technology and products. We seek to protect our proprietary position by filing patent applications in the United States and in certain foreign jurisdictions related to our novel technologies, product and product candidates that are important to our business. This process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Moreover, if we license technology or product candidates from third parties in the future, these license agreements may not permit us to control the preparation, filing and prosecution of patent applications, or to maintain or enforce the patents, covering this intellectual property. These agreements could also give our licensors the right to enforce the licensed patents without our involvement, or to decide not to enforce the patents at all. Therefore, in these circumstances, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued which protect our technology or products, in whole or in part, or

which effectively prevent others from commercializing competitive technologies and products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection.

The laws of foreign countries may not protect our rights to the same extent as the laws of the United States. For example, patent law in many countries restricts the patentability of methods of treatment of the human body more than U.S. law does. In addition, we may not pursue or obtain or be able to pursue or obtain patent protection in all major markets. Assuming the other requirements for patentability are met, currently, the first to file a patent application is generally entitled to the patent. However, prior to March 16, 2013, in the United States, the first to invent was entitled to the patent. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions

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are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our patents or pending patent applications, or that we were the first to file for patent protection of such inventions. In addition, the Leahy-Smith America Invents Act of 2011 (the "Act"), which reformed certain patent laws in the U.S., may create additional uncertainty. The significant changes engendered by the Act include 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 USPTO after grant, including inter partes review and post grant review.

Moreover, we may be subject to a third party anonymously submitting prior art to a patent office or may become involved in addressing patentability objections based on third party submission of references, or may become involved in oppositions, derivation proceedings, reexamination, inter partes review, post grant review, interference proceedings or other patent office proceedings or litigation, in the United States or elsewhere, challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize our product or current or future product candidates.

Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non-infringing manner. In addition, other companies may attempt to circumvent any regulatory data protection or market exclusivity that we obtain under applicable legislation, which may require us to allocate significant resources to preventing such circumvention. Legal and regulatory developments in the European Union and elsewhere may also result in clinical trial data and other information, that would ordinarily be treated as trade secret, submitted as part of a marketing authorization application becoming publicly available. The EMA Policy on publication of clinical data and other such information, as well as the current application of European Union freedom of information regulations, could impact our proprietary information (comprising both clinical and non-clinical data and other information) that would normally be maintained by a regulatory body as commercially confidential. Such developments could enable other companies to circumvent our intellectual property rights and use our clinical trial data or other information to obtain marketing authorizations in the European Union and in other jurisdictions. Such developments may also require us to allocate significant resources or engage in litigation to prevent other companies from circumventing or violating our intellectual property rights. Our attempts to prevent third parties from circumventing our intellectual property and other rights may ultimately be unsuccessful. We may also fail to take the required actions or pay the necessary fees to maintain our patents.

For example, during 2015, we were notified by the EMA that it had received from another pharmaceutical company a request under Regulation (EC) No 1049/2001 seeking access to aspects of our marketing authorization for Translarna for the treatment of nmDMD. Following the decision of the EMA to release such documentation with only minimal redactions we initiated litigation before the General Court of the European Union to prevent disclosure of this information, and in July 2016, the Court took the interim measure of ordering the EMA not to release our documents until the substantive case has been decided (by the General Court and/or in possible appeal proceedings). The EMA has appealed the interim measure to the Court of Justice of the European Union but the Court of Justice dismissed the appeal in the first quarter of 2017. While we expect to continue to object to the disclosure of any information that we consider commercially confidential, there can be no assurance that we will be successful in the aforementioned litigation or in any future challenge that may be raised and we may not ultimately be successful in preventing disclosure of the data in our marketing authorization for Translarna for the treatment of nmDMD.

An issued patent may be challenged as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged on such a basis in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing

similar or identical technology and products, or limit the duration of the patent protection of our technology and products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our patents, trademarks, copyrights or other intellectual property. To counter infringement or unauthorized use, we may be required to file claims, which can be expensive and time consuming. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their intellectual property or defenses, such that they do not infringe our intellectual property or that our intellectual property is invalid or

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unenforceable. In addition, in a patent infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, in whole or in part, construe the patent's claims narrowly or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question.

Third parties may initiate legal proceedings alleging that our patents are invalid and unenforceable or that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.

Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market and sell our product and our product candidates and use our proprietary technologies without infringing the intellectual property and other proprietary rights of third parties. There is considerable intellectual property litigation in the biotechnology and pharmaceutical industries, and we may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our products and technology, including interference, derivation, inter partes review or post-grant review proceedings before the U.S. Patent and Trademark Office. The risks of being involved in such litigation and proceedings may also increase as our product candidates approach commercialization, and as we gain greater visibility as a public company. Third parties may assert infringement claims against us based on existing or future intellectual property rights. We may not be aware of all such intellectual property rights potentially relating to our product and our product candidates. Since patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all, with new publications occurring continuously, there may be patents or patent applications relating to our product or our product candidates that we are unaware of. There may also be pending or future patent applications that, if issued, would block us from commercializing Translarna. Thus, we do not know with certainty whether Translarna, or any of our other product candidates, or our commercialization thereof, would or would not infringe any third party's intellectual property.

If we are found to infringe a third party's intellectual property rights, or in order to avoid or settle litigation, we could be required to obtain a license to continue developing and marketing our products and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us, and could require us to make substantial payments. We could be forced, including by court order, to cease commercializing the infringing technology or product. In addition, we could be found liable for monetary damages, including treble damages and attorneys fees if we are found to have willfully infringed a patent or other intellectual property right. A finding of infringement could prevent us from commercializing our product or our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

For example, it is possible that one or more third parties might bring a patent infringement or other legal proceeding against us regarding Translarna. We are aware of an issued U.S. patent and international patent applications that purport to disclose or contain claims to chemical scaffolds that are sufficiently broad that they could be read to encompass ataluren, the active ingredient in Translarna, even though neither the issued U.S. patent nor any of the international patents or patent applications specifically discloses ataluren. In order to successfully challenge the validity of any issued U.S. patent that may allegedly include ataluren within the scope of a granted claim, we would need to overcome that patent's presumption of validity in district court or prove unpatentability by a preponderance of the evidence before the USPTO. There is no assurance that a court or the USPTO would find these claims to be invalid or unpatentable, respectively. In addition, we believe that the public notice given by our testing of ataluren in clinical trials for the purpose of seeking FDA approval would be a valid defense against any infringement claims in the United States based on the availability of any statutory research exemptions. However, there can be no assurance that our interpretation of the exemption would be upheld, were the exemption interpreted as covering only our preclinical research activities, and not the commercialization of ataluren.

We may be subject to claims by third parties asserting that we or our employees have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

Many of our employees were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these employees have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee's former employer. Litigation may be necessary to defend against these claims.

In addition, while we typically require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own. Our and their assignment

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agreements may not be self-executing or may be breached, and we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our intellectual property. If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to management.

Intellectual property litigation could cause us to spend substantial resources and could distract our personnel from their normal responsibilities.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development, sales, marketing or distribution activities. We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

In addition to seeking patents for some of our technology and products, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. However, we cannot guarantee that we have executed these agreements with each party that may have or have had access to our trade secrets or that the agreements we have executed will provide adequate protection. Any party with whom we have executed such an agreement may breach that agreement and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If any of our trade secrets were to be obtained or independently developed by a competitor, our competitive position would be harmed.

We have not yet registered our trademarks in all of our potential markets, and failure to secure those registrations could adversely affect our business.

Our trademark applications may be refused registration, and our registered trademarks may not be maintained or may be found to be unenforceable. During trademark examination proceedings, our trademark applications may be rejected. Although we are given an opportunity to respond to those rejections, we may not be able to overcome them. In addition, in the U.S. Patent and Trademark Office and Trademark Offices in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications or to seek cancellation of registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such proceedings. In addition, if we do not secure registrations for our trademarks, we may encounter difficulty enforcing our trademark rights against third parties in the jurisdictions where we do not have registered rights.

If we are not able to obtain adequate trademark protection or regulatory approval for our brand names, including Translarna, we may be required to re-brand affected products, which could cause delays in getting such products to market and substantially increase our costs.

To protect our rights in any trademark we intend to use for our product or our product candidates, including Translarna, we may seek to register such trademarks. Trademark registration is territory-specific and we must apply for trademark registration in the United States as well as any other country where we intend to commercialize our product or product candidates. Failure to obtain trademark registrations may place our use of the trademarks at risk or make them subject to legal challenges, which could force us to choose alternative names for our product or product candidates. In addition, the FDA, and other regulatory authorities outside the United States, conduct an independent review of proposed product names for pharmaceuticals, including an evaluation of the potential for confusion with other pharmaceutical product names for medications, which could result in medication errors in prescribing, dispensing and consumption. These regulatory authorities may also object to a proposed

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product name if they believe the name inappropriately makes or implies a therapeutic claim. If the FDA or other regulatory authorities outside the United States object to any of our proposed product names, we may be required to adopt alternative names for our product or product candidates. If we adopt alternative names, either because of our inability to obtain a trademark registration or because of objections from regulatory authorities, we would lose the benefit of our existing trademark applications and the rights attached thereto. Consequently, we may be required to expend significant additional resources in an effort to adopt a new product name that would be registrable under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA and other regulatory authorities, which could cause delays in getting our products to market and substantially increase our costs. Furthermore, we may not be able to build a successful brand identity for a new trademark in a timely manner or at all, which would limit our ability to commercialize our product or our product candidates.

Risks Related to Employee Matters and Managing Growth

Our future success depends on our ability to retain our chief executive officer and other key executives and to attract, retain and motivate qualified personnel.

We are highly dependent on Dr. Stuart W. Peltz, our co-founder and Chief Executive Officer, and the other principal members of our executive and scientific teams. Although we have formal employment agreements with each of our executive officers, these agreements do not prevent our executives from terminating their employment with us at any time. We do not maintain “key person” insurance on any of our executive officers. The loss of the services of any of these persons might impede the achievement of our research, development and commercialization objectives.

Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel will also be critical to our success. We may not be able to attract and retain these personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us.

We are in the process of expanding our development, regulatory, and sales and marketing capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

In connection with our commercialization plans and business strategy, including our commercial launch of Translarna for the treatment of nmDMD, we have experienced and may to continue to experience significant growth in our employee base for sales, marketing, operational, managerial, financial, human resources, drug development, quality, regulatory and medical affairs and other areas. This growth has imposed and will continue to impose significant added responsibilities on members of management, including the need to recruit, hire, retain, motivate and integrate additional employees. Also, our management may have to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. To manage our recent and anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. In addition, we may need to adjust the size of our workforce as a result of changes to our expectations for our business, which can result in diversion of management attention, disruptions to our business, and related expenses. For example, following our receipt of the Refuse to File letter from the FDA in 2016, we implemented a reorganization of our operations in March 2016 that resulted in a one-time charge for the related work-force reduction. The physical expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

Risks Related to our Common Stock

Servicing the Convertible Notes will require a significant amount of cash. We may not have sufficient cash flow from our business to make payments on our debt, and we may not have the ability to raise the funds necessary to settle

conversions of, or to repurchase, the Convertible Notes upon a fundamental change, which could adversely affect our business, financial condition and results of operations.

In August 2015, we incurred indebtedness in the amount of $150.0 million in aggregate principal with additional accrued interest under the Convertible Notes, for which interest is payable semi-annually in arrears on February 15 and August 15 of each year, beginning on February 15, 2016. Our ability to make scheduled payments of the principal of, to pay interest on or to refinance the Convertible Notes depends on our future performance, which is subject to economic, financial, competitive and

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other factors beyond our control. Our business may not generate cash flow from operations in the future sufficient to service our debt, including the Convertible Notes. If we are unable to generate cash flow, we may be required to adopt one or more alternatives, such as selling assets, restructuring debt or obtaining additional equity capital on terms that may be unfavorable to us or highly dilutive. Our ability to refinance our indebtedness will depend on the capital markets and our financial condition at the time we seek to refinance such indebtedness. We may not be able to engage in any of these activities or engage in these activities on desirable terms, which could result in a default on our debt obligations.

In addition, upon conversion of the Convertible Notes unless we elect to deliver solely shares of our common stock to settle such conversion (other than paying cash in lieu of delivering any fractional shares), we will be required to make cash payments in respect of the Convertible Notes being converted. However, we may not have enough available cash or be able to obtain financing at the time we are required to repurchase Convertible Notes, to pay the Convertible Notes at maturity or to pay cash upon conversions of Convertible Notes. In addition, our ability to repurchase Convertible Notes or to pay cash upon conversions of Convertible Notes may be limited by law, by regulatory authority or by agreements governing our future indebtedness. Our failure to repurchase Convertible Notes at a time when the repurchase is required by the indenture, to make interest payments on the Convertible Notes when due under the indenture or to pay any cash payable on future conversions of the Convertible Notes as required by the indenture would constitute a default under the indenture. An event of default under the indenture governing the Convertible Notes or the fundamental change itself could also lead to a default under agreements governing our future indebtedness. If the repayment of any such related indebtedness were to be accelerated after any applicable notice or grace periods, we may not have sufficient funds to repay the indebtedness, repurchase the Convertible Notes, make interest payments on the Convertible Notes or make cash payments upon conversions of the Convertible Notes.

In addition, even if holders of the Convertible Notes do not elect to convert their Convertible Notes, we could be required under applicable accounting rules to reclassify all or a portion of the outstanding principal of the Convertible Notes as a current rather than long-term liability, which would result in a material reduction of our net working capital. Any of these factors could materially and adversely affect our business, financial condition and results of operations.

Provisions in our corporate charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our corporate charter and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which our stockholders might otherwise receive a premium for their shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- provide for a classified board of directors such that not all members of the board are elected at one time;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from the board;
- establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;
- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- limit who may call stockholder meetings;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a “poison pill” that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
- require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our charter or bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

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The price of our common stock may be volatile and fluctuate substantially, which could result in substantial losses for purchasers of our common stock and lawsuits against us and our officers and directors.

Our stock price has been and will likely continue to be volatile. The stock market in general and the market for smaller pharmaceutical and biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, our stockholders may not be able to sell their common stock at or above the price at which they purchased it. The market price for our common stock may be influenced by many factors, including:

- any developments related to our ability or inability to advance Translarna for the treatment of nmDMD in the United States in a timely manner or at all, whether pursuant to the file over protest process with the FDA, or otherwise, and including whether we will be required to complete any additional clinical and non-clinical trials or analyses;
- our ability to maintain our marketing authorization for Translarna for the treatment of nmDMD in the EEA, which is subject to the specific obligation to conduct Study 041 and is also subject to annual review and renewal by the European Commission following reassessment of the benefit-risk balance of the authorization by the EMA;
- any developments related to Study 041, including with respect to design, timing, conduct, and enrollment, and developments with respect to any clinical or non-clinical trial that may be required by other regulatory agencies, including the FDA for Translarna for the treatment of nmDMD;
- results of clinical trials of Translarna and any other product candidate that we develop;
- announcements by us or our competitors of significant acquisitions, licenses, strategic collaborations, joint ventures, collaborations or capital commitments;
- other developments concerning our regulatory submissions;
- whether regulators in other territories agree with our interpretation of the results of ACT DMD;
- our ability to advance the commercialization of Translarna for the treatment of nmDMD;
- the success of competitive products or technologies;
- the development and regulatory status of our SMA program with Roche and the SMA Foundation;
- results of clinical trials of product candidates of our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and
- the other factors described in this “Risk Factors” section.

Companies that have experienced volatility in the market price of their stock have frequently been the subject of securities class action and shareholder derivative litigation. See Part I, Item 3. Legal Proceedings in this Annual Report on Form 10-K for information concerning litigation initiated against us and certain of our officers during the first quarter of 2016. In addition, we could be the target of other such litigation in the future. Class action and derivative lawsuits, whether successful or not, could result in substantial costs, damage or settlement awards and a diversion of our management’s resources and attention from running our business, which could materially harm our reputation, financial condition and results of operations.

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We are currently incurring and expect to continue to incur increased costs as a result of operating as a public company, including compliance with Section 404 of the Sarbanes-Oxley Act of 2002, and our management is and will continue to be required to devote substantial time to compliance initiatives. In addition, the failure to establish and maintain adequate finance infrastructure and accounting systems and controls could impair our ability to comply with the financial reporting and internal controls requirements for publicly traded companies.

As a public company, we incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act of 2002, the Dodd-Frank Act, the listing requirements of The NASDAQ Global Select Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel have and will need to continue to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have and will continue to increase our legal and financial compliance costs and will continue to make some activities more time-consuming and costly. For example, these rules and regulations have made it more difficult and more expensive for us to obtain director and officer liability insurance.

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, we are required to furnish a report by our management on the effectiveness of our internal control over financial reporting and an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. Compliance with Section 404, including documentation and evaluation of our internal control over financial reporting, is both costly and challenging. If we are not able to comply with the requirements of Section 404 of the Sarbanes-Oxley Act in a timely manner each year, we could be subject to sanctions or investigations by the Securities and Exchange Commission, the NASDAQ Stock Market or other regulatory authorities which would require additional financial and management resources and could adversely affect the market price of our common stock. Furthermore, if we cannot provide reliable financial reports or prevent fraud, our business and results of operations could be harmed and investors could lose confidence in our reported financial information.

Because we do not anticipate paying any cash dividends on our capital in the foreseeable future, capital appreciation, if any, will be our stockholders sole source of gain.

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the development and growth of our business. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be our stockholders sole source of gain for the foreseeable future.

Sales of a substantial number of shares of our common stock in the public market by our existing stockholders could significantly reduce the market price of our common stock.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. These sales, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock.

We have issued a significant number of equity awards under our equity compensation plans or as inducement grants to new hire employees pursuant to Nasdaq rules. The shares underlying these awards are or, with respect to certain option grants, will be registered on a Form S-8 registration statement. As a result, upon vesting these shares can be freely exercised and sold in the public market upon issuance, subject to volume limitations applicable to affiliates. The exercise of options and the subsequent sale of the underlying common stock or the sale of restricted stock upon vesting could cause a decline in our stock price. These sales also might make it difficult for us to sell equity securities in the future at a time and at a price that we deem appropriate.

Certain of our employees, executive officers and directors have entered or may enter into Rule 10b5-1 plans providing for sales of shares of our common stock from time to time. Under a Rule 10b5-1 plan, a broker executes trades pursuant to parameters established by the employee, director or officer when entering into the plan, without further direction from the employee, officer or director. A Rule 10b5-1 plan may be amended or terminated in some circumstances. Our employees, executive officers and directors may also buy or sell additional shares outside of a Rule 10b5-1 plan when they are not in possession of material, nonpublic information.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

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Our principal facilities consist of approximately 90,000 square feet of research and office space located at 100, 200 and 250 Corporate Court, Middlesex Business Center, South Plainfield, New Jersey, that we occupy under a lease that expires in 2019, with two consecutive five-year renewal options to renew the lease after 2019. We lease approximately 6,500 square feet of office space in Dublin, Ireland, that we occupy under a lease that expires in 2024. We also lease office space in other countries to support our operations as a global organization, but these leases are not material to us.

Item 3. Legal Proceedings

In March 2016, three purported securities class action lawsuits were commenced in the United States District Court for the District of New Jersey (one each on March 3, 10, and 11), naming as defendants the Company, our Chief Executive Officer, and our Chief Financial Officer. The lawsuits have been consolidated into one action captioned In re PTC Therapeutics, Inc. Securities Litigation, No. 16-1224 (KM). A consolidated amended complaint was filed on January 13, 2017. On February 14, 2017, the defendants filed a motion to dismiss the consolidated amended complaint. The action alleges violations of Sections 10(b) and 20(a) and Rule 10b-5 of the Securities Exchange Act of 1934 in connection with allegedly false and misleading statements made by the Company about its business, operations, and prospects as it relates to the NDA for Translarna for the treatment of nmDMD that the Company submitted to the FDA in December 2015. The plaintiffs seek, among other things, compensatory damages for purchasers of the Company’s common stock between November 6, 2014 and February 23, 2016, as well as attorneys’ fees and costs.

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PART II

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

Market Information

Our common stock has been publicly traded on the NASDAQ Global Select Market under the symbol "PTCT" since June 20, 2013. Prior to that time, there was no public market for our common stock.

The following table sets forth, for the periods indicated, the high and low sales prices per share of our common stock as reported on the NASDAQ Global Select Market:

	High	Low
Year ended December 31, 2016		
First quarter	$31.89	$5.27
Second quarter	$10.15	$5.78
Third quarter	$14.35	$5.64
Fourth quarter	$14.57	$4.03
Year ended December 31, 2015		
First quarter	$77.87	$46.92
Second quarter	$78.72	$46.17
Third quarter	$62.15	$24.63
Fourth quarter	$35.76	$22.67

Holders

As of February 24, 2017, there were 34 holders of record of our common stock. This number does not include beneficial owners whose shares are held in street name.

Dividends

We have never declared or paid cash dividends on our common stock, and we do not expect to pay any cash dividends on our common stock in the foreseeable future.

Recent Sales of Unregistered Securities

Inducement stock option awards

Pursuant to the NASDAQ inducement grant exception, during the quarter ended December 31, 2016, we issued options to purchase an aggregate of 39,200 shares of common stock to certain new hire employees at a weighted-average exercise price of $12.37 per share. The shares underlying these option awards have been registered on a Form S-8 registration statement.

Purchase of Equity Securities

We did not purchase any of our registered equity securities during the period covered by this Annual Report on Form 10-K.

Item 6. Selected Financial Data

The following table sets forth certain financial data with respect to our business. The selected consolidated financial data is derived from, and should be read in conjunction with, our Consolidated Financial Statements and related Notes and Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations", and other information contained elsewhere in this Annual Report on Form 10-K.

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	Year ended December 31,				
	2016	2015	2014	2013	2012
	(In thousands, except per share data)				
Statement of Operations Data:					
Revenues:					
Net product revenue	$81,447	$33,696	$717	$—	$—
Collaboration and grant revenue	1,258	3,070	24,528	34,696	33,946
Total revenues	82,705	36,766	25,245	34,696	33,946
Operating expenses:					
Research and development	117,633	121,816	79,838	54,875	46,139
Selling, general and administrative	97,130	82,080	44,820	25,219	14,615
Total operating expenses	214,763	203,896	124,658	80,094	60,754
Loss from operations	(132,058)	(167,130)	(99,413)	(45,398)	(26,808)
Interest (expense) income, net	(8,276)	(2,367)	1,180	(6,084)	(1,210)
Loss on extinguishment of debt	—	—	—	(130)	—
Other (expense) income, net	(1,207)	(465)	(213)	38	1,783
Loss before income tax (expense) benefit	(141,541)	(169,962)	(98,446)	(51,574)	(26,235)
Income tax (expense) benefit	(569)	(485)	4,693	—	—
Net loss	(142,110)	(170,447)	(93,753)	(51,574)	(26,235)
Deemed dividend	—	—	—	(18,249)	—
Gain on exchange of convertible preferred stock in connection with recapitalization	—	—	—	3,391	159,954
Less beneficial conversion charge	—	—	—	—	(378)
Net (loss) income attributable to common stockholders	$(142,110)	$(170,447)	$(93,753)	$(66,432)	$133,341
Net (loss) income attributable to common stockholders per share:					
Basic	$(4.17)	$(5.07)	$(2.97)	$(5.18)	$219.76
Diluted	$(4.17)	$(5.07)	$(2.97)	$(5.18)	$42.50
Weighted-average shares outstanding:					
Basic	34,044,584	33,626,248	31,565,310	12,829,411	3,328
Diluted	34,044,584	33,626,248	31,565,310	12,829,411	17,205

	As of December 31,				
	2016	2015	2014	2013	2012
	(In thousands)				
Balance Sheet Data:					
Cash, cash equivalents, and marketable securities	$231,666	$338,925	$315,241	$142,467	$2,726
Working Capital	211,662	310,563	291,096	131,890	(23,564)
Total assets*	269,345	365,281	333,219	151,903	13,072
Long-term debt*	98,216	91,848	—	49	4,883
Accumulated deficit	(735,108)	(592,998)	(422,551)	(328,798)	(277,224)
Total stockholders' equity (deficiency)	119,583	226,001	298,467	136,542	(99,640)

* Reclassified debt issuance costs of $2.8 million related to the Convertible Notes as of December 31, 2015 from Total Assets and Long-term debt in connection with the adoption of ASU 2015-03.

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

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The following discussion of our financial condition and results of operations should be read in conjunction with our financial statements and the notes to those financial statements appearing elsewhere in this Annual Report on Form 10-K. This discussion contains forward-looking statements that involve significant risks and uncertainties. As a result of many factors, such as those set forth in Part I, Item 1A. Risk Factors, of this Annual Report on Form 10-K, our actual results may differ materially from those anticipated in these forward-looking statements.

We are a global biopharmaceutical company focused on the discovery, development and commercialization of novel medicines using our expertise in RNA biology. We have discovered all of our compounds currently under development using our proprietary technologies. We plan to continue to develop these compounds both on our own and through selective collaboration arrangements with leading pharmaceutical and biotechnology companies. Our internally discovered pipeline addresses multiple therapeutic areas, including rare disorders and oncology.

During the year ended December 31, 2016, we recognized $81.4 million in sales of Translarna™ (ataluren), our lead product, for the treatment of nonsense mutation Duchenne muscular dystrophy, or nmDMD. Translarna is currently available in over 25 countries on a commercial basis or through a reimbursed early access program, or EAP. We hold worldwide commercialization rights to Translarna for all indications in all territories.

Translarna received marketing authorization from the European Commission in August 2014 for the treatment of nmDMD in ambulatory patients age 5 years and over in the 31 member states of the European Economic Area, or EEA. nmDMD is a rare, life threatening disorder. Our marketing authorization in the EEA is subject to annual review and renewal by the European Commission following reassessment by the European Medicines Agency, or EMA, of the benefit-risk balance of the authorization, which we refer to as the annual EMA reassessment. This marketing authorization is further subject to a specific obligation to conduct and submit the results of a18-month, placebo-controlled trial, followed by an 18-month open-label extension, which we refer to together as Study 041. The final report on the trial and open-label extension is to be submitted by us to the EMA by the end of the third quarter of 2021.

Each country, including each member state of the EEA, has its own pricing and reimbursement regulations. In order to commence commercial sale of product pursuant to our Translarna marketing authorization in any particular country in the EEA, we must finalize pricing and reimbursement negotiations with the applicable government body in such country. As a result, our commercial launch will continue to be on a country-by-country basis. We also have made, and expect to continue to make, product available under EAP programs, both in countries in the EEA and other territories. Our ability to negotiate, secure and maintain reimbursement for product under commercial and EAP programs can be subject to challenge in any particular country and can also be affected by political, economic and regulatory developments in such country.

Translarna is an investigational new drug in the United States. During the first quarter of 2017, we filed a New Drug Application, or NDA, for Translarna for the treatment of nmDMD over protest with the United States Food and Drug Administration, or FDA. The FDA has granted a standard review for the NDA and has set a target review date under the Prescription Drug User Fee Act, or PDUFA, of October 24, 2017. The PDUFA date is the goal date for the FDA to complete its review of the NDA, however, such date is not binding on the agency and there can be no assurance that the FDA will complete its review of our NDA by the PDUFA goal date.

Filing over protest is a procedural path permitted by FDA regulations that allows a company to have its NDA filed and reviewed when there is a disagreement with regulators over the acceptability of the NDA submission. The NDA, which seeks approval of Translarna for the treatment of nmDMD in the United States, was initially submitted by us in December 2015. In February 2016, following our initial submission, we received a Refuse to File letter from the FDA stating that our NDA was not sufficiently complete to permit a substantive review. Specifically, we were notified in the letter that, in the view of the FDA, both the Phase 2b and Phase 3 ACT DMD trials were negative and do not provide substantial evidence of effectiveness and that our NDA did not contain adequate information regarding the abuse potential of Translarna. Additionally, the FDA stated that we had proposed a post-hoc adjustment of ACT DMD that eliminates data from a majority of enrolled patients. During July 2016, we appealed the refuse to file decision via the FDA's formal dispute resolution process, however, this appeal was denied by the FDA's Office of Drug Evaluation I in October 2016. There is significant risk that, notwithstanding any dialogue we have had or any further dialogue we may be able to initiate with the FDA, pursuant to the file over protest process or otherwise, the agency will continue to

disagree with our interpretation of the results of ACT DMD and the totality of clinical data from our trials, and will not grant marketing approval for Translarna for the treatment of nmDMD.

In March 2016, following receipt of the Refuse to File letter, we commenced implementation of a reorganization of our operations intended to improve efficiency and better align our costs and employment structure with our strategic plans. We completed the reorganization in June 2016 and recorded a one-time charge of $2.5 million for the year ended December 31, 2016 for severance and related workforce reduction expenses.

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On March 2, 2017, we announced that the primary and secondary endpoints were not achieved in ACT CF, our Phase 3 double-blind, placebo-controlled, 48-week clinical trial comparing Translarna to placebo in nmCF patients six years of age or older not receiving chronic inhaled aminoglycosides. The safety profile of Translarna in the ACT CF study was consistent with previous studies and no new safety signals were identified. Based on the results of ACT CF, we plan to discontinue our current clinical development of Translarna for nmCF and close ongoing extension studies of Translarna for the treatment of nmCF. We have withdrawn our type II variation submission with the EMA, which sought approval of Translarna for the treatment of nmCF in the EEA.

Based on its understood mechanism of action, we believe that Translarna may have benefit in the treatment of patients with genetic disorders that arise as a result of a nonsense mutation. We are pursuing studies for Translarna in additional indications: mucopolysaccharidosis type I caused by nonsense mutation, or nmMPS I, nonsense mutation aniridia, and nonsense mutation Dravet syndrome/CDKL5.

We continue to advance the development of our spinal muscular atrophy, or SMA, collaboration with F. Hoffman-La Roche Ltd and Hoffman-La Roche Inc., which we refer to collectively as Roche, and the Spinal Muscular Atrophy Foundation, or SMA Foundation. Sunfish, a two-part clinical study in pediatric and adult type 2 and type 3 SMA patients initiated in the fourth quarter of 2016, followed by the initiation of Firefish, a two-part clinical study in infants with type 1 SMA. Both Sunfish and Firefish are investigating the safety, tolerability and efficacy of the compound RG7916 in the applicable patient populations. Part one of each study is a dose-finding study with the primary objectives of evaluating the safety, pharmacokinetics, or PK, and pharmacodynamics of RG7916 in patients and to select the dose for part two of the applicable study. Part one of each study is expected to be followed by a pivotal part two with the primary objective of evaluating the efficacy of RG7916. Commencement of the pivotal part two portion of either Sunfish or Firefish will trigger a single $20 million milestone payment to us from Roche. We anticipate that both Sunfish and Firefish will move into the pivotal second part of the respective study during 2017.

In addition, we have a pipeline of product candidates that are in early clinical and preclinical development. A Phase 1 first-in-human, dose-escalation safety and PK open-label clinical study for our product candidate, PTC596, in advanced cancer patients with solid tumors recently completed. Data from this study is expected during 2017.

On March 16, 2017, we announced that we have entered into an asset purchase agreement with Marathon Pharmaceuticals, LLC, under which we have agreed to acquire all rights to Emflaza™ (deflazacort), subject to the satisfaction or waiver of certain conditions. Emflaza received approval from the FDA on February 9, 2017 as a treatment of Duchenne muscular dystrophy in patients five years of age and older. Additional information concerning the planned acquisition is discussed in Note 17. Subsequent Events in the consolidated financial statements and Item 1A. Risk Factors, each appearing elsewhere in this Annual Report on Form 10-K. Unless otherwise stated or the context otherwise requires, we have not reflected in this Annual Report on Form 10-K the changes to our business that may occur if we consummate the planned acquisition.

Overview—Funding

The success of Translarna, and any other product candidates we may develop, depends largely on obtaining and maintaining reimbursement from governments and third-party insurers. During 2016, our revenues were primarily generated from sales of Translarna for the treatment of nmDMD in territories where we are permitted to distribute Translarna under our early access programs, or EAPs, and in countries in the EEA where we were able to obtain acceptable commercial pricing and reimbursement terms.

See “Item 1. Business—Commercial Matters—Market Access Considerations” for additional information and “Item 1A. Risk Factors—Our initial commercial launch of Translarna has begun in, and is expected to continue to take place in, countries that tend to impose strict price controls, which may adversely affect our revenues. Failure to obtain and maintain acceptable pricing and reimbursement terms for Translarna for the treatment of nmDMD in the EEA and other countries where Translarna is available would delay or prevent us from marketing our product in such regions, which would adversely affect our anticipated revenue, growth and business.”

To date, we have financed our operations primarily through our offering of 3.00% convertible senior notes due August 15, 2022, or the Convertible Notes offering, our public offerings of common stock in February 2014 and in October 2014, our initial public offering of common stock in June 2013, private placements of our preferred stock, collaborations, bank debt and convertible debt financings and grants and clinical trial support from governmental and

philanthropic organizations and patient advocacy groups in the disease areas addressed by our product candidates. As of December 31, 2016, we had an accumulated deficit of $735.1 million. We had a net loss of $142.1 million and $170.4 million for the fiscal years ended December 31, 2016 and 2015, respectively.

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We anticipate that our expenses will further increase in connection with the expansion of our global infrastructure as we continue to establish an international presence and commercialize Translarna for the treatment of nmDMD, including sales and marketing, legal and regulatory, distribution and manufacturing and administrative and employee-based expenses. In addition to the foregoing, we expect to continue to incur significant costs in connection with Study 041 and our open label extension trials of Translarna for the treatment of nmDMD as well as our studies for nmMPS I, nonsense mutation aniridia and nonsense mutation Dravet syndrome/CDKL5. We also expect to incur ongoing research and development expenses for our other product candidates, including our cancer stem cell program. In addition, we may incur substantial costs in connection with our efforts to advance our regulatory submissions. We have begun seeking and intend to continue to seek marketing authorization for Translarna for the treatment of nmDMD in territories outside of the EEA and we may also seek marketing authorization for Translarna for other indications. These efforts may significantly impact the timing and extent of our commercialization expenses.

We may seek to expand and diversify our product pipeline through opportunistically in-licensing or acquiring the rights to products, product candidates or technologies and we may incur expenses, including with respect to transaction costs, subsequent development costs or any upfront, milestone or other payments or other financial obligations associated with any such transaction, which would increase our future capital requirements.

With respect to our outstanding Convertible Notes, cash interest payments are payable on a semi-annual basis in arrears, which will require total funding of $4.5 million annually. Furthermore, as a result of our initial public offering in June 2013, we have incurred and expect to continue to incur additional costs associated with operating as a public company. These costs include significant legal, accounting, investor relations and other expenses that we did not incur as a private company. Additionally, we could be forced to expend significant resources in the defense of the pending securities class action lawsuits brought against us and certain of our executives, as described under Part I, Item 3. Legal Proceedings in this Annual Report on Form 10-K. See also, “The price of our common stock may be volatile and fluctuate substantially, which could result in substantial losses for purchasers of our common stock and lawsuits against us and our officers and directors” under Part I, Item 1A. Risk Factors - Risks Related to Our Common Stock.

We will need to generate significant revenues to achieve and sustain profitability, and we may never do so. Accordingly, we may need to obtain substantial additional funding in connection with our continuing operations. Adequate additional financing may not be available to us on acceptable terms, or at all. If we are unable to raise capital when needed or on attractive terms, we could be forced to delay, reduce or eliminate our research and development programs or our commercialization efforts.

Financial operations overview

To date, our net product sales have consisted solely of sales of Translarna for the treatment of nmDMD in territories outside of the U.S. Our process for recognizing revenue is described below under “Critical accounting policies and significant judgments and estimates—Revenue recognition”.

Roche and the SMA Foundation Collaboration. In November 2011, we entered into a license and collaboration agreement, or licensing agreement, with Roche and the SMA Foundation pursuant to which we are collaborating with Roche and the SMA Foundation to further develop and commercialize compounds identified under our spinal muscular atrophy program with the SMA Foundation. The research component of this agreement terminated effective December 31, 2014. The licensing agreement included a $30 million upfront payment made in 2011 which was recognized on a deferred basis over the research term, and the potential for up to $460 million in milestone payments and royalties on net sales.

In August 2013, we announced the selection of a development candidate, RG7800. The achievement of this milestone triggered a $10.0 million payment to us from Roche, which we recorded as collaboration revenue for the year ended December 31, 2013.

In January 2014, we initiated a Phase 1 clinical program for RG7800, which triggered a $7.5 million milestone payment to us from Roche which we recorded as collaboration revenue for the year ended December 31, 2014.

In November 2014, we announced that our joint development program in Spinal Muscular Atrophy (SMA) with Roche and the SMA Foundation (SMAF) has started a Phase 2 study for RG7800 in adult and pediatric patients. The achievement of this milestone triggered a $10 million payment to us from Roche which we recorded as collaboration revenue for the year ended December 31, 2014.

Grant revenue. From time to time, we receive grant funding from various institutions and governmental bodies. The grants are typically for early discovery research, and generally such grant programs last from two to five years.
Research and development expense

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Research and development expenses consist of the costs associated with our research activities, as well as the costs associated with our drug discovery efforts, conducting preclinical studies and clinical trials, manufacturing development efforts and activities related to regulatory filings. Our research and development expenses consist of:

- external research and development expenses incurred under agreements with third-party contract research organizations and investigative sites, third-party manufacturing organizations and consultants;
- employee-related expenses, which include salaries and benefits, including share-based compensation, for the personnel involved in our drug discovery and development activities; and
- facilities, depreciation and other allocated expenses, which include direct and allocated expenses for rent and maintenance of facilities, depreciation of leasehold improvements and equipment, and laboratory and other supplies.

We use our employee and infrastructure resources across multiple research projects, including our drug development programs. We track expenses related to our clinical programs and certain preclinical programs on a per project basis. We expect our research and development expenses to increase in connection with our ongoing activities, particularly in connection with Study 041 for Translarna for the treatment of nmDMD, our studies of Translarna in nmMPS I, nonsense mutation aniridia, and nonsense mutation Dravet syndrome/CDKL5 and activities under our cancer stem cell program. The timing and amount of these expenses will depend upon the outcome of our ongoing clinical trials and the costs associated with our planned clinical trials. The timing and amount of these expenses will also depend on the costs associated with potential future clinical trials of our product or product candidates and the related expansion of our research and development organization, regulatory requirements, advancement of our preclinical programs and product and product candidate manufacturing costs.

The following table provides research and development expense for our most advanced principal product development programs, for the years ended December 31, 2016, 2015, and 2014.

	Year ended December 31,		
	2016	2015	2014
	(in thousands)		
Translarna (nmDMD, nmCF, nmMPS I, aniridia and Dravet)	$84,566	$83,521	$56,707
Antibacterial	208	9,388	7,512
Cancer stem cell	7,473	8,422	4,307
Next generation nonsense readthrough	6,428	7,951	6,506
Other research and preclinical	18,958	12,534	4,806
Total research and development	$117,633	$121,816	$79,838

The successful development of our product and product candidates is highly uncertain. This is due to the numerous risks and uncertainties associated with developing drugs, including the uncertainty of:

- the scope, rate of progress and expense of our clinical trials and other research and development activities;
- the potential benefits of our product and product candidates over other therapies;
- our ability to market, commercialize and achieve market acceptance for our product or any of our product candidates that we are developing or may develop in the future, including our ability to negotiate pricing and reimbursement terms acceptable to us;
- clinical trial results;
- the terms and timing of regulatory approvals; and
- the expense of filing, prosecuting, defending and enforcing patent claims and other intellectual property rights.

A change in the outcome of any of these variables with respect to the development of Translarna or any other product candidate could mean a significant change in the costs and timing associated with the development of that product candidate. For example, if the EMA or FDA or other regulatory authority were to require us to conduct clinical trials beyond those which we currently anticipate will be required for the completion of clinical development of Translarna or any other product candidate or

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if we experience significant delays in enrollment in any of our clinical trials, we could be required to expend significant additional financial resources and time on the completion of clinical development.

Selling, general and administrative expense

Selling, general and administrative expenses consist primarily of salaries and other related costs for personnel, including share-based compensation expenses, in our executive, legal, commercial, business development, finance, accounting, information technology and human resource functions. Other selling, general and administrative expenses include facility-related costs not otherwise included in research and development expense; advertising and promotional expenses; costs associated with industry and trade shows; and professional fees for legal services, including patent-related expenses, accounting services, miscellaneous selling costs and finishing costs incurred to direct product to commercial use.

We expect that selling, general and administrative expenses will increase in future periods as a result of our continued efforts to establish an expanded international presence in Europe and other territories and our continued efforts to commercialize Translarna for the treatment of nmDMD, including increased payroll, expanded infrastructure, commercial operations, increased consulting, legal, accounting and investor relations expenses.

Interest (expense) income, net

Interest (expense) income, net consists of interest income earned on investments and interest expense from the Convertible Notes outstanding.

Critical accounting policies and significant judgments and estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our financial statements, which we have prepared in accordance with generally accepted accounting principles in the United States. The preparation of these financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements, as well as the reported revenues and expenses during the reporting periods. Actual results may differ from these estimates under different assumptions or conditions.

Revenue recognition

We recognize revenue when amounts are realized or realizable and earned. Revenue is considered realizable and earned when the following criteria are met: (1) persuasive evidence of an arrangement exists; (2) delivery has occurred or services have been rendered; (3) the price is fixed or determinable; and (4) collection of the amounts due are reasonably assured.

Net Product Sales

To date, our net product sales have consisted solely of sales of Translarna for the treatment of nmDMD in territories outside of the U.S. We began recognizing revenue for payments received under reimbursed EAPs for Translarna in nmDMD patients in select countries in the third quarter of 2014. We have now established a pattern of collectability and, since January 2015, we recognize revenue from product sales when there is persuasive evidence that an arrangement exists, title to product and associated risk of loss has passed to the customer, the price is fixed or determinable, collectability is reasonably assured and we have no further performance obligations in accordance with Financial Accounting Standards Board ("FASB") Accounting Standards Codification ("ASC") Subtopic 605-15, Revenue Recognition—Products.

We have recorded revenue on sales where Translarna is available either on a commercial basis or through a reimbursed EAP program. Orders for Translarna are generally received from hospital and retail pharmacies and, in some cases, one of our third-party partner distributors. Revenue is recognized when risk of ownership has transferred. Our third-party distributors act as intermediaries between us and end users and do not typically stock significant quantities of Translarna. The ultimate payor for Translarna is typically a government authority or institution or a third-party health insurer.

We record revenue net of allowances, including estimated third party discounts and rebates. Allowances are recorded as a reduction of revenue at the time revenues from product sales are recognized. These allowances are adjusted to reflect known changes in factors and may impact such allowances in the quarter those changes are known.

We expect that net product sales will fluctuate quarter-over-quarter. In some countries, including Brazil, orders for named patient sales may be for multiple months of therapy which can lead to an unevenness in orders. In addition, net

product sales may fluctuate quarter-over-quarter as a result of government actions, economic pressures and political unrest. Net product sales may be significantly impacted by multiple factors, including, among other things, decisions by regulatory authorities, in particular the FDA and the EMA with respect to our submissions for Translarna for the treatment of nmDMD and our ability to

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successfully negotiate favorable pricing and reimbursement processes on a timely basis in the countries in which we have or may obtain regulatory approval, including the United States, EEA and other territories.

Collaboration and Grant Revenue

The terms of collaboration agreements typically include payments of one or more of the following: nonrefundable, upfront license fees; milestone payments; research funding; and royalties on future product sales. If applicable, we generate service revenue through collaboration and grant agreements that provide for fees for research and development services or additional payments upon achievement of specified events.

We evaluate all contingent consideration earned, such as a milestone payment, using the criteria as provided by the FASB guidance on the milestone method of revenue recognition. At the inception of a collaboration arrangement, we evaluate if milestone payments are substantive. The criteria requires that (1) we determine if the milestone is commensurate with either its performance to achieve the milestone or the enhancement of value resulting from our activities to achieve the milestone; (2) the milestone be related to past performance; and (3) the milestone be reasonable relative to all deliverable and payment terms of the collaboration arrangement. If these criteria are met then the contingent milestones can be considered as substantive milestones and will be recognized as revenue in the period that the milestone is achieved. We recognize royalties as earned in accordance with the terms of various research and collaboration agreements. If not substantive, the contingent consideration is allocated to the existing units of accounting based on relative selling price and recognized following the same basis previously established for the associated unit of accounting.

We recognize reimbursements for research and development costs under collaboration agreements as revenue as the services are performed. We record these reimbursements as revenue and not as a reduction of research and development expenses as we have the risks and rewards as the principal in the research and development activities.

Our principal obligation under our grant agreements is to conduct the internal or external research in the specific field funded by the grant. We determine, through the grant's normal research process, which research and development projects to pursue. We recognize grant revenues as the research activities are performed. If the grant includes an upfront payment, we defer the amount and recognize it as revenue as the expenditures are incurred.

Inventories and Cost of Product Revenues

In 2014, we were notified that the European Commission granted marketing authorization for Translarna for the treatment of nmDMD in ambulatory patients aged five years and older. The conditional marketing authorization allows us to market Translarna for the treatment of nmDMD in the 31 member states of the EEA. Our launch in these countries is on a country by country basis. This marketing authorization is subject to annual review and renewal by the European Commission following reassessment by the EMA of the benefit-risk balance of the authorization, as well as our satisfaction of any specific obligation or other requirement placed upon the marketing authorization, including conducting and reporting results from Study 041, as described below.

In January 2016, we submitted the final clinical study report from ACT DMD to the EMA in fulfillment of the initial specific obligation placed on our marketing authorization. The primary efficacy endpoint of ACT DMD was not achieved with statistical significance. We made our submission to the EMA as a type II variation request that sought to have this initial specific obligation to our marketing authorization removed and a full marketing authorization granted. In February 2016, we also submitted a marketing authorization renewal request with the EMA.

In January 2017, the European Commission renewed our marketing authorization, subject to the specific obligation to conduct Study 041. Because the EMA did not grant our request for full marketing authorization, the authorization remains subject to annual EMA reassessment. The last granted marketing authorization renewal is effective, unless extended, through August 5, 2017. We submitted a marketing authorization renewal request to the EMA in February 2017. We plan to seek to renew the marketing authorization on an annual basis until a marketing authorization that is not subject to any specific obligation is granted, if ever.

If, in any annual renewal cycle, the EMA determines that the balance of benefits and risks of using Translarna for the treatment of nmDMD has changed materially or that we have not or are unable to comply with any specific obligation or other requirement that has been or may be placed on the marketing authorization, the European Commission could, at the EMA's recommendation, vary, suspend, withdraw or refuse to renew the marketing authorization for Translarna or impose other specific obligations or restrictions on the marketing authorization.

Although there continues to be substantial risk that regulators could, in the future, suspend or not renew our marketing authorization in the EEA for Translarna for the treatment of nmDMD, we have determined that we will capitalize inventory with respect to the Translarna finished product for commercial use effective January 1, 2017 and commence the expensing of

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cost of goods sold based on the marketing authorization renewal granted by the EC. Had we capitalized as inventory all of our Translarna product that is available for commercial sale on hand as of December 31, 2016, the value of that inventory would have been approximately $1.7 million. In addition, had we expensed the cost of Translarna product sold as a cost of sales, the gross profit margin would have been greater than 90%, which we believe is consistent with the cost of producing small molecule therapeutics for orphan drug diseases in the pharmaceutical industry.

Accrued expenses

As part of the process of preparing our financial statements, we are required to estimate accrued expenses. This process involves communicating with our applicable personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of actual cost. The majority of our service providers invoice us monthly in arrears for services performed. We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us. Examples of estimated accrued expenses include:

- fees paid to contract research organizations in connection with preclinical and toxicology studies and clinical trials;
- fees paid to investigative sites in connection with clinical trials;
- fees paid to contract manufacturers in connection with the production of clinical trial materials; and
- professional service fees.

Share-based compensation

We expect to grant additional stock options that will result in additional share-based compensation expense. We measure the cost of employee services received in exchange for an award of equity instruments based on the grant date fair value of the award. For service type awards, share-based compensation expense is recognized on a straight-line basis over the period during which the employee is required to provide service in exchange for the entire award. For awards that vest or begin vesting upon achievement of a performance condition, we estimate the likelihood of satisfaction of the performance condition and recognize compensation expense when achievement of the performance condition is deemed probable using an accelerated attribution model.

In 2016, we issued a total of 1,500,645 stock options to various employees. Of those, 155,200 were non-statutory stock option inducement grants made pursuant to the NASDAQ inducement grant exception as a material component of our new hires' employment compensation. All other stock option grants were made under our 2013 Long Term Incentive Plan.

The fair values of grants made in the year ended December 31, 2016 were contemporaneously estimated on the date of grant using the following assumptions:

	2016	2015	2014
Risk-free interest rate	1.30 - 2.24%	1.48 - 2.18%	0.11 - 2.04%
Expected volatility	67 - 78%	67 - 69%	70 - 91%
Expected term	5.05 - 10.00 years	5.50 - 9.12 years	5.50 - 6.25 years

We assumed no expected dividends for all grants. The weighted average grant date fair value of options granted during the years ended December 31, 2016, 2015 and 2014 was $17.31, $50.81, and $22.39 per share, respectively. The fair value of options is calculated using the Black-Scholes option pricing model to determine the fair value of stock options on the date of grant based on key assumptions, such as expected volatility and expected term. As a new public company, we do not have sufficient history to estimate the volatility of our common stock price or the expected life of the options. Therefore, we calculate expected volatility based on a historical volatility analysis of peers that were similar to us with respect to industry, stage of life cycle, size, and financial leverage and will continue to do so until the historical volatility of our common stock is sufficient to measure expected volatility for future option grants. We use the "simplified method" to determine the expected term of options. Under this method, the expected term represents the average of the vesting period and the contractual term. The risk-free rate of the option is based on U.S. Government Securities Treasury Constant Maturities yields at the date of grant for a term similar to the expected term of the option.

Restricted Stock Awards—Restricted stock awards are granted subject to certain restrictions, including service conditions. The grant-date fair value of restricted stock awards, which has been determined based upon the market value of our common stock on the grant date, is expensed over the vesting period.

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Restricted Stock Units—Restricted stock units are granted subject to certain restrictions, including in some cases service or time conditions (restricted stock). The grant-date fair value of restricted stock units, which has been determined based upon the market value of the Company's shares on the grant date, is expensed over the vesting period.
The following table summarizes information on our restricted stock awards and units:

	Restricted Stock Awards and Units	
	Number of Shares	Weighted Average Grant Date Fair Value
Unvested at December 31, 2015	344,335	$ 10.85
Granted	141,185	$ 30.86
Vested	(163,635)	$ 10.85
Forfeited	(50,234)	$ 18.93
Unvested at December 31, 2016	271,651	$ 19.76

Stock Appreciation Rights—Stock appreciation rights (SARs) entitle the holder to receive, upon exercise, an amount of our common stock or cash (or a combination thereof) determined by reference to appreciation, from and after the date of grant, in the fair market value of a share of our common stock over the measurement price based on the exercise date.

In May 2016, a total of 897,290 SARs were granted to non-executive employees (the 2016 SARs). The 2016 SARs will vest annually in equal installments over four years and will be settled in cash on each vest date, requiring us to remeasure the SARs at each reporting period until vesting occurs. For the period ending December 31, 2016, we recorded $0.9 million in compensation expense related to the 2016 SARs.

Employee Stock Purchase Plan—In June 2016, we established an Employee Stock Purchase Plan (ESPP or the Plan) for certain eligible employees. The Plan is administered by our Board of Directors or a committee appointed by the Board. The total number of shares available for purchase under the Plan is one million shares of our common stock. Employees may participate over a six-month period through payroll withholdings and may purchase, at the end of the six-month period, our common stock at a purchase price of at least 85% of the closing price of a share of our common stock on the first business day of the offering period or the closing price of a share of our common stock on the last business day of the offering period, whichever is lower. No participant will be granted a right to purchase our common stock under the Plan if such participant would own more than 5% of the total combined voting power of our or any subsidiary of ours after such purchase. For the period ending December 31, 2016, we recorded $0.2 million in compensation expense related to the ESPP.
We recorded share-based compensation expense in the statement of operations related to incentive stock options, nonstatutory stock options, restricted stock awards, restricted stock units and the ESPP as follows:

	Year ended December 31,		
(in thousands)	2016	2015	2014
Research and development	$16,812	$16,138	$9,739
Selling, general and administrative	18,197	17,841	9,571
Total	$35,009	$33,979	$19,310

As of December 31, 2016, 2015 and 2014 there was approximately $60.8 million, $73.8 million and $38.4 million, respectively, of total unrecognized compensation cost related to unvested share-based compensation arrangements granted under the Company's 2013 Long Term Incentive Plan and prior equity awards plans or made pursuant to the NASDAQ inducement grant exception for new hires. This cost is expected to be recognized as share-based compensation expense over the weighted average remaining service period of approximately 2.17 years.

Warrant liability

Warrants to purchase our common stock with nonstandard antidilution provisions, regardless of the probability or likelihood that may conditionally obligate the issuer to ultimately transfer assets, are classified as liabilities and are recorded at their estimated fair value at each reporting period. Any change in fair value of these warrants is recorded as gain (loss) on warrant valuation each reporting period in Other income (expense) on our statement of operations.

Convertible notes offering

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In August 2015, we issued, at par value, $150.0 million aggregate principal amount of 3.0% convertible senior notes due 2022, which we refer to as the Convertible Notes. The Convertible Notes bear cash interest at a rate of 3.0% per year, payable semi-annually on February 15 and August 15 of each year, beginning on February 15, 2016. The Convertible Notes will mature on August 15, 2022, unless earlier repurchased or converted. The net proceeds to us from the offering were $145.4 million after deducting the initial purchasers' discounts and commissions and the offering expenses payable by us.

The Convertible Notes are governed by an indenture (the Convertible Notes Indenture) with U.S Bank National Association as trustee (the Convertible Notes Trustee).

Holders may convert their Convertible Notes at their option at any time prior to the close of business on the business day immediately preceding February 15, 2022 only under the following circumstances: (1) during any calendar quarter commencing on or after September 30, 2015 (and only during such calendar quarter), if the last reported sale price of our common stock for at least 20 trading days (whether or not consecutive) during a period of 30 consecutive trading days ending on the last trading day of the immediately preceding calendar quarter is greater than or equal to 130% of the conversion price on each applicable trading day; (2) during the five business day period after any five consecutive trading day period (the "measurement period") in which the trading price (as defined in the Convertible Notes Indenture) per $1,000 principal amount of Convertible Notes for each trading day of the measurement period was less than 98% of the product of the last reported sale price of our common stock and the conversion rate on each such trading day; (3) during any period after we have issued notice of redemption until the close of business on the scheduled trading day immediately preceding the relevant redemption date; or (4) upon the occurrence of specified corporate events. On or after February 15, 2022, until the close of business on the business day immediately preceding the maturity date, holders may convert their Convertible Notes at any time, regardless of the foregoing circumstances. Upon conversion, we will pay cash up to the aggregate principal amount of the Convertible Notes to be converted and deliver shares of its common stock in respect of the remainder, if any, of its conversion obligation in excess of the aggregate principal amount of Convertible Notes being converted.

The conversion rate for the Convertible Notes was initially, and remains, 17.7487 shares of our common stock per $1,000 principal amount of the Convertible Notes, which is equivalent to an initial conversion price of approximately $56.34 per share of our common stock.

We may not redeem the Convertible Notes prior to August 20, 2018. We may redeem for cash all or any portion of the Convertible Notes, at our option, on or after August 20, 2018 if the last reported sale price of its common stock has been at least 130% of the conversion price then in effect on the last trading day of, and for at least 19 other trading days (whether or not consecutive) during, any 30 consecutive trading day period ending on, and including, the trading day immediately preceding the date on which we provide notice of redemption, at a redemption price equal to 100% of the principal amount of the Convertible Notes to be redeemed, plus accrued and unpaid interest to, but excluding, the redemption date. No sinking fund is provided for the Convertible Notes, which means that we are not required to redeem or retire the Convertible Notes periodically.

If we undergo a "fundamental change" (as defined in the Indenture governing the Convertible Notes Indenture), subject to certain conditions, holders of the Convertible Notes may require us to repurchase for cash all or part of their Convertible Notes at a repurchase price equal to 100% of the principal amount of the Convertible Notes to be repurchased, plus accrued and unpaid interest to, but excluding, the fundamental change repurchase date.

The Convertible Notes Indenture contains customary events of default with respect to the Convertible Notes, including that upon certain events of default (including our failure to make any payment of principal or interest on the Convertible Notes when due and payable) occurring and continuing, the Convertible Notes Trustee by notice to us, or the holders of at least 25% in principal amount of the outstanding Convertible Notes by notice to us and the Convertible Notes Trustee, may, and the Convertible Notes Trustee at the request of such holders (subject to the provisions of the Convertible Notes Indenture) shall, declare 100% of the principal of and accrued and unpaid interest, if any, on all the Convertible Notes to be due and payable. In case of certain events of bankruptcy, insolvency or reorganization, involving us or a significant subsidiary, 100% of the principal of and accrued and unpaid interest on the Convertible Notes will automatically become due and payable. Upon such a declaration of acceleration, such principal and accrued and unpaid interest, if any, will be due and payable immediately.

Income taxes

As part of the process of preparing our financial statements, we are required to estimate our income taxes in each of the jurisdictions in which we operate. This process involves estimating our actual current tax expense together with assessing temporary differences resulting from differing treatments of items for tax and accounting purposes. These differences result in deferred tax assets and liabilities. At December 31, 2016 and 2015, we recorded a full valuation allowance against our net deferred tax assets of approximately $183.0 million and $139.6 million, respectively. The change in the valuation allowance during the years ended December 31, 2016 and 2015 was approximately $43.4 million and $16.3 million, respectively. A full

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valuation allowance has been recorded since, in the judgment of management, these assets are not more likely than not to be realized. The ultimate realization of deferred tax assets is dependent upon the generation of future taxable income during periods in which those temporary differences and carryforwards become deductible or are utilized. As of December 31, 2016, we have approximately $285.8 million and $213.2 million of federal and state net operating loss carryforwards, respectively.

As a result of realization requirements of the guidance issued by the FASB, certain deferred tax assets that arose directly from tax deductions related to equity compensation in excess of compensation recognized for financial reporting are excluded from the total deferred tax assets. As of December 31, 2016, approximately $50.4 million of the federal net operating loss carryforwards are related to the exercise of employee stock options and vesting of restricted stock, and we will record a tax benefit of approximately of $17.1 million through capital in excess of par value if such losses are realized.

As of December 31, 2016, credit carryforwards for federal and state purposes are approximately $14.4 million and $7.3 million, respectively. In addition the Orphan Drug Credit Carryover available as of December 31, 2016 is approximately $60.1 million. The federal net operating loss carryforwards begin to expire in 2021, while the federal credit carryforwards begin to expire in 2019. State net operating loss carryforwards begin to expire in 2030, and the state credit carryforwards began to expire in 2016. Sections 382 and 383 of the Internal Revenue Code of 1986 subject the future utilization of net operating losses and certain other tax attributes, such as research and experimental tax credits, to an annual limitation in the event of certain ownership changes, as defined. We have undergone an ownership change and have determined that a “change in ownership” as defined by IRC Section 382 of the Internal Revenue Code of 1986, as amended, and the rules and regulations promulgated thereunder, did occur in June of 2013. Accordingly, about $231.5 million of our net operating loss carryforwards are limited and we can only use $16.7 million for the first five years from the ownership change and $5.7 million per year going forward. Therefore, $169.2 million of the net operating losses will be freed up over the next 20 years and $62.3 million are expected to expire unused which are not included in the deferred tax assets listed above. In summary, there are $285.8 million of net operating losses available, out of which $169.2 million are limited by IRC Section 382. At December 31, 2016, there is $175.1 million available for immediate use and an additional $16.7 million will free up in 2017.

Year ended December 31, 2016 compared to year ended December 31, 2015

The following table summarizes revenues and selected expense and other income data for the year ended December 31, 2016 and 2015:

	Year ended December 31,		Change 2016 vs.
(in thousands)	2016	2015	2015
Net product revenue	$81,447	$33,696	$47,751
Collaboration and grant revenue	1,258	3,070	$(1,812)
Research and development expense	117,633	121,816	$(4,183)
Selling, general and administrative expense	97,130	82,080	$15,050
Interest expense, net	(8,276)	(2,367)	$(5,909)
Income tax expense	(569)	(485)	$(84)

Net product revenue. Net product revenue was $81.4 million for the year ended December 31, 2016, an increase of $47.8 million, from net product revenue of $33.7 million for the year ended December 31, 2015. We have recorded revenue on sales where Translarna is available either on a commercial basis or through a reimbursed EAP program. As of January 1, 2015, we have recognized revenue for Translarna as product is shipped, given we have established a pattern of collectability. The increase in net product revenue was primarily due to the increase in net product sales in existing markets where Translarna is available as well as continued geographic expansion into new territories.

Collaboration and grant revenue. Collaboration and grant revenue was $1.3 million for the year ended December 31, 2016, a decrease of $1.8 million, or 59%, from collaboration and grant revenue of $3.1 million for the year ended December 31, 2015. The decrease in collaboration and grant revenue was primarily due to the recognition of deferred grant revenue in fiscal year 2015 from an agreement entered into in fiscal year 2014.

Research and development expense. Research and development expense was $117.6 million for the year ended December 31, 2016, a decrease of $4.2 million, or 3%, from $121.8 million for the year ended December 31, 2015. The decrease resulted primarily from lower costs associated with research activities of $8.5 million. These decreases were partially

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offset by increased personnel costs of $2.6 million, including $0.8 million of one-time severance related charges, and increased costs related to the manufacture of drug products of $2.0 million.

Selling, general and administrative expense. Selling, general and administrative expense was $97.1 million for the year ended December 31, 2016, an increase of $15.1 million, or 18%, from $82.1 million for the year ended December 31, 2015. The increase resulted primarily from higher personnel costs of $11.0 million, including $1.6 million of one-time severance related charges, and an increase in share-based compensation expense of $1.3 million. The remainder of the increase is primarily due to costs associated with the expanded commercial launch of Translarna across Europe and other regions.

Interest expense, net. Net interest expense was $8.3 million for the year ended December 31, 2016, an increase of $5.9 million, or 250% from net interest expense of $2.4 million for the year ended December 31, 2015. The increase in interest expense was primarily due to increased interest expense accrued in connection with the semi-annual interest payments due on our Convertible Notes beginning in 2016 for the full year as compared to partial year expense in 2015 partially offset by interest income related to investments.

Income tax expense. Income tax expense was $0.6 million for the year ended December 31, 2016, an increase of $0.1 million, or 17%, from $0.5 million for the year ended December 31, 2015. We incurred income tax expense related to certain foreign income taxes. We are subject to income taxes in the United States, although currently not a tax payer, and various foreign jurisdictions, and our foreign tax liabilities are largely dependent upon the distribution of pre-tax earnings among these different jurisdictions.

Year ended December 31, 2015 compared to year ended December 31, 2014

The following table summarizes revenues and selected expense and other income data for the years ended December 31, 2015 and 2014:

	Year ended December 31,		Change 2015 vs.
(in thousands)	2015	2014	2014
Net product revenue	$33,696	$ 717	$32,979
Collaboration and grant revenue	3,070	24,528	$(21,458)
Research and development expense	121,816	79,838	$41,978
Selling, general and administrative expense	82,080	44,820	$37,260
Interest (expense) income, net	(2,367)	1,180	$(3,547)
Income tax (expense) benefit	(485)	4,693	$(5,178)

Net product revenue. Net product revenue was $33.7 million for the year ended December 31, 2015, an increase of $33.0 million, from net product revenue of $0.7 million for the year ended December 31, 2014. We have recorded revenue on sales where Translarna is available either on a commercial basis or through a reimbursed EAP. As of January 1, 2015, we have recognized revenue for Translarna as product is shipped, given we have established a pattern of collectability. We recognized $1.4 million of revenue in 2015 attributable to product sales in 2014 which were deferred in 2014 when we recognized revenue on a cash basis.

Collaboration and grant revenue. Collaboration and grant revenue was $3.1 million for the year ended December 31, 2015, a decrease of $21.5 million, or 87%, from collaboration and grant revenue of $24.5 million for the year ended December 31, 2014. The decrease in collaboration revenue was primarily due to milestone payments received from Roche for program achievements in the SMA program in 2014 of $17.5 million as well as lower collaboration revenue for the comparable period.

Research and development expense. Research and development expense was $121.8 million for the year ended December 31, 2015, an increase of $42.0 million, or 53%, from $79.8 million for the year ended December 31, 2014. The increase resulted primarily from increased clinical trial expenses of $12.8 million associated with our ongoing clinical trials, increased costs of $9.5 million incurred in the manufacturing of drug product, an increase in personnel related costs of $9.2 million related to increased headcount primarily due to international expansion, and an increase in non-cash, stock-based compensation expense of $6.4 million.

Selling, general and administrative expense. Selling, general and administrative expense was $82.1 million for the year ended December 31, 2015, an increase $37.3 million or 83% from $44.8 million for the year ended December 31,

2014. The increase resulted primarily from increased non-cash stock-based compensation expense of $8.3 million, increased personnel

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costs of $14.9 million related to increased headcount primarily due to international expansion, and increased costs related to our commercial launch activities and costs associated with establishing our international infrastructure.

Interest (expense) income,net. Net interest expense was $2.4 million for the year ended December 31, 2015, a decrease of $3.5 million from net interest income of $1.2 million for the year ended December 31, 2014. The increase in interest expense was primarily due to increased interest expense accrued in connection with the semi-annual interest payments due on our Convertible Notes beginning in 2016 partially offset by interest income related to investments.

Income tax (expense) benefit. Income tax expense was $0.5 million for the year ended December 31, 2015 and income tax benefit was $4.7 million for the year ended December 31, 2014. We incurred income tax expense related to certain foreign income taxes. We are subject to income taxes in the United States, although currently not a tax payer, and various foreign jurisdictions, and our foreign tax liabilities are largely dependent upon the distribution of pre-tax earnings among these different jurisdictions. We recognized a tax benefit of $4.9 million related to our sale of net operating losses and research and development credits in the New Jersey Technology Business Tax Certificate Transfer Program for the year ended December 31, 2014. We did not participate in this program during the year ended December 31, 2015.

Liquidity and capital resources

Sources of liquidity

Since inception, we have incurred significant operating losses.

As a growing commercial-stage biopharmaceutical company, we are engaging in significant commercialization efforts for Translarna for nmDMD while also devoting a substantial portion of our efforts on research and development programs related to Translarna and our other product candidates. To date, all of our product revenue has been attributable to sales of Translarna for the treatment of nmDMD in territories outside of the United States. Our ongoing ability to generate revenue from sales of Translarna for the treatment of nmDMD is dependent upon our ability to maintain our marketing authorization in the EEA and secure market access through commercial programs following the conclusion of pricing and reimbursement terms at sustainable levels in the member states of the EEA or through EAP programs in the EEA and other territories. The marketing authorization requires annual review and renewal by the European Commission following reassessment by the EMA of the benefit-risk balance of the authorization and is subject to the specific obligation to conduct Study 041.

We have historically financed our operations primarily through the issuance and sale of our common stock in public offerings, the private placements of our preferred stock, collaborations, bank debt, convertible debt financings and grants and clinical trial support from governmental and philanthropic organizations and patient advocacy groups in the disease areas addressed by our product candidates. We expect to continue to incur significant expenses and operating losses for at least the next several years. The net losses we incur may fluctuate significantly from quarter to quarter.

In February 2014, we closed a public offering of 5,163,265 shares of common stock at a public offering price of $24.50 per share, including 673,469 shares pursuant to the exercise by the underwriters of an overallotment option. We received net proceeds from the public offering of approximately $118.4 million after deducting underwriting discounts and commissions and other offering expenses payable by us.

In October 2014, we closed a public offering of 3,450,000 shares of common stock at a public offering price of $36.25 per share, including 450,000 shares pursuant to the exercise by the underwriters of their option to purchase additional shares. We received net proceeds from the public offering of approximately $117.6 million after deducting underwriting discounts and commissions and other offering expenses payable by us.

In August 2015, we closed a private offering of $150 million in aggregate principal amount of 3.00% convertible senior notes due 2022, or the Convertible Notes, including the exercise by the initial purchasers of an option to purchase an additional $25 million in aggregate principal amount of the Convertible Notes. The Convertible Notes bear cash interest payable on February 15 and August 15 of each year, beginning on February 15, 2016. The Convertible Notes are senior unsecured obligations of ours and will mature on August 15, 2022, unless earlier converted, redeemed or repurchased in accordance with their terms prior to such date. We received net proceeds from the offering of approximately $145.4 million, after deducting the initial purchasers' discounts and commissions and the estimated offering expenses payable by us.

Cash flows

As of December 31, 2016, we had cash and cash equivalents and marketable securities of $231.7 million. The following table provides information regarding our cash flows and our capital expenditures for the periods indicated.

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	Years ended December 31,		
(in thousands)	2016	2015	2014
Cash provided by (used in):			
Operating activities	(103,566)	(124,337)	(57,274)
Investing activities	104,481	(20,811)	(145,168)
Financing activities	968	154,061	237,126

Net cash used in operating activities was $103.6 million, $124.3 million, and $57.3 million for the years ended December 31, 2016, 2015 and 2014, respectively. The cash used in operating activities primarily related to supporting clinical development, including the manufacture of drug product, commercial launch activities for Translarna and costs associated with the expansion of our international infrastructure for the years ended December 31, 2016, 2015, and 2014.

Net cash provided by investing activities was $104.5 million for the year ended December 31, 2016 and was primarily related to net sales and redemptions of marketable securities. Net cash used in investing activities was $20.8 million and $145.2 million for the years ended December 31, 2015 and 2014, respectively. Cash used in investing activities was primarily related to net purchases of marketable securities with funds raised from the issuance of Convertible Notes in August 2015 and public offerings in February and October 2014 for the years ended December 31, 2015 and 2014, respectively.

Net cash provided by financing activities in 2016 was due to proceeds from the exercise of stock options. Net cash provided by financing activities in 2015 was primarily attributable to the $145.4 million in net proceeds from the issuance of the Convertible Notes in August 2015. Net cash provided by financing activities in 2014 was primarily attributable to approximately $118.4 million in net proceeds from the public offering in February 2014 and approximately $117.6 million in net proceeds from the public offering in October 2014.

Funding requirements

We anticipate that our expenses will further increase in connection with the expansion of our global infrastructure as we continue to establish an international presence and commercialize Translarna for the treatment of nmDMD, including sales and marketing, legal and regulatory, distribution and manufacturing and administrative and employee-based expenses. In addition to the foregoing, we expect to continue to incur significant costs in connection with Study 041 and our open label extension trials of Translarna for the treatment of nmDMD as well as our studies for nmMPS I, nonsense mutation aniridia and nonsense mutation Dravet syndrome/CDKL5. We also expect to incur ongoing research and development expenses for our other product candidates, including our cancer stem cell program. In addition, we may incur substantial costs in connection with our efforts to advance our regulatory submissions. We have begun seeking and intend to continue to seek marketing authorization for Translarna for the treatment of nmDMD in territories outside of the EEA and we may also seek marketing authorization for Translarna for other indications. These efforts may significantly impact the timing and extent of our commercialization expenses.

In addition, our expenses will increase if and as we:

- are required to complete any additional clinical and non-clinical trials or analyses in order to advance Translarna for the treatment of nmDMD in the United States or elsewhere;
- are required to take other steps, in addition to Study 041, to maintain our current marketing authorization in the EEA for Translarna for the treatment of nmDMD or to obtain further marketing authorizations for Translarna for the treatment of nmDMD or other indications;
- initiate or continue the research and development of Translarna for additional indications and of our other product candidates;
- seek to discover and develop additional product candidates;
- seek to expand and diversify our product pipeline through strategic transactions;
- maintain, expand and protect our intellectual property portfolio;
- add operational, financial and management information systems and personnel, including personnel to support our product development and commercialization efforts; and

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- complete our planned acquisition of Emflaza, subject to satisfying closing conditions and obtaining applicable regulatory approvals, integrate the acquired assets into our business, and seek to satisfy contractual and regulatory obligations that will be assumed by us following closing of the planned acquisition.

We believe that our cash flows from product sales, together with existing cash and cash equivalents, including the net proceeds from our offering of 3.00% convertible senior notes due August 15, 2022, or the Convertible Notes, public offerings of common stock, marketable securities and research funding that we expect to receive under our collaborations, will be sufficient to fund our operating expenses and capital expenditure requirements for at least the next twelve months. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we currently expect.

Our future capital requirements will depend on many factors, including:

- our ability to maintain the marketing authorization in the EEA for Translarna for the treatment of nmDMD, including whether the EMA determines on an annual basis that the benefit-risk balance of Translarna supports renewal of our marketing authorization in the EEA, on the current approved label;
- the costs, timing and outcome of Study 041;
- the costs, timing and outcome of our efforts to advance Translarna for the treatment of nmDMD in the United States, whether pursuant to the file over protest process with the FDA, or otherwise, and including, whether we will be required to perform additional clinical and non-clinical trials or complete additional analyses at significant cost which, if successful, may enable FDA review of an NDA submission by us and, ultimately, may support approval of Translarna for nmDMD in the U.S.;
- the progress and results of our pediatric study of Translarna for the treatment of nmDMD, our open label extension clinical trials of Translarna for the treatment of nmDMD as well as our studies for nmMPS I and nonsense mutation aniridia and nonsense mutation Dravet syndrome/CDKL5 and activities under our cancer stem cell program;
- the scope, costs and timing of our commercialization activities, including product sales, marketing, legal, regulatory, distribution and manufacturing, for nmDMD and any of our other product candidates that may receive marketing authorization or any additional indications or territories in which we receive authorization to market Translarna;
- the costs, timing and outcome of regulatory review of our other product candidates and Translarna in other territories or for indications other than nmDMD;
- the timing and scope of growth in our employee base;
- the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials for Translarna for additional indications and for our other product candidates;
- revenue received from commercial sales of Translarna or any of our other product candidates;
- our ability to successfully negotiate adequate pricing and reimbursement processes on a timely basis, or at all, in the countries in which we may obtain regulatory approval, including the countries in the EEA;
- our ability to obtain additional and maintain existing reimbursed named patient and cohort EAP programs for Translarna for the treatment of nmDMD on adequate terms, or at all;
- the ability and willingness of patients and healthcare professionals to access Translarna through alternative means if pricing and reimbursement negotiations in the applicable territory do not have a positive outcome, including in Germany;
- the costs of preparing, filing and prosecuting patent applications, maintaining, and protecting our intellectual property rights and defending against intellectual property-related claims;
- the extent to which we acquire or invest in other businesses, products, product candidates, and technologies, including the success of any acquisition, in-licensing or other strategic transaction we may pursue, and the costs of subsequent development requirements and commercialization efforts, including with respect to our planned acquisition of Emflaza; and
- our ability to establish and maintain collaborations, including our collaborations with Roche and the SMA Foundation, and our ability to obtain research funding and achieve milestones under these agreements.

With respect to our outstanding Convertible Notes, cash interest payments are payable on a semi-annual basis in arrears, which will require total funding of $4.5 million annually. Furthermore, as a result of our initial public offering in June 2013, we have

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incurred and expect to continue to incur additional costs associated with operating as a public company. These costs include significant legal, accounting, investor relations and other expenses that we did not incur as a private company. Additionally, we could be forced to expend significant resources in the defense of the pending securities class action lawsuits brought against us and certain of our executives, as described under Part I, Item 3. Legal Proceedings in this Annual Report on Form 10-K.

We will need to generate significant revenues to achieve and sustain profitability, and we may never do so. We may need to obtain substantial additional funding in connection with our continuing operations. Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs primarily through a combination of equity offerings, debt financings, collaborations, strategic alliances, grants and clinical trial support from governmental and philanthropic organizations and patient advocacy groups in the disease areas addressed by our product and product candidates and marketing, distribution or licensing arrangements. Adequate additional financing may not be available to us on acceptable terms, or at all. To the extent that we raise additional capital through the sale of equity or convertible debt securities, our shareholders ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or to grant licenses on terms that may not be favorable to us.

If we are unable to raise additional funds through equity or debt financings when needed or on attractive terms, we may be required to delay, limit, reduce or terminate our product development or commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Contractual obligations

The following table summarizes our significant contractual obligations and commercial commitments as of December 31, 2016.

(in thousands)	Total	Less than 1 year	1 - 3 years	4 - 5 years	More than 5 years
Operating lease obligations (1)	3,286	1,483	1,744	59	—
Long-term debt obligations, including interest (2)	177,000	4,500	13,500	159,000	—
Total contractual obligations	180,286	5,983	15,244	159,059	—

(1) We lease office space for our principal office in South Plainfield, New Jersey under a noncancelable operating lease with a term that extends through February 2019. In addition, we lease office space in various countries for our international employees primarily through workspace providers.

(2) Our long-term debt obligations reflect our obligations under the 2022 notes to pay interest on the $150.0 million aggregate principal amount of the 2022 notes and to make principal payments on the 2022 notes at maturity or upon conversion.

The preceding table excludes contingent contractual payments that we may become obligated to make. Under various agreements, we will be required to pay royalties and milestone payments upon the successful development and commercialization of products, including the following agreements with The Wellcome Trust Limited, or Wellcome Trust, and the SMA Foundation.

We have entered into funding agreements with Wellcome Trust for the research and development of small molecule compounds in connection with our cancer stem cell and antibacterial programs. As we have discontinued development under our antibacterial program, we no longer expect that milestone and royalty payments from us to Wellcome Trust will apply under that agreement, resulting in a change to the total amount of development and regulatory milestone payments we may become obligated to pay for this program. Under our cancer stem cell program funding agreement, to the extent that we develop and commercialize program intellectual property on a for-profit basis ourselves or in collaboration with a partner (provided we retain overall control of worldwide commercialization), we may become

obligated to pay to Wellcome Trust development and regulatory milestone payments and single-digit royalties on sales of any research program product. Our obligation to pay such royalties would continue on a country-by-country basis until the longer of the expiration of the last patent in the program intellectual property in such country covering the research program product and the expiration of market exclusivity of such product in such country. We made the first development milestone payment of $0.8 million to Wellcome Trust under the cancer

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stem cell program funding agreement during the second quarter of 2016. Additional development and regulatory milestone payments of up to an aggregate of $22.4 million may become payable by us under this agreement.
We have also entered into a sponsored research agreement with the SMA Foundation in connection with our spinal muscular atrophy program. We may become obligated to pay the SMA Foundation single-digit royalties on worldwide net product sales of any collaboration product that we successfully develop and subsequently commercialize or, with respect to collaboration products we outlicense, a specified percentage of certain payments we receive from our licensee. We are not obligated to make such payments unless and until annual sales of a collaboration product exceed a designated threshold. Our obligation to make such payments would end upon our payment to the SMA Foundation of a specified amount.
We have employment agreements with certain employees which require the funding of a specific level of payments, if certain events, such as a change in control or termination without cause, occur.

Off-Balance Sheet Arrangements
We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined under Securities and Exchange Commission rules.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk
We are exposed to market risk related to changes in interest rates. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments are in short-term securities. Our available for sale securities are subject to interest rate risk and will fall in value if market interest rates increase. At any time, sharp changes in interest rates can affect the fair value of the investment portfolio and its interest earnings. There were no investments classified as long-term at December 31, 2016. At December 31, 2016, we held $231.7 million in cash and cash equivalents and short-term investments. After a review of our marketable investment securities, we believe that in the event of a hypothetical ten percent increase in interest rates, the resulting decrease in fair value of our marketable investment securities would be insignificant to the consolidated financial statements.
Currently, we do not hedge these interest rate exposures. We maintain an investment portfolio in accordance with our investment policy. The primary objectives of our investment policy are to preserve principal, maintain proper liquidity and to meet operating needs. Although our investments are subject to credit risk, our investment policy specifies credit quality standards for our investments and limits the amount of credit exposure from any single issue, issuer or type of investment. Our investments are also subject to interest rate risk and will decrease in value if market interest rates increase. However, due to the conservative nature of our investments and relatively short duration, interest rate risk is mitigated. We do not own derivative financial instruments. Accordingly, we do not believe that there is any material market risk exposure with respect to derivative or other financial instruments.
As a result of our foreign operations, we face exposure to movements in foreign currency exchange rates, including the British Pound, Euro and Swiss Franc against the U.S. dollar. The current exposures arise primarily from cash, accounts receivable, intercompany receivables and payables, and product sales denominated in foreign currencies. Both positive and negative impacts to our international product sales from movements in foreign currency exchange rates may be partially mitigated by the natural, opposite impact that foreign currency exchange rates have on our international operating expenses. For the year ended December 31, 2016, we recognized foreign currency transaction losses, net of $0.6 million. A hypothetical ten percent increase or decrease in the exchange rate between the U.S. dollar and the British Pound, Euro or Swiss Franc from the December 31, 2016 rate would not have a significant impact on our cash flows. We are not currently engaged in any foreign currency hedging activities. We will evaluate the use of derivative financial instruments to hedge our exposure as the needs and risks should arise.
In August 2015, we issued $150 million of 3.00% convertible senior notes due August 15, 2022, or the Convertible Notes. We do not have economic interest rate exposure on the Convertible Notes as they have a fixed annual interest rate of 3.00%. However, the fair value of the Convertible Notes is exposed to interest rate risk. We do not carry the Convertible Notes at fair value on our balance sheet but present the fair value of the principal amount for disclosure purposes. Generally, the fair value of the Convertible Notes will increase as interest rates fall and decrease as interest

rates rise. The Convertible Notes are also affected by the price and volatility of our common stock and will generally increase or decrease as the market price of our common stock changes. The estimated fair value of the Convertible Notes was approximately $85.2 million as of December 31, 2016.

Item 8. Financial Statements and Supplementary Data

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Report of independent registered public accounting firm

The Board of Directors and Stockholders of PTC Therapeutics, Inc.

We have audited the accompanying consolidated balance sheets of PTC Therapeutics, Inc. as of December 31, 2016 and 2015, and the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2016. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of PTC Therapeutics Inc. at December 31, 2016 and 2015, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2016, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), PTC Therapeutics Inc.'s internal control over financial reporting as of December 31, 2016, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated March 16, 2017 expressed an unqualified opinion thereon.

/s/ ERNST & YOUNG LLP

Iselin, New Jersey

March 16, 2017

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Report of independent registered public accounting firm

The Board of Directors and Stockholders of PTC Therapeutics, Inc.

We have audited PTC Therapeutics, Inc. internal control over financial reporting as of December 31, 2016, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). PTC Therapeutics, Inc. management is responsible for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Report of Management on Internal Control Over Financial Reporting. Our responsibility is to express an opinion on the company's internal control over financial reporting based on our audit.

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

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

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

In our opinion, PTC Therapeutics, Inc. maintained, in all material respects, effective internal control over financial reporting as of December 31, 2016, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the consolidated balance sheets of PTC Therapeutics, Inc. as of December 31, 2016 and 2015 and the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2016 and our report dated March 16, 2017 expressed an unqualified opinion thereon.

/s/ ERNST & YOUNG LLP

Iselin, New Jersey

March 16, 2017

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PTC Therapeutics, Inc.
Consolidated Balance Sheets
In thousands

	December 31,	
	2016	2015
Assets		
Current assets:		
Cash and cash equivalents	$58,321	$58,022
Marketable securities	173,345	280,903
Prepaid expenses and other current assets	4,691	5,930
Trade receivables, net	24,929	11,094
Total current assets	261,286	355,949
Fixed assets, net	7,429	8,974
Deposits and other assets	630	358
Total assets	$269,345	$365,281
Liabilities and stockholders’ equity		
Current liabilities:		
Accounts payable and accrued expenses	$48,759	$45,247
Deferred revenue	—	139
Other current liabilities	865	