PTC THERAPEUTICS, INC.
Form 10-K
March 02, 2015

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(MarkOne)

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

For the fiscal year ended: December 31, 2014

o **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	**07080**
(Address of Principal Executive Offices)	(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 o No ý

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 o No ý

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 ý No o

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. o

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 ý No o

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

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

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, 2014, the last business day of the registrant's most recently completed second fiscal quarter, was $683,512,510. 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, 2015, the registrant had 33,688,913 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 2015 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, 2014.

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PTC Therapeutics, Inc.

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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," "should," "continue," and 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:

- the timing and conduct of our clinical trials of Translarna (ataluren) for the treatment of Duchenne muscular dystrophy, cystic fibrosis and mucopolysaccharidosis type I, or MPS I, caused by nonsense mutations, as well as our trials 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;

- our ability to commercialize Translarna in general, and specifically as a treatment for Duchenne muscular dystrophy caused by nonsense mutations, or 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 may obtain regulatory approval, including the countries in the European Economic Area;

- the timing of and our ability to obtain additional marketing approvals of Translarna and our other product candidates, and the ability of Translarna and our other product candidates to meet existing or future regulatory standards;

- our ability to obtain additional and maintain existing reimbursed named patient and cohort early access programs on adequate terms;

- our estimates regarding the potential market opportunity for Translarna, including the size of eligible patient populations and our ability to identify such patients;

- our ability to expand the approved product label of Translarna for the treatment of nmDMD;

- the timing and scope of our commercial infrastructure expansion, including the growth of our international presence in Europe and in other territories;

- 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;

- our sales, marketing and distribution capabilities and strategy, including the ability of our third-party manufacturers to manufacture and deliver Translarna in commercially sufficient quantities and the ability of our single specialty pharmacy distributor to process orders in a timely manner and satisfy its 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;

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- our plans to pursue development of Translarna for additional indications other than Duchenne muscular dystrophy, cystic fibrosis and MPS I, caused by nonsense mutations;

- our ability to maintain the marketing authorization of Translarna for the treatment of nmDMD in the European Economic Area, which is conditioned upon completion of our Phase 3 confirmatory trial in nmDMD, among other things, and subject to annual review and renewal by the EMA following its reassessment of the risk-benefit balance of the authorization;

- our ability to advance our earlier stage programs, including our antibacterial program;

- our plans to pursue research and development of other product candidates;

- the potential advantages of Translarna;

- our estimates regarding expenses, future revenues, 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;

- 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 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," 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 orally administered, small molecule therapeutics targeting an area of RNA biology we refer to as post-transcriptional control. 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. 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. Our internally discovered pipeline addresses multiple therapeutic areas, including rare disorders, oncology and infectious diseases.

Our lead product, Translarna (ataluren) received marketing authorization from the European Commission, or EC, 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. Our authorization in the EEA is subject to annual review and renewal by the European Medicines Agency, or EMA, following its reassessment of the risk-benefit balance of the authorization, which we refer to as the annual EMA reassessment. This marketing authorization is further conditioned on our ability to complete our global, confirmatory Phase 3 clinical trial in nmDMD, which we refer to as ACT DMD, and submit the final report, including additional efficacy and safety data from the trial, during 2015. See "Business Regulation in the European Union" on page 40 and "Risk Factors Risks Related to Regulatory Approval of our Product and Product Candidates" on page 77 for further detail regarding the EMA's approval process, including a description of the risk-benefit balance.

We launched Translarna on a commercial basis in Germany in December 2014 and expect to expand our launch activities across the EEA throughout 2015 and future years, subject to successful completion of pricing and reimbursement negotiations. Concurrently, we have been pursuing reimbursed early access programs, or EAP programs, in selected countries where those mechanisms exist, both within the EEA and in those countries outside of the EEA that will reference the EMA approval. In December 2014, we began filing our New Drug Application, or NDA, with the U.S. Food and Drug Administration, or FDA, on a rolling basis for Translarna for the treatment of nmDMD. Our ACT DMD trial is ongoing with top-line data expected in the fourth quarter of 2015. Assuming positive data, we intend to complete our NDA submission in late 2015 and, if granted priority review and approval by the FDA, believe we have the potential to begin commercialization in the U.S. shortly thereafter.

We are currently enrolling a global, confirmatory Phase 3 clinical trial of Translarna for the treatment of cystic fibrosis caused by nonsense mutations, or nmCF. We refer to this trial as ACT CF. We anticipate completing enrollment in this trial by the end of 2015 with top-line data about a year later. In the second half of 2015, we intend to file a variation to our marketing authorization of Translarna in the European Economic Area, described above, to seek approval for the treatment of nmCF. See "Business Regulation in the European Union" on page 40 for further detail regarding the variation process. If approved, such variation will likely be subject to annual review and renewal by the EMA and conditioned upon our ability to provide comprehensive clinical data from ACT CF in a similar manner as our marketing authorization for Translarna in nmDMD.

We are also pursuing the development of Translarna for the treatment of mucopolysaccharidosis type I caused by nonsense mutation, or nmMPS I. We are initiating our Phase 2 proof-of-concept

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clinical study in nmMPS I and expect data by the end of 2015. We expect to initiate a proof-of-concept study for Translarna in at least one additional indication during 2015.

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 nmDMD, nmCF and MPS I.

Based on its understood mechanism of action, Translarna may have benefit in the treatment of patients with any genetic disorder that arises as a result of a nonsense mutation. The marketing authorization granted by the EC, described above, was primarily based upon the safety and efficacy results of our prior Phase 2b clinical trial of Translarna for the treatment of nmDMD. We believe that by incorporating our learnings from our completed trials in Translarna, including natural history data and our analysis, we have been able to enhance our trial designs for ACT DMD and ACT CF. We completed our Phase 2b clinical trial of Translarna for the treatment of nmDMD in 2009 and we completed a Phase 3 clinical trial of Translarna for the treatment of nmCF in 2011. While we did not achieve the primary efficacy endpoint in either trial with the pre-specified level of statistical significance, we believe that the collective data from these trials, including retrospective and subgroup analyses that we have performed, provide strong support for concluding that Translarna was active and showed clinically meaningful improvements over placebo in these trials.

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. In January 2014, a Phase 1 single ascending dose, placebo-controlled clinical study in healthy volunteers was initiated. The primary objectives of this trial were to explore safety and pharmacokinetics of the drug candidate, RG7800. Preliminary findings in the Phase 1 study indicate that RG7800 was well-tolerated at all dose levels studied. Additionally, RG7800 demonstrated a dose-dependent effect on splicing of the SMN2 gene, as shown by a change in the ratio of full-length SMN2 mRNA to SMN2 mRNA without exon 7 (SMND7), which may be interpreted as proof of mechanism in terms of the expected pharmacodynamic effect. MOONFISH, a Phase 2, multi-center, randomized, double-blind, placebo-controlled, multiple-dose clinical trial in SMA patients was initiated in November 2014. We received $17.5 million in milestone payments from Roche during 2014 in connection with these program advancements.

In addition, we have a pipeline of product candidates that are in early clinical and preclinical development. Our cancer stem cell program targeting chemotherapy resistant cancers successfully completed IND-enabling studies in 2014 and is expected to begin a Phase 1 clinical study in the first half of 2015. Our preclinical and discovery programs are focused on the development of new treatments for multiple therapeutic areas, including neuromuscular disease, oncology and infectious disease. 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.

Significant Developments in 2014

Translarna authorized in the European Economic Area: In August 2014, PTC's lead product, Translarna, received marketing authorization in the 31 member states of the EEA for the treatment of nmDMD, representing the first ever approved treatment for the underlying cause of the disease. Reimbursed early access programs were authorized in a number of countries both within and outside of the EEA throughout the second half of the year. In December 2014, PTC launched Translarna on a commercial basis in Germany. PTC's approval in the EEA is subject to annual EMA reassessment and is further conditioned on the completion of, and submission of the final report for, ACT DMD, during 2015.

Rolling New Drug Application submitted for Translarna in the U.S.: In December 2014, PTC began submitting a rolling NDA to the FDA for the approval of Translarna in nmDMD. We

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expect to launch Translarna for nmDMD in the U.S. in the first half of 2016, subject to FDA review.

Confirmatory Phase 3 ACT CF trial initiated: In June 2014, PTC initiated ACT CF. PTC intends to file a variation to its marketing authorization for Translarna in the EEA described above to seek approval for the treatment of nmCF in the second half of 2015. If approved, such variation will likely be subject to annual review and renewal by the EMA and conditioned upon our ability to provide comprehensive clinical data from ACT CF in a similar manner as our marketing authorization for Translarna in nmDMD.

SMA program completed Phase 1 study in healthy volunteers and began Phase 2 study in SMA patients: In the spring of 2014, the Phase 1 clinical study was successfully completed. All doses studied were safe and well tolerated. Additionally, a dose-dependent effect on SMN2 splicing as shown by a change in the ratio of full-length SMN2 mRNA to SMN2 mRNA without exon 7 (SMND7) was demonstrated, which is interpreted as proof of mechanism in terms of the expected pharmacodynamic effect. In November 2014, a Phase 2 clinical study, called MOONFISH, was initiated in SMA patients.

Products and Development Programs

The following table summarizes key information about our most advanced product development programs. All of the compounds in these programs are new chemical entities that we identified using our proprietary technologies.

Program	Development status	Partner
Translarna for nmDMD	Marketing authorization granted by EC(1)	N/A
Translarna for nmCF	Confirmatory Phase 3 ACT DMD fully enrolled; top-line data expected in fourth quarter of 2015 Confirmatory Phase 3 ACT CF trial ongoing Enrollment in ACT CF expected by end of 2015	N/A
Translarna for nmMPS I	Initiating Phase 2 proof-of-concept study	N/A
Spinal muscular atrophy	Phase 1 clinical study completed	Roche SMA Foundation
Cancer stem cell program (PTC596)	Phase 2 clinical study initiated	N/A
Antibacterial (PTC672)	Phase 1 clinical study to be initiated in first half of 2015 Initiating IND-enabling studies	N/A

(1) Subject to annual EMA reassessment and the completion of, and submission of the final report for, ACT DMD, during 2015.

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 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

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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 nmDMD, nmCF and nmMPS I, and other genetic disorders for which a nonsense mutation is the cause of the disease. Genetic tests are available for many genetic disorders, including Duchenne muscular dystrophy, cystic fibrosis and MPS I, 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 involved over 750 individuals dosed with Translarna.

Nonsense mutation Duchenne muscular dystrophy (nmDMD)

Muscular dystrophies are genetic disorders involving progressive muscle wasting and weakness. Duchenne muscular dystrophy is the most common and one of the most severe types of muscular dystrophy. Duchenne muscular dystrophy 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, Duchenne muscular dystrophy occurs almost exclusively in young boys. According to Parent Project Muscular Dystrophy, Duchenne muscular dystrophy occurs in approximately 1 in 3,500 live male births. Based on this prevalence data, we estimate that Duchenne muscular dystrophy affects a total of approximately 15,000 boys and adolescents in the United States. Based on data from Orphanet, a public reference portal for information on rare disorders and orphan drugs, we estimate that Duchenne muscular dystrophy affects a total of approximately 19,000 boys and adolescents in the European Union. Genetic tests are available to determine if a patient's Duchenne muscular dystrophy 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 Duchenne muscular dystrophy in approximately 13% of patients. Overall, we estimate that the potential opportunity for a treatment for nonsense mutation DMD is approximately 7,000 patients worldwide including 2,000 patients in the United States, 2,500 patients in the European Union and 2,500 patients in the rest-of-world including Latin America, Japan and Australia. nmDMD is an ultra-rare, life threatening disorder. Without treatment, patients with Duchenne muscular dystrophy typically lose walking ability by their early teens, require ventilation support in their late teens and, eventually, die due to heart and lung failure. The average age of death for Duchenne muscular dystrophy patients is in their mid-twenties.

Commercial efforts for Translarna in nonsense mutation Duchenne muscular dystrophy

In August 2014, we were notified that the European Commission, or EC, granted marketing authorization for Translarna for the treatment of nmDMD in ambulatory patients aged five years and older. The marketing authorization allows us to market Translarna in the European Economic Area, or EEA, which is comprised of the 28 member states of the European Union plus Norway, Iceland and Liechtenstein. Our marketing authorization is subject to our satisfaction of certain conditions and subject to annual review and renewal by the European Medicines Agency, or EMA, following its reassessment of the risk-benefit balance of the authorization. We submitted a marketing authorization renewal request to the EMA in February 2015. We plan to seek to renew the marketing authorization on an annual basis until our obligations have been fulfilled. As part of the marketing authorization granted by the EC, we are required to complete ACT DMD and submit the final report, including additional efficacy and safety data from the trial by the end of 2015.

This authorization was primarily based on safety and efficacy results and our retrospective analyses of study data submitted from our 48-week, 174-patient Phase 2b double-blind, placebo controlled trial. Our post-hoc retrospective analysis from this trial showed that nmDMD patients treated with Translarna (40 mg/kg given daily) walked on average 31.3 meters farther than patients on placebo, as

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measured by the change in six-minute walk distance from baseline to Week 48. Positive trends in the rate of decline in ambulation was observed in patients receiving Translarna based on an analysis of time to 10 percent worsening in six-minute walk distance. Safety results showed that Translarna was generally well tolerated. Serious adverse events were infrequent and none were considered to be related to Translarna.

During 2014 we engaged in significant commercialization efforts with respect to Translarna for the treatment of nmDMD. In connection with the expansion of our global presence, we established our international headquarters in Dublin, Ireland. We commenced our commercial launch of Translarna in Germany in December 2014, and expect other key countries in the EEA to follow throughout 2015 and beyond, subject to successful completion of pricing and reimbursement negotiations. In the second half of 2014, we began submitting country-specific market access submissions for our initial launch countries. The market access process, including pricing and reimbursement negotiations, varies from country to country and can take over 18 months in certain circumstances. We ultimately intend to market Translarna in all markets in the EEA where market access is possible. We currently expect Translarna to be priced at levels consistent with the pricing for other therapies for the treatment of rare disorders where high unmet medical need exists.

In parallel, during 2014 we sought and received authorization for reimbursed early access programs for Translarna for nmDMD patients in selected territories, which we refer to as our EAP program. Our EAP program is intended to make Translarna available to patients before commercial product becomes available in those countries in accordance with local regulations. Funded named patient programs for Translarna, which form part of our EAP program, have already been authorized in Spain, Israel, Turkey, Columbia and Greece. In July 2014, the French National Agency for Medicines and Health Products Safety granted a Temporary Authorization for Use, or ATU cohort, and in December 2014, Translarna was approved for reimbursement on a cohort basis in Italy. Under a named patient program a physician on behalf of the specific, or "named" patient requests access to Translarna, whereas, the ATU cohort in France and the reimbursement program in Italy allows for a broader temporary authorization for use for nmDMD meeting the inclusion criteria.

We expect to seek regulatory approval for Translarna in those territories outside of the European Economic Area that will reference the marketing authorization in the EEA described above as the basis for a local market authorization process. This will include specific countries where we have elected to market Translarna through a third-party distributor/marketing partner.

During the fourth quarter of 2014 we initiated a rolling new drug application, or NDA with the FDA for Translarna as a treatment for nmDMD. We believe this process gives the FDA an opportunity to conduct a meaningful review of most of the segments of our NDA, ahead of reviewing our ACT DMD data. We expect that the submission of the ACT DMD data will complete our rolling NDA and allow for FDA review. Concurrently, in preparation for a potential U.S. launch in the first half of 2016, we have begun building out our commercial team and infrastructure in the U.S.

Ongoing clinical development of Translarna in nonsense mutation Duchenne Muscular Dystrophy

We are currently conducting a global, confirmatory Phase 3 clinical trial to evaluate the efficacy and safety of Translarna (ataluren) in patients with nmDMD, which we refer to as the Ataluren Confirmatory Trial in DMD, or ACT DMD. ACT DMD is a multicenter, randomized, double-blind, placebo controlled Phase 3 clinical trial. In September 2014, we completed enrollment of approximately 230 patients at investigational sites worldwide in ACT DMD and top-line data is expected in the fourth quarter of 2015. In designing ACT DMD, we sought to reflect the views expressed by both the EMA and the FDA in our discussions with these regulatory authorities. We believe that these trial results, if favorable, could serve as the basis for full approval by the EMA and the FDA of Translarna for the treatment of nmDMD. We expect to be able to submit applications for full marketing approval of

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Translarna for the treatment of nmDMD in both the European Union and the United States by the end of 2015.

The primary objective of ACT DMD is to evaluate the effect of Translarna on ambulation. The primary efficacy endpoint specified in our trial protocol is mean change from baseline over 48 weeks in distance walked during a 6-minute walk test, which we also refer to as 6-minute walk distance. The 6-minute walk test is well established as an endpoint for a number of different rare and orphan diseases involving muscle wasting and weakness. Following completion of our Phase 2b clinical trial described below, the 6-minute walk test has become the most common primary endpoint currently used in Duchenne muscular dystrophy clinical trials. Supportive analyses of ambulation in our trial protocol includes proportion of patients with at least 10% worsening in 6-minute walk distance at week 48 of the trial compared to baseline; time from baseline to persistent 10% worsening in 6-minute walk distance; and change from baseline in percent of predicted 6-minute walk distance compared to healthy boys matched for age and height, which we refer to as %- predicted 6-minute walk distance.

Secondary endpoints in the trial include change in timed tests of muscle function based on time to climb four stairs, descend four stairs and run/walk 10 meters. Timed function tests are well established in the clinical evaluation of Duchenne muscular dystrophy and are generally accepted to be predictive of future loss of ambulation. Restoration of dystrophin stabilizes muscle membranes, so that the integrity of muscle fibers is maintained, but does not directly increase muscle strength. As a result, we believe that timed function tests provide a more sensitive measure of treatment effect than measures of muscle strength. In addition, because many Duchenne muscular dystrophy patients have very low baseline muscle strength, it is difficult to demonstrate a difference in the rate of decline of muscle strength in these patients. The trial protocol also includes as secondary endpoints a composite of muscle function tests specifically designed for ambulant Duchenne muscular dystrophy patients, referred to as the North Star Ambulatory, and a PTC-developed disease symptom survey that will be based on patient-reported changes in activities of daily living.

The ACT DMD trial protocol specifies certain key inclusion criteria for patients enrolled in the trial: the patient must be seven through 16 years of age; at baseline, the patient must walk no more than 80% of predicted 6-minute walk distance compared to healthy boys matched for age and height, but have the ability to walk at least 150 meters during the 6-minute walk test; 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. We are performing study assessments at clinic visits every eight weeks. Patients enrolled in ACT DMD will undergo 48 weeks of blinded treatment prior to the final analysis and will be stratified based on age, baseline 6-minute walk distance, and duration of prior use of corticosteroids.

At the completion of blinded treatment, an open label continuation trial is available to patients who successfully complete the trial in countries where Translarna is not commercially available at that time. Patients in the continuation trial will receive Translarna in the same dosing regimen as in ACT DMD.

The study population and outcome measures that we are using in ACT DMD are based on, and reflect our analysis of the results of, our completed Phase 2b clinical trial for the treatment of nmDMD, including data regarding disease progression, referred to as natural history data, based on patient age and baseline walking ability. Specifically, in our Phase 2b clinical trial:

- Patients who were younger than seven years of age tended to have stable or increasing 6-minute walk distance over 48 weeks. We believe that this reflects the fact that growth and development predominate over disease progression at these ages. Patients seven years of age and older typically had declining 6-minute walk distance over 48 weeks, indicating that they were in the

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decline phase of the disease. Accordingly, to focus on patients likely to be in the decline phase of the disease, our Phase 3 clinical trial design requires that patients be at least seven years of age.

The 6-minute walk distance for patients at least seven years of age decreased at different rates over 48 weeks depending on their baseline 6-minute walk distance. Patients whose baseline 6-minute walk distance was greater than 350 meters tended to have stable 6-minute walk distance over 48 weeks. Patients with baseline 6-minute walk distance of less than 350 meters generally declined over 48 weeks, some to the point of becoming non-ambulatory. Accordingly, to focus on patients likely to be in the decline phase of the disease, our ACT DMD trial design requires that patients must walk no more than 80% of predicted 6-minute walk distance compared to healthy boys matched for age and height.

In addition, we performed a post-hoc, retrospective subgroup analysis of patients from our completed Phase 2b clinical trial who would meet the enrollment criteria for ACT DMD. This analysis showed a much larger treatment effect in mean change in 6-minute walk distance over 48 weeks between Translarna and placebo in this subgroup than in the overall population included in the Phase 2b clinical trial.

In light of the natural history data from our Phase 2b clinical trial and this retrospective subgroup analysis, ACT DMD is focused on patients in the decline phase of the disease based on age and baseline 6-minute walk distance. The intent of focusing on patients in the decline phase of the disease is to enhance the demonstration of Translarna's effect to slow decline in walking ability. In addition, we believe that by only enrolling patients who are being treated with systemic corticosteroids, the variability of 6-minute walk distance results will be reduced. Notwithstanding that we expect a larger treatment effect and less variability of results in ACT DMD than in our Phase 2b clinical trial, the sample size of patients in our ACT DMD is designed to be large enough to achieve statistical significance even if we achieve the same treatment effect and similar variability as in our Phase 2b clinical trial.

Completed clinical trials of Translarna in nonsense mutation Duchenne muscular dystrophy

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 6-minute walk distance 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 6-minute walk distance at week 48 of the trial compared to baseline and time to persistent 6-minute walk distance 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 6-minute walk test, 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

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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 6-minute walk distance, 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 6-minute walk distance from baseline to 48 weeks specified in the trial protocol in the intent-to-treat, or ITT, population. The ITT population included all 174 randomized patients with a valid 6-minute walk test available at baseline and at least one post-baseline visit. Analysis of the results of the ITT population showed that 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 6-minute walk distance 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 6-minute walk distance 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 Duchenne muscular dystrophy 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 6-minute walk distance 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 6-minute walk distance data were non-normally distributed, our pre-specified analysis used rank-transformed data in which the 6-minute walk distance 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 6-minute walk distance 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 6-minute walk distance 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 6-minute walk distance values that did not accurately reflect their pre-treatment ambulatory ability. These baseline 6-minute walk tests were incorrectly classified as valid by the investigative site, and the

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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	
		Translarna	Translarna
		40 mg/kg/day	80 mg/kg/day
Summary of change from baseline to week 48	**Placebo N=57**	**N=57**	**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 6-minute walk distance 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 6-minute walk distance 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 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 40 mg group to the 80 mg group were nausea (12.3% for placebo, 14.0% for the 40 mg group and 16.7% for the 80 mg group), abdominal pain (7.0% for placebo, 12.3% for the 40 mg group and

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16.7% for the 80 mg group), pain in extremity (10.5% for placebo, 12.3% for the 40 mg group and 13.3% for the 80 mg group), flatulence (7.0% for placebo, 8.8% for the 40 mg group and 11.7% for the 80 mg group) and nasal congestion (7.0% for placebo, 8.8% for the 40 mg group and 10.0% for the 80 mg group). 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 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)

Cystic fibrosis is among the most common life-threatening genetic disorders worldwide. It is caused by a mutation in the DNA that results in either the absence or very low levels of the cystic fibrosis transmembrane conductance regulator, or CFTR, protein. Cystic fibrosis results in the body producing abnormally thick and sticky mucus that clogs multiple organs, including the lungs, pancreas and liver. Cystic fibrosis leads to progressive loss of lung function, potentially life-threatening lung infections, permanent pancreatic damage and malnutrition. The average age of death for cystic fibrosis patients is approximately 27 years.

According to the Cystic Fibrosis Foundation, cystic fibrosis occurs in approximately one of every 3,500 live births in the United States, with approximately 1,000 new cases diagnosed each year in the United States. Commercially available genetic testing can determine if a patient's cystic fibrosis is caused by a nonsense mutation. According to the Cystic Fibrosis Foundation, the disease affects approximately 30,000 adults and children in the United States. Based on data from the Journal of Cystic Fibrosis, we believe the disease affects between approximately 37,000 and 42,000 adults and children in the European Union. Based on information from the Cystic Fibrosis Foundation, we estimate that nonsense mutations are the cause of cystic fibrosis in approximately 10% of patients, or approximately 3,000 patients in the United States and approximately 3,700 to 4,200 patients in the European Union.

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Mutations causing cystic fibrosis are categorized in five different classes, Class I through Class V. Class I consists of nonsense mutations and is the most severe because there is absence of CFTR production and no CFTR on the surface of the lung cells. Patients from six to 18 years of age with two Class I mutations, one on each of a pair of genes, have on average 10% lower forced expiratory volume in one second, or FEV_1, measures than patients with two Class II mutations. FEV_1 is a measure of the volume of air that has been exhaled at the end of the first second of forced expiration. Translarna targets Class I mutations. Class II mutations are targeted by corrector drugs, which promote the production or movement of CFTR protein from within the cell to the cell surface. In contrast, the milder mutations, Class III, IV and V, are targeted by potentiator drugs, which enhance the effect of abnormal CFTR that is already present on the cell surface.

There is currently no marketed therapy approved to correct defective CFTR production and function in patients with nmCF. For nmCF patients, available treatments do not address the underlying cause of the disease and are designed only to alleviate the symptoms of the disease. These treatments include chest physical therapy to clear the thick mucus from the lungs, antibiotics to treat lung infections and a mucus-thinning drug designed to reduce the number of lung infections and improve lung function. In addition, the majority of cystic fibrosis patients take pancreatic enzyme supplements to assist with food absorption in digestion.

Ongoing clinical development of Translarna in nonsense mutation cystic fibrosis

At the end of the second quarter of 2014, we initiated a global, confirmatory Phase 3 clinical trial to evaluate the efficacy and safety of Translarna (ataluren) in patients with nonsense mutation cystic fibrosis which we refer to as the Ataluren Confirmatory Trial in CF, or ACT CF. ACT CF is a randomized, double-blind, placebo-controlled, study of Translarna in patients six years of age or older with nmCF not receiving chronic inhaled aminoglycosides. We plan to conduct this trial in approximately 208 patients and we expect to complete enrollment for this trial in the second half of 2015 and have initial, top-line data available approximately one year later.

The primary objective of ACT CF is to evaluate the effect of Translarna on pulmonary function relative to placebo. The primary efficacy endpoint specified in our trial protocol is relative change in percent of predicted forced expiratory volume in one second, or FEV_1. Percent of predicted FEV_1, or %-predicted FEV_1, is based on a comparison to healthy individuals matched for age, height and gender. Secondary efficacy endpoints in the trial include pulmonary exacerbation rate, based on specified signs and symptoms; respiratory health quality of life measures assessed by the CFQ-R respiratory domain; and body weight and body mass index.

The ACT CF trial protocol specifies certain key inclusion criteria for patients enrolling in the trial including that the patient must be at least six years of age, have sweat chloride in excess of a specified level as evidence of the severity of the disease, and have %-predicted FEV_1 between 40% and 90% of those predicted for healthy people of similar age, sex, and height.

The ACT CF trial protocol provides for the exclusion of patients from the trial if, among other things, they are receiving chronic inhaled aminoglycoside antibiotics or have used aminoglycosides within 28 days prior to screening, have recently been treated with intravenous antibiotics, have major complications of lung disease, or have previously received Translarna treatment.

Study assessments will be performed at clinic visits every eight weeks during the 48 weeks of blinded treatment prior to the final analysis. Patients will be stratified based on age, screening %-predicted FEV_1 and chronic use of inhaled antibiotics.

The study population and outcome measures that we are using in ACT CF are based on, and reflect our analysis of the results of, our completed Phase 3 clinical trial for the treatment of nmCF, including data regarding relative change from baseline in %-predicted FEV_1, and other earlier work.

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We believe that the data from this trial showed a positive trend favoring Translarna versus placebo on lung function in patients not receiving chronic inhaled tobramycin. 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 support the hypothesis that inhaled tobramycin may interfere with Translarna's mechanism of action. Specifically, in patients not receiving chronic inhaled tobramycin in our completed Phase 3 clinical trial, we observed a difference in mean relative change from baseline in %-predicted FEV_1 at week 48 of 5.7% favoring Translarna (nominal p=0.008), consistent with the targeted treatment effect size. Patients receiving chronic inhaled tobramycin did not show a benefit for Translarna compared to placebo in %-predicted FEV_1. In contrast, the treatment effect was similar in patients receiving colistin or aztreonam compared to patients not receiving colistin or aztreonam. Additionally, patients not receiving chronic inhaled tobramycin had a 41% lower pulmonary exacerbation rate on Translarna than placebo (nominal p=0.005). Patients receiving chronic inhaled torbramycin did not show a benefit in pulmonary exacerbation rate on Translarna as compared to placebo.

Accordingly, to focus on the patient population that we believe can most readily demonstrate the effect of Translarna, patients receiving chronic inhaled aminoglycoside antibiotics or who have used aminoglycosides within 28 days prior to screening are not eligible to participate in ACT CF.

At the completion of blinded treatment, an open label continuation trial will be available to patients who successfully complete the confirmatory Phase 3 ACT CF clinical trial in countries where Translarna is not commercially available at that time for the treatment of nmCF. Patients in the continuation trial will receive Translarna in the same dosing regimen as in ACT CF.

Summary of regulatory status and strategy for Translarna in nmCF

Prior to initiating ACT CF we concluded discussions with the EMA and FDA concerning the results of our prior completed Phase 3 clinical trial and our proposed trial protocol for ACT CF. Our interactions with the FDA regarding the clinical development design options which would have the potential to support an NDA in 2013 did not achieve a consensus between the EMA and FDA views. However, based on these interactions, we nonetheless proceeded with ACT CF consistent with feedback from the EMA on our trial design.

The EMA recognized that there is an unmet medical need and advised us that it would consider a marketing authorization application, or MAA, for marketing authorization of Translarna for patients with nmCF based on the data from our prior completed Phase 3 clinical trial. The EMA advised us of topics related to the outcomes observed in our prior completed Phase 3 clinical trial that may need to be addressed in any submitted MAA. For example, the EMA noted that, with respect to our completed Phase 3 clinical trial, additional discussion may be required to address the clinical relevance of the observed relative change in %-predicted FEV_1 after taking into account all possible biases and confounders, other possible explanations of the lack of statistical significance observed in relative change in %-predicted FEV_1 other than the interference of inhaled antibiotic tobramycin with Translarna's mechanism of action, the lack of clear support of treatment effect from secondary or tertiary endpoints, the evolution of the relative change in %-predicted FEV1 over 48 weeks in the placebo group being worse than expected, and additional matters.

Following our discussions with the EMA in relation to a potential MAA filing for Translarna in nmCF, the EMA granted us marketing authorization for Translarna in nmDMD, which is conditioned upon the successful completion of ACT DMD and subject to annual review and renewal by the EMA following its reassessment of the risk-benefit balance of the authorization. As a result, we currently intend to submit a variation to this marketing authorization with the EMA to seek to include Translarna in nmCF in the second half of 2015. Our submission will use the clinical results achieved in

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our prior Phase 3 clinical trial, however, because we believe that the EMA's Committee for Medicinal Products for Human Use, or CHMP, will consider the status of ACT CF enrollment important at the time of our submission we are holding our variation until ACT CF is well underway. Approval of the marketing authorization variation will depend on the EMA's assessment of the relative risks and benefits of conditional approval and our ability to provide comprehensive clinical data from a post-approval confirmatory trial, such as ACT CF. We may not be able to demonstrate the required relative risk-benefit profile or the likelihood that we can provide the required confirmatory trial data for Translarna for this indication. There is substantial risk that the EMA will not grant us approval of Translarna for the treatment of nmCF on a conditional basis or at all.

We had interactions with the FDA in 2012 and 2013 with regards to, respectively, our completed Phase 3 clinical trial of Translarna for the treatment of nmCF and the clinical trial design which would have the potential to support an NDA. While we have incorporated feedback from the FDA into our ACT CF trial design, we believe that certain key recommendations from the FDA are not appropriate. Two of the key recommendations that we are in disagreement with are the designation of FEV_1, CF pulmonary exacerbations, and body mass index as three co-primary endpoints for the trial and a suggested three-year trial duration. FEV_1 is the primary endpoint in ACT CF, with CF pulmonary exacerbations and body mass index key secondary endpoints, which is consistent with other clinical trials currently ongoing in cystic fibrosis and our earlier discussions with the FDA. Additionally, we believe that extending the study duration to three years would result in a number of complications that would ultimately limit the robustness of the data and conclusions that could be drawn from the results.

During 2014, the FDA granted priority review of an NDA submitted by an unaffiliated company based on data from two Phase 3 clinical trials for the treatment of cystic fibrosis caused by a Class II mutation. These trials used absolute change in percent predicted forced expiratory volume in one second as the primary endpoint and absolute change in body mass index and number of pulmonary exacerbations as two key secondary endpoints. We believe the endpoints utilized in these trials are consistent with the endpoints we are utilizing in ACT CF. Additionally, we believe that the results achieved in these trials support our position that stabilization or moderate improvement in FEV_1 outcomes over the course of 48 weeks is clinically meaningful in more severe classes of cystic fibrosis. However, there can be no assurance that the FDA will agree with our interpretation of this data or the conclusions we have reached, even if we successfully achieve the primary and secondary endpoints established for ACT CF.

Completed clinical trials of Translarna in nonsense mutation cystic fibrosis

Phase 3 trial in nonsense mutation cystic fibrosis

Overview. In June 2012, we announced the results of a multicenter, international, randomized, double-blind, placebo controlled Phase 3 clinical trial assessing the effects of Translarna in 238 patients with nmCF. The primary objective of this trial was to evaluate the effect of Translarna on pulmonary function relative to placebo. The primary efficacy endpoint was relative change in %-predicted FEV_1. The trial assessed pulmonary exacerbation rate as a secondary efficacy endpoint.

Patients enrolled in this trial were at least six years of age, weighed at least 16 kilograms and had a %-predicted FEV_1 between 40% and 90%, sweat chloride in excess of a specified level, a minimum level of resting oxygen saturation in the blood, and documentation of a nonsense mutation in at least one copy of the CFTR gene. We excluded patients from the trial if they had any change in treatment or prophylaxis for cystic fibrosis related conditions within four weeks prior to start of study treatment, had evidence of pulmonary exacerbation or acute upper or lower respiratory tract infection, were treated with intravenous antibiotics or had major complications of lung disease.

We stratified patients in this trial based on age, baseline %-predicted FEV_1 and chronic use of inhaled antibiotics. Patients were randomized in a 1:1 ratio to receive placebo or Translarna at a daily

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dose of 40 mg/kg. The trial protocol specified a clinic visit every eight weeks to assess FEV_1. The treatment duration was 48 weeks.

We designed the trial to detect a mean relative change in %-predicted FEV_1 from baseline to end of treatment at week 48 that was at least 6% greater in the Translarna arm than in the placebo arm. Of the 238 total patients, 120 patients received Translarna and 118 patients received placebo, with 34 patients withdrawing prematurely, including 20 patients on Translarna and 14 patients on placebo. As specified in the trial protocol, the ITT population included all randomized patients who had FEV_1 data available at baseline and at least one post-baseline visit, resulting in 116 patients on Translarna and 116 patients on placebo being included in the ITT population.

The percent of the initial total value that was changed is referred to as relative change. The change in percentage that is representative of the difference alone is referred to as absolute change. For example, when 50% changes to 55%, the result is a 10% relative change and a 5% absolute change.

Primary analysis. The primary analysis of relative change in %-predicted FEV_1 in this trial showed a 3.0% difference (2.5% decrease on Translarna, 5.5% decrease on placebo) at week 48 favoring Translarna (p=0.124), which was not statistically significant. An analysis of relative change in %-predicted FEV_1 based on the average treatment effect across all post-baseline visits showed a statistically significant difference of 2.5% favoring Translarna compared to placebo (1.8% decrease on Translarna, 4.3% decrease on placebo; p=0.0478). The analysis of treatment effect across all visits was part of the pre-specified statistical model for this trial and has served as the primary analysis of FEV_1 data in other cystic fibrosis therapeutic trials conducted by other companies. The analysis of absolute change in %-predicted FEV_1 at week 48 showed a 1.8% difference (1.3% decrease on Translarna, 3.1% decrease on placebo; p=0.136).

Subgroup analysis of patients not receiving inhaled antibiotics. As described above, we pre-specified three stratification factors in this trial: age, baseline FEV_1, and chronic use of inhaled antibiotics. In this trial, there was a statistically significant interaction (nominal p=0.0072) between treatment and chronic inhaled antibiotic use. As discussed in more detail below, we believe that the inhaled antibiotic tobramycin interfered with Translarna's mechanism of action. The interactions between treatment and age and between treatment and baseline %-predicted FEV_1 were not significant.

For the subgroup of patients not receiving chronic inhaled antibiotics, the difference in mean relative changes from baseline in %-predicted FEV_1 at week 48 was 6.7% favoring Translarna (nominal p=0.013). The average treatment effect across all post-baseline visits was 5.6% (nominal p=0.0006). For absolute change in %-predicted FEV_1, the average treatment effect across all post-baseline visits was 2.4% (nominal p=0.037). In contrast, patients that received chronic inhaled antibiotics and Translarna did not exhibit a difference compared to patients that received chronic inhaled antibiotics and placebo.

Approximately 37% of patients in the trial were receiving the chronic inhaled antibiotic tobramycin, and approximately 45% of patients were receiving no chronic inhaled antibiotic. Other chronic inhaled antibiotics that patients received were colistin or aztreonam. We performed analyses comparing patients not receiving chronic inhaled tobramycin to patients receiving chronic inhaled tobramycin. In patients not receiving chronic inhaled tobramycin, the difference in mean relative change from baseline in %-predicted FEV_1 at week 48 was 5.7% favoring Translarna (nominal p=0.008), consistent with the targeted treatment effect size. Patients receiving chronic inhaled tobramycin did not show a benefit for Translarna compared to placebo in %-predicted FEV_1. In contrast, the treatment effect was similar in patients receiving colistin or aztreonam compared to patients not receiving colistin or aztreonam.

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Both tobramycin and Translarna act through modulation of the ribosomal machinery. We believe that the binding of tobramycin to the ribosome may interfere with Translarna's mechanism of action. We explored this hypothesis in a functional cell-based translation assay. In this experiment, Translarna-induced read-through of premature stop codons was diminished when the cells were exposed to Translarna together with tobramycin or gentamicin, but not when Translarna was administered together with colistin or aztreonam, both of which are non-aminoglycosides.

Pulmonary exacerbation rate. The secondary endpoint in this trial was pulmonary exacerbation rate, which is a measure of frequency of lung infections related to cystic fibrosis. FEV_1 and pulmonary exacerbation rate are the two most clinically important outcome measures in cystic fibrosis trials. In the ITT population, we observed a 23% lower pulmonary exacerbation rate in patients receiving Translarna than placebo (p=0.099). This result was not statistically significant. However, we also saw the tobramycin subgroup effect in this endpoint. Patients not receiving chronic inhaled tobramycin had a 41% lower pulmonary exacerbation rate on Translarna than placebo (nominal p=0.005). Patients receiving chronic inhaled torbramycin did not show a benefit in pulmonary exacerbation rate on Translarna as compared to placebo.

Tertiary Endpoints. In this trial, we assessed CFTR function by nasal transepithelial difference, or TEPD, and sweat chloride concentration as tertiary endpoints. TEPD is assessed by means of a standardized, though complex, minimally invasive procedure. In the procedure, a small plastic catheter is used to assess electrical differences across the outer cell membrane of nasal mucosa cells in the nostril. Nasal TEPD is physiologically meaningful because nasal mucosa closely reflects CFTR activity in the lung epithelium. Because of the role of the CFTR protein in transporting chloride across cell membranes and because of the absence of this protein in cystic fibrosis patients, these patients have an abnormal TEPD chloride conductance. Sweat chloride concentration is a commonly used test to diagnose cystic fibrosis and is a measurement of CFTR activity in the sweat gland.

A number of clinical trials for CFTR restoration therapies have used sweat chloride concentration and nasal TEPD as pharmacodynamic endpoints. However, these two endpoints can exhibit varying results, likely because of differences in CFTR regulation and function in the sweat glands as compared to the nasal or lung mucosa, or variation in tissue penetration of different drugs.

Nasal TEPD results were positive in our prior Phase 2 clinical trials discussed below, but sweat chloride testing was not positive in either Phase 2 clinical trial or in our Phase 3 clinical trial. In contrast with our Phase 2 clinical trials, in which we assessed TEPD at a small number of experienced sites, in the Phase 3 clinical trial, TEPD assessments were performed at all centers. This trial was the first time most centers had performed TEPD assessments. In this trial, TEPD results showed high variability and an unexpectedly high response rate on placebo.

The other tertiary endpoints in this trial were hourly cough rate, respiratory domain score from a questionnaire, inflammatory markers and lung computed tomography. Differences between Translarna and placebo for each of these endpoints were small and not statistically significant.

Safety and tolerability. Translarna was generally well tolerated in this clinical trial, 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 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%

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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.

Open label, extension trials of Translarna for treatment of nmCF

In May 2014, we initiated an open label, extension trial for up to 80 patients in order to obtain additional safety and efficacy information in patients with nmCF who participated in our completed Phase 3 clinical trial and are not receiving chronic inhaled aminoglycoside antibiotics. The primary objective of this extension trial is to determine the long-term safety and tolerability of Translarna in patients with nmCF, as assessed by adverse events and laboratory abnormalities. The secondary objective of this study includes the assessment of the efficacy of Translarna, as measured by FEV_1 and pulmonary exacerbation rate, and change from baseline in other safety parameters (e.g., 12-lead ECG measurements, vital signs). As of December 31, 2014, available data from this extension trial indicated no change in the safety profile for Translarna in patients with nmCF.

In December 2013, we completed an open label, extension trial that is providing additional safety information for the long term administration of Translarna in patients with cystic fibrosis who successfully completed 48 weeks of treatment in our completed Phase 3 clinical trial. In addition, this trial was designed to provide supportive long-term efficacy information to better understand the long-term effects of Translarna on pulmonary function and pulmonary exacerbations. This trial enrolled 191 of the patients who completed the double-blind Phase 3 clinical trial described above. Patients in this trial received 40 mg/kg of Translarna a day for a 96 week treatment period. Study assessments were performed at clinic visits every four weeks to eight weeks depending upon the type of outcome measure. The most common adverse events during this completed open label, extension trial were cystic fibrosis pulmonary exacerbation (81.7%), cough (28.8%) and viral upper respiratory tract infection (28.8%). These are the same common adverse events, and are similar in frequency, as those seen in our completed Phase 3 clinical trial. The serious adverse events observed during this trial that were considered possibly related to Translarna were abdominal pain, back pain, difficulty urinating, hydronephrosis, interstitial nephritis, kidney stones, pancreatitis and renal failure. Determination of relatedness of the serious adverse event to Translarna was made by the trial investigator, based on his or her judgment.

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Phase 2 clinical trials of Translarna for treatment of nmCF

In 2006, we completed two open label Phase 2 clinical trials of Translarna for the treatment of nmCF in a combined total of 47 patients age 18 years or older (at one site in Israel and four sites in the U.S.). In 2008, we completed a third open label Phase 2 clinical trial of Translarna for the treatment of nmCF in 30 patients between 6 and 18 years of age (at one site in France and two sites in Belgium). Each of these three trials had a treatment duration of 28 days and was designed in a comparable manner with the goals of obtaining indications of pharmacological activity and to assess dose-response, safety and pharmacokinetics. Each trial had two treatment cycles consisting of a two-week period of continuous Translarna treatment (with either 16 mg/kg per day or 40 mg/kg per day), and then a two-week follow-up period without Translarna treatment, with participants evaluated at the beginning and end of each two-week period in each cycle. We also conducted an open label, extension trial with a treatment duration of three months for the patients who completed the trial at the site in Israel.

The objective in each of these trials was to determine the change in CFTR-mediated chloride conductance in respiratory cells as measured between the beginning and end of treatment for each study participant. To make this determination, we measured the patient's TEPD. TEPD values are expressed in millivolts, or mV. A chloride conductance equal to or more electrically negative than 5.0 mV is generally considered to be in the normal range.

In all trials except those conducted at sites in the U.S., there were statistically significant improvements at the end of the Translarna treatment period in mean total chloride conductance and in the percentage of patients with a total chloride conductance response of at least a 5.0 mV improvement. There were also improvements in the percentage of patients with a chloride conductance in the normal range at the end of treatment. These results indicated the presence of pharmacological activity. These improvements were generally followed in the adult trials by reversions toward baseline with cessation of treatment during the follow-up period. In the trial conducted at sites in the U.S., we did not observe improvements in mean total chloride conductance.

Translarna was generally well tolerated in these trials. Only one serious adverse event was considered possibly related to Translarna. Adverse events that were potentially drug-related were generally mild in severity. These adverse events included pain during urination in several patients. This issue resolved successfully with increased hydration. There were no clinically meaningful safety concerns identified in patients' physical examinations, vital sign measurements or electrocardiograms.

Mucopolysaccharidosis type I (nmMPS I)

Mucopolysaccharidosis I, or MPS I, is a rare genetic disorder that affects many body systems and that leads to organ damage. It is caused by a defect in the gene that makes an enzyme called alpha-L-iduronidase. Because of this defect, cells either produce the enzyme in low amounts or cannot produce it at all. The enzyme is needed to break down substances called "glycosaminoglycans" (GAGs), which are by-products of chemical reactions in the body's cells. If GAGs are not broken down, they build up in the cell, eventually leading to cell, tissue, and organ damage.

Based on their symptoms, patients are classified as having either severe or attenuated MPS I. In the severe form of MPS I, the disease generally presents within the first year of life, features progressive developmental delay and severe progressive physical problems, and usually results in death before 10 years of age without therapeutic intervention. The attenuated form of MPS I is more variable but is associated with onset between ages 3 and 10 years of age, a lifespan ranging from 20 to 30 years of age to near-normal, and near-normal to normal intelligence. Almost all patients with MPS I, across the continuum of disease severity, experience progressive arthropathy affecting all joints and eventually leading to the loss of, or severe restriction of, range of motion

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Globally, MPS I occurs in about 1 in every 100,000 births. It is estimated that 60% to 80% of patients have their disease as a result of a nonsense mutation, which we refer to as nmMPS I. Enzyme replacement therapies do not sufficiently address the central nervous system, skeletal or cardiac symptoms associated with the disorder. Prognosis of patients with MPS I is poor and there is an urgent need for the development of new treatments targeting the underlying cause of MPS I.

Clinical Development of Translarna in nonsense mutation Mucopolysaccharidosis type I

We are currently initiating a Phase 2, multicenter, proof-of-concept study to evaluate the safety and pharmacokinetics of Translarna in patients with nmMPS I during 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. Initial data from this proof-of-concept study is expected by the end of 2015.

Spinal muscular atrophy program

Spinal muscular atrophy is a genetic neuromuscular disease characterized by muscle wasting and weakness. The disease generally manifests early in life. Spinal muscular atrophy 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 produces SMN protein that is less effective because, unlike SMN1, SMN2 does not include a particular nucleotide sequence known as exon 7. According to the SMA Foundation, spinal muscular atrophy is the leading genetic cause of death in infants and toddlers. We estimate that spinal muscular atrophy 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. There is currently no marketed therapy approved to treat the underlying cause of spinal muscular atrophy. Currently available treatments for spinal muscular atrophy are only palliative.

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 spinal muscular atrophy 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 compounds are orally bioavailable, 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 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 and in November 2014, upon the initiation of a Phase 2 clinical study. We also previously received $13.3 million in sponsored research funding for this program from the Spinal Muscular Atrophy Foundation.

The Phase 1 single-ascending dose clinical study in 48 healthy volunteers completed in the first half of 2014 demonstrated that all doses studied were safe, well-tolerated and demonstrated a dose-dependent effect on SMN2 splicing as shown by a change in the ratio of full-length SMN2 mRNA

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to SMN2 mRNA without exon 7 (SMND7), which is interpreted as proof of mechanism in terms of the expected pharmacodynamic effect.

The Phase 2 placebo-controlled, randomized, multiple-dose study will enroll approximately 48 patients with SMA and investigate the safety and tolerability of an investigational survival of motor neuron 2 (SMN2) gene splicing modifier (RG7800) over 12 weeks.

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.

During 2014, we completed preclinical studies for our product candidate, PTC596, for the treatment of chemotherapy resistant cancers through the targeting of cancer stem cells. PTC596 is a first-in-class, oral, potent and selective inhibitor that targets tumor stem cell populations by reducing the function, activity and amount of 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* tests, PTC596 has preferentially depleted cancer stem cells in assays with tumor cell lines from glioblastoma, fibrosarcoma, prostate and colon cancers. Conversely, the cytotoxic chemotherapies carboplatin, temozolomide, methotrexate and indibulin enriched the population of cancer stem cells in this assay.

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 chemotherapy paclitaxel were both effective at controlling 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 either untreated tumors or tumors treated with paclitaxel when transplanted into another mouse. PTC596 has been well tolerated at effective doses in animals. Preliminary data from these 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-resistant cancers. We submitted an investigational new drug application, or IND, for PTC596 with the FDA during the fourth quarter of 2014. In the first half of 2015, we plan to initiate a Phase 1 first-in-human, dose-escalation safety and pharmacokinetic open-label clinical study in advanced cancer patients with solid tumors.

We received grant funding of $5.4 million for our cancer stem cell program from the Wellcome Trust prior to 2014.

Antibacterial program

We have identified and are chemically optimizing several small molecule compounds for the treatment of infections caused by multidrug-resistant Gram-negative bacteria. Our goal is to select lead development compounds that have the potential to be formulated for both intravenous and oral administration. Wellcome Trust awarded us a $5.0 million grant for this program, of which we have received approximately $4.2 million as of December 31, 2014.

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During the third quarter of 2014, we declared a development candidate in our antibacterial program. We are in the process of initiating IND-enabling preclinical safety studies for this compound, PTC672, to allow submission of an investigational new drug application, or IND supporting initiation of clinical assessment. PTC672 is derived from the novel chemical scaffold and has the potential to address the significant need for new treatment options to combat multi-drug resistant Gram-negative *Neisseria gonorrhoeae*. PTC672 is an orally bioavailable, new chemical entity with a novel mechanism of action distinct from all approved antibiotics. PTC672 acts selectively, inhibiting only *Neisseria* and sparing beneficial bacteria, which we believe may be a significant advantage in treating gonorrhea compared to using broad-acting antibiotics.

The increasing prevalence of infections caused by multidrug-resistant bacteria is a global health problem and represents a critical unmet medical need. Many infections caused by multidrug-resistant pathogens occur in patients receiving medical care for serious conditions in hospitals, long-term acute care facilities, such as those providing wound care or ventilation, or nursing homes. Infections acquired in these settings, commonly referred to as nosocomial infections, frequently result in severe pneumonia and infections of the urinary tract and bloodstream. The majority of these cases of pneumonia and infections of the urinary tract and bloodstream are caused by Gram-negative bacteria.

We have identified a novel structural class of molecules that kill bacteria by targeting bacterial DNA synthesis. When tested using *in vitro* minimum inhibitory concentration, or MIC, assays, our compounds have demonstrated broad spectrum antibacterial activity against numerous Gram-negative bacteria, including *E. coli., A. baumannii, K. pneumoniae, H. influenzae, M. catarrhalis, and N. gonorrhoeae.*. We believe that the key differentiating factor of our compounds is their potent antibacterial activity against multidrug-resistant bacteria that are refractory to current drugs, including carbapenems and fluoroquinolones. Through chemical optimization, we have improved MIC levels 100-fold against Gram-negative pathogens and expanded the spectrum of activity to include select Gram-positive species, such as *Staphylococcus aureus*. We also have identified what we believe to be the key structural feature that contributed to activity against drug-resistant pathogens. In animal studies, several analogs within this class of molecules have exhibited good exposure upon intravenous administration and protected mice against lethal *E. coli* infection. We have also identified chemotypes within the broad structural class that selectively inhibit *Neisseria* species. All isolates of *Neisseria gonorrhoeae* tested in vitro, including quinolone-resistant and multi-drug resistant strains, are sensitive to our compounds. Experiments demonstrated that these molecules are effective in a mouse model of gonorrhea after a single oral dose.The Centers for Disease Control and Protection has identified antibiotic resistant *N. gonorrhoeae* as one of the top three urgent threats to public health. Gonorrhea is estimated to affect greater than 800,000 people yearly in the United States.

Scientific Background of Post-Transcriptional Control Processes

Post-transcriptional control processes are the events that occur in cells following the transcription of DNA to make mRNA. These processes regulate how long an mRNA molecule lasts in the cell and how efficiently the mRNA is used to produce its 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 by exons, is interrupted by stretches of nucleotides called introns that are removed immediately after the gene is transcribed from DNA to the precursor messenger RNA, or pre-mRNA. The process of intron removal is called splicing.

The 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 directly code for proteins, 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

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the cell with the UTRs on the mRNA can modulate the translational efficiency of mRNA and how mRNA is degraded and eliminated from the cell.

Our Approach

Our approach to drug discovery and development is to systematically target post-transcriptional control processes that can be modulated 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-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, 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.

We identify target proteins of potential biological and medical relevance to human disease and assess their regulation through UTRs and clinical feasibility. For targets that we select, we precisely identify the UTRs of the target gene.

We use 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 spinal muscular atrophy.

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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 spinal muscular atrophy. 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 nonsense suppression. 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 nonsense suppression at the premature stop codon to produce a full-length protein. In addition to increasing read-through, small molecules that stabilize nonsense-containing mRNAs can enhance the effect of a compound that acts through the nonsense suppression mechanism.

Nonsense suppression also can be designed to identify molecules that can enhance the nonsense suppression effect of Translarna and other nonsense suppression agents to prevent 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 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.

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 spinal muscular atrophy sponsored research program with the SMA Foundation and to research other small molecule compounds with potential for therapeutic use in patients with spinal muscular atrophy. 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.

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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. To date, 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 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 spinal muscular atrophy. 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

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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.

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 milestones, we received $1.6 million in 2013, $0.8 million in 2014 and $0.7 million in the first quarter of 2015. The balance of the grant is payable based on our achievement of an additional milestone.

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), PTC672 (for our antibacterial 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.

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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, we may become obligated to pay to Wellcome Trust development and regulatory milestone payments of up to an aggregate of $35.6 million and single-digit royalties on sales of any research program product.

Continuing financial obligations antibacterial program. To the extent that we develop and commercialize program intellectual property on a for-profit basis ourselves, we may become obligated to pay to Wellcome Trust development and regulatory milestone payments of up to an aggregate of $33.3 million and single-digit royalties on sales of any research program product.

Additional continuing financial obligations cancer stem cell and antibacterial programs. 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. 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.

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.

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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 February 11, 2015, we owned or exclusively licensed a total of 83 U.S. patents and 75 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. Our patent portfolio includes 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 patent rights relating to ataluren (brand name, Translarna) owned by us consist of 18 issued U.S. patents relating to composition of matter, methods of use, formulation 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, including patent term adjustment, 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, absent patent term adjustment. An issued U.S. patent relating to therapeutic method of use is currently scheduled to expire in 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 three granted European patents relating to composition of matter, dosing (low dose regimen) and methods of manufacture of ataluren, as well as one allowed European patent relating to a high dose regimen, and multiple pending European patent applications relating to composition of matter, methods of use and formulations. The expiration dates of the granted and allowed European patents occur for composition of matter in 2024, for low dose and high dose regimen in 2026 and 2027, respectively, 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 market exclusivity 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

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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 obtaining a Supplementary Protection Certificate (SPC). We are presently applying for SPCs in individual countries in which we have a European patent. 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.

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 facilities for the production of clinical or commercial quantities of Translarna or for the compounds that we are testing in our preclinical programs. We currently rely, and expect to continue to rely, on third parties for the manufacture of Translarna and any other product or product candidate that we may develop, other than small amounts of compounds that we synthesize ourselves for preclinical testing.

We obtain our supply of the bulk drug substance for Translarna from two third-party manufacturers and the bulk drug substance for our antibacterial and oncology programs through another third-party manufacturer. We engage a separate manufacturer to provide bulk drug product and expect to finalize our validation of another bulk drug manufacturer in mid-2015. We engage a separate manufacturer to provide fill and finish services for our finished commercial and clinical product and are in the process of completing arrangements with two additional providers to provide these services, initially for our clinical product in early to mid-2015, with commercial product services expected to commence for at least one provider in late 2015. We obtain our supplies of Translarna and

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our other product candidates from these manufacturers pursuant to agreements that include specific supply timelines and volume expectations. 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. If any of these manufacturers should become unavailable to us for any reason, we believe that there are a number of potential replacements, 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 2014, and none are currently expected in 2015. 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.

We currently have a contract with a pharmacy and hospital distributor in the European Union that distributes Translarna for both commercial and clinical programs. We are finalizing our business relationship with a third party logistics provider in the European Union, which we expect to be in place in the first half of 2015.

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 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.

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The competition for Translarna 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 Duchenne muscular dystrophy. Other currently available treatments for Duchenne muscular dystrophy are only palliative. Corticosteroids, such as prednisone and deflazacort are often prescribed to treat some of the symptoms of the disease. Other biopharmaceutical companies are developing treatments for Duchenne muscular dystrophy based on a different scientific approach known as exon-skipping, including BioMarin Pharmaceutical Inc. (following its acquisition of Prosensa Therapeutic in early 2015) and Sarepta Therapeutics. Summit Corporation also has a product candidate in early clinical development designed to increase the production of the protein utrophin, which is functionally similar to dystrophin, to treat Duchenne muscular dystrophy. Nobelpharma, a Japanese company, is currently sponsoring a Phase 2 clinical trial in Japan of its product candidate NPC-14 (arbekacin sulfate), which is a generically available aminoglycoside antibiotic, in boys with nmDMD.

Translarna for nmCF. There are currently no marketed therapeutics approved to treat the underlying cause of nmCF. Vertex Pharmaceuticals' CFTR potentiator drug Kalydeco (ivacaftor) is approved by the FDA and in other territories as a treatment for cystic fibrosis in patients six years of age and older who have a type of mutation in the CFTR gene known as a gating mutation. Vertex Pharmaceuticals also is developing two other product candidates for the treatment of cystic fibrosis in patients who have a type of mutation in the CFTR gene known as a process block mutation. We do not believe that Kalydeco or Vertex's other product candidates, which are designed for the treatment of patients with a mutation other than a nonsense mutation, are applicable for the treatment of patients with nmCF, except possibly in very rare instances in which a patient is heterozygous with both a nonsense mutation and a gating or blocking mutation. Other current treatments for cystic fibrosis are designed to alleviate the symptoms of the disease and depend upon the stage of the disease and the organs involved. Clearing mucus from the lungs is an important part of the daily cystic fibrosis treatment regimen. Chest physical therapy is a form of airway clearance that involves vigorous clapping on the back and chest to dislodge the thick mucus from the lungs. Other treatments for cystic fibrosis include TOBI (tobramycin), an aerosolized antibiotic used to treat lung infections that is marketed by Chiron Corporation, and Pulmozyme, a mucus-thinning drug shown to reduce the number of lung infections and improve lung function, that is marketed by Genentech, Inc. We believe that Translarna is the only product candidate in clinical trials that is designed to treat the underlying cause of nmCF by restoring CFTR activity.

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

Sales and marketing

We began establishing a small commercial organization in Europe in 2013 in support of a potential launch of Translarna. During 2014, our European commercial organization began to grow following the adoption of a positive opinion by the EMA's Committee for Medicinal Products for Human Use regarding our marketing authorization application for the treatment nmDMD. As of December 31, 2014, our international team was comprised of approximately 20 employees, including members of our commercial team who will work with the physicians and patient advocacy groups who are involved in the treatment of patients suffering from nmDMD. This team is comprised of country managers, field-based commercial, legal and finance support, medical affairs, medical information, marketing, quality and supply chain. We have benefitted from significant interest in launching Translarna with strong commercial hires bringing significant experience launching new therapies in the rare disease space. In

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addition, in select territories, we have engaged full time consultants, marketing partners and distribution partners to assist us with our international commercialization efforts. We are evaluating additional 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 where permitted in the EEA and in other permitted territories using both internal and external resources. We expect that our internal team and partnership network will continue to grow in support of the launch in order to maximize access to patients.

During 2014, we sought and received authorization to distribute Translarna under EAP programs in Columbia, Spain, Israel, Turkey, France and Italy. We intend to pursue EAP programs in additional territories, including Brazil, Argentina and Australia, during 2015. We ultimately intend to make Translarna for the treatment of nmDMD available to all eligible patients. In 2015, we anticipate further growing our commercial team in support of additional launches in the EEA and these EAP programs. We also anticipate beginning to establish our preliminary commercial presence both in the U.S. and Japan in anticipation of potential future commercial launch activities.

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.

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.

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.

The new drug approval, or NDA, process

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or the FDCA, and implementing regulations. 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

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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 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 New Drug Application, 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 investigational new drug application, or IND, to 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

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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 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 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 will 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

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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. The applicant also may appeal the decision through the FDA's formal dispute resolution process, which involves appealing the decision through the Center for Drug Evaluation and Research and, ultimately, to the Commissioner of Food and Drugs if necessary. 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 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. 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 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 GMP. 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.

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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 each 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 preclude 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, 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 itself 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. 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 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 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

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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, that 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. Both the PDMA 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 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, 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, and nmMPS I. 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. Competitors may receive approval of different drugs or biologics for the indications for which the orphan product has exclusivity.

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Fast track designation

We have obtained fast track designation from the FDA for our product candidate Translarna for the treatment of nmDMD. The FDA's fast track program is a process designed to facilitate the development and review of new drugs that are intended to treat serious or life threatening conditions and that demonstrate the potential to address unmet medical needs for the conditions. Fast track designation applies to the product for the specific indication for which it is being studied. Thus, it is the development program for a specific drug for a specific indication that receives fast track designation. The sponsor of a product designated as being in a fast track drug development program may engage in close early communication with the FDA including through timely meetings and feedback on clinical trials. Products in the fast track drug development program also may receive priority review or accelerated approval, and sponsors may be able to submit portions of an application on a rolling basis rather than as one complete submission. The FDA may notify a sponsor that its program is no longer classified as a fast track development program if the fast track designation is no longer supported by emerging data or the designated drug development program is no longer being pursued.

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 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.

The FDCA also provides three years of market exclusivity for 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

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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.

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 and nmMPS I. 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 market exclusivity following a marketing authorization. During this market exclusivity period, neither the European Medicines Agency, nor the European Commission nor the 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 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.

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 MAAs 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 nmCF, 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

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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 MAA 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 an MAA 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 risk-benefit 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 risk-benefit 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.

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. For example, we intend to file a variation to our marketing authorization of Translarna for the treatment of nmDMD to seek inclusion of Translarna for nmCF during the second half of 2015. In the case of the introduction of an additional therapeutic indication, the timeframe for the variation procedure is 90 days (plus 10 days for validation) to finalize the EMA assessment, followed by the time required for the European Commission to issue its decision varying the existing conditional marketing authorization. However, in the framework of a variation application assessment procedure, the EMA may send one or more supplementary requests for 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

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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 two months for the marketing authorization holder to submit its responses to such supplementary requests. The 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 two-month procedure. If the CHMP opinion is favorable, the European Commission will vary the marketing authorization to introduce the additional therapeutic indication within 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 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.

In connection with the marketing authorization granted for Translarna for the treatment of nmDMD in the EEA, we are required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products that are in addition to the other conditions of the marketing application described above. We 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 our compliance with applicable requirements, and we 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

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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 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 MAAs 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 an MAA, 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:

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 well being 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

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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. The U.S. government, state legislatures and foreign governments 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. For example, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 expanded Medicare coverage for drug purchases by the elderly and changed the way Medicare covers and pays for pharmaceutical products. Cost reduction initiatives and other provisions of this law may decrease the coverage and reimbursement rate that we may receive for any approved products. Likewise, 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 by increasing the minimum level of Medicaid rebates payable by manufacturers of brand-name drugs from 15.1% to 23.1%, effective 2011, extending the Medicaid rebate to Medicaid managed care plans, changing the Medicaid rebate rates for line extensions or new formulations of oral solid dosage form, mandating discounts for certain Medicare Part D beneficiaries, and imposing non-deductible annual fee on pharmaceutical manufacturers or importers who sell "branded prescription drugs," effective 2011, expanding the types of entities eligible for the "Section 340B discounts" for outpatient drugs, requires manufacturers to participate in a coverage gap discount program, under which they must agree to offer 50% point-of-sale discounts off negotiated prices of applicable branded drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D; and creating a process for approval of biologic therapies that are similar or identical to approved biologics.

Other legislative changes since the enactment of the Affordable Care Act include the American Taxpayer Relief Act of 2012, or the ATRA, which delayed for another two months the budget cuts mandated by the sequestration provisions of the Budget Control Act of 2011. The ATRA, among other things, also reduced Medicare payments to several providers, including hospitals, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. In March 2013, the President signed an executive order implementing sequestration, and in April 2013, the 2% Medicare reductions went into effect. In December 2013, Congress amended the Budget Control Act to provide greater discretionary spending in 2014 and 2015 than originally budgeted and provide relief from the FDA user fee for two years; this legislation also extended the prohibition against reducing payments to Medicare providers by more than 2% for two years (i.e., until 2023). In December 2015, Congress passed an omnibus funding bill (the Consolidated and Further Continuing Appropriations Act, 2015) and a tax extenders bill, both of which may negatively impact coverage and reimbursement of healthcare items and services.

There is increasing pricing pressure from managed care organizations, government agencies and programs that could negatively affect the company's sales and profit margins. In the United States, these include practices of managed care groups, federal and state exchanges, and institutional and governmental purchasers. Changes to the health care system enacted as part of health care reform in the United States, as well as increased purchasing power of entities that negotiate on behalf of Medicare, Medicaid, and private sector beneficiaries, could negatively impact the company's sales and profit margins. Such pressures may also increase the risk of litigation or investigations by the government regarding pricing calculations. The pharmaceutical industry will likely face greater

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regulation and political and legal action in the future. In this healthcare regulatory climate, there may be significant delays in and impediments to obtaining coverage and reimbursement for newly approved drugs. Any regulatory approval of our products is limited to specific diseases and indications for which our products have been deemed safe and effective by the FDA. Coverage by federal healthcare programs 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. In the United States and markets in other countries, sales of any products for which we 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 Medicare and Medicaid, private health insurers and other organizations. Obtaining reimbursement for orphan drugs may be particularly difficult because of the higher prices typically associated with drugs directed at smaller populations of patients. In addition, third-party payors are likely to impose strict requirements for reimbursement in the use of a higher priced drug. Net prices for products 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 products from countries where they may be sold at lower prices than in the United States.

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 FDA 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 products. Our product candidates may not be considered cost-effective. In the future, we may need to conduct direct head-to-head studies to demonstrate clinical superiority and cost-effectiveness. Our 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. In addition, there is an increasing emphasis on managed care in the United States that may negatively impact pharmaceutical pricing.

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 candidate to other available therapies in order to obtain reimbursement or pricing approval.

Freedom of Information Requests

We are also subject both in the U.S. and ex-U.S. to various regulatory schemes regarding freedom of information requests. We have been and may, from time to time, be notified by the EMA that we had received a request regarding public access to documents held by institutions of the EU related to our marketing authorization applications. We 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

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information request for documents that they hold relating to our company, for example, regarding our product or our product candidates. For example, we have been notified by the EMA that it received a request regarding public access to documents held by institutions of the EU related to our marketing authorization applications. While we are likely to object to the disclosure of any information that we consider commercially confidential, there can be no assurance that we will be successful if any such challenge is raised.

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 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.

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 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. Several other countries, including the United Kingdom, have enacted similar anti-kickback, fraud and abuse laws and regulations.

The federal False Claims Act imposes civil penalties, including through civil whistleblower or *qui tam* actions, against 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 these laws 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 $5,500 to $11,000 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

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product from reimbursement under government programs, debarment, criminal fines, and imprisonment.

HIPAA also imposes criminal liability 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.

The federal Physician Sunshine Act requirements under 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, and physician ownership and investment interests. Payments made to physicians and research institutions for clinical trials are included within the ambit of this law. Statutory requirements to disclose publicly payments made to physicians have also been enacted in certain European Union member states.

Pharmaceutical manufacturers will be required to report and disclose investment interests held by physicians and their immediate family members during the preceding calendar year. Manufacturers were required to make these first reports for information collected in 2013 by March 31, 2014. Such information is to be made publicly available by the Secretary of Health and Human Services in a searchable format beginning September 30, 2014. Failure to submit required information may result in civil monetary penalties of up to $150,000 per year (and up to $1.0 million per year for "knowing failures") for all payments, transfers of value or ownership or investment interests not reported in an annual submission. 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 False Claims Act.

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. 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, imposes criminal liability for executing a scheme to defraud any healthcare benefit program and also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information.

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.

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Customers

Our current customers are generally specialty pharmacies and hospitals located in one of the foreign countries in which Translarna for the treatment of nmDMD is available pursuant to an early access program. We are authorized under early access programs in several countries in the EEA, and Israel, Turkey and Columbia. Translarna is only commercially available for sale in Germany.

The success of Translarna, and any other product candidates we may develop, depends largely on obtaining and maintaining government reimbursement. See "Pharmaceutical Pricing and Reimbursement" above and "Risk Factors Risks Related to Regulatory Approval of our Product and Product Candidates" for further discussion. In some countries, such as 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, the company 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. 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. Allowances for government and other third-party rebates and discounts are established at the time of delivery. These allowances are adjusted to reflect known changes in factors and may impact such allowances in the quarter those changes are known.

A discussion of the risks attendant to our international operations is set forth in Item 1A. "Risk Factors."

Research and Development Expenses

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."

Employees

As of December 31, 2014, we had 193 employees, of whom 187 were employed on a full-time basis, and 33 full-time consultants. Our research and development team is comprised of 63 employees. Approximately 55 of our employees hold an M.D. or Ph.D. degree. 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.

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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.

Risks Related to Our Financial Position and Need for Additional Capital

We have incurred significant losses since our inception. We expect to incur significant expenses in connection with the continued expansion of our global operations and execution of our commercial strategy for Translarna (ataluren) in European Economic Area and other territories, our efforts to obtain broader and additional regulatory approvals for Translarna, and the development of our product pipeline. We expect to continue to incur operating losses for at least the next several years and may never generate profits from operations or maintain profitability.

Since inception, we have incurred significant operating losses. As of December 31, 2014, we had an accumulated deficit of $422.6 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 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.

We are a growing commercial-stage biopharmaceutical company, but prior to 2014 we devoted substantially all of our efforts on research and development, including clinical trials. In August 2014, the European Commission granted marketing authorization for Translarna (ataluren) for the treatment of Duchenne muscular dystrophy caused by nonsense mutations, or nmDMD, in ambulatory patients aged five years and older. The marketing is subject to annual review and renewal by the EMA following its reassessment of the risk-benefit balance of the authorization, which we refer to as the annual EMA reassessment, and is further conditioned on our ability to complete ACT DMD and submit the final report, including additional efficacy and safety data from the trial, during 2015. See "Business Regulation in the European Union on page 40" and "Risk Factors Risks Related to Regulatory Approval of our Product Candidates on page 77" for further detail regarding the EMA's approval process, including a description of the risk-benefit balance.

The marketing authorization described above allows us to market Translarna in the 31 member states of the European Economic Area, or EEA. We commenced our commercial launch of Translarna in Germany in December 2014 and we expect to commercially launch in other key countries in the EEA throughout 2015 and beyond, subject to completion of pricing and reimbursement negotiations. Concurrently, in preparation for a potential U.S. launch in the first half of 2016, we have begun building out our commercial team and infrastructure in the U.S. We anticipate that our expenses will increase substantially in connection with the expansion of our global infrastructure as we continue to establish an international presence and our efforts to commercialize Translarna for the treatment of nmDMD, including significant sales and marketing, legal and regulatory, and distribution and manufacturing expenses.

In addition, we expect to continue to incur significant costs in connection with our ongoing confirmatory Phase 3 clinical trials for Translarna for the treatment of nmDMD and nmCF as well as our Phase 2 proof-of-concept study for nmMPS I. We also expect to incur ongoing research and

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development expenses for Translarna in additional indications as well as for our other product candidates, including in connection with our Phase 1 clinical study under our cancer stem cell program, which is planned to initiate in the first half of 2015, and our IND-enabling studies under our antibacterial program. In addition, we may incur substantial costs in connection with our rolling NDA submission with the FDA for Translarna for the treatment of nmDMD and our currently anticipated submission of a marketing authorization variation with the EMA to seek to include Translarna for the treatment of nmCF in the second half of 2015. We have begun seeking and intend to continue to seek marketing approval for Translarna for the treatment of nmDMD in territories outside of the EEA and we may also seek marketing approval 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:

- 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;
- maintain, expand and protect our intellectual property portfolio; and
- add operational, financial and management information systems and personnel, including personnel to support our product development and commercialization efforts.

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:

- successfully completing confirmatory Phase 3 clinical trials of Translarna for the treatment of either or both of nmDMD and nmCF and successfully initiating clinical trials of Translarna for the treatment of additional indications, including nmMPS I, and successfully advancing our other programs and collaborations, including our cancer stem cell, antibacterial and SMA programs;
- establishing a global commercial infrastructure, including the sales, marketing and distribution capabilities to effectively market and sell Translarna in Europe, the United States, and other parts of the world;
- successfully 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 on a timely basis, or at all, in the countries in which we have and may obtain regulatory approval;
- negotiating and securing adequate reimbursement from other third-party payors for Translarna;
- launching commercial sales of Translarna for the treatment of nmDMD in accordance with our estimated timeline;
- maintaining the marketing authorization of Translarna for the treatment of nmDMD in the EEA and satisfying all related conditions and ongoing requirements;

identifying patients eligible for treatment with Translarna;

obtaining approval to market Translarna for the treatment of other indications, and expanding the territories in which we are approved to market Translarna for the treatment of nmDMD;

expanding the approved product label of Translarna for the treatment of nmDMD;

protecting our rights to our intellectual property portfolio related to Translarna; and

contracting for the manufacture of commercial quantities of Translarna;

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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.

We expect to incur significant expenses related to the establishment of an expanded international presence and the commercialization of Translarna, including costs related to product sales and marketing, legal and regulatory, and distribution and manufacturing, which may further increase as we expand the geographic area covered by our commercial launch and in the event we receive additional approvals for the use of Translarna or any of our other product candidates. In addition, we expect our research and development expenses to increase in connection with our ongoing activities, particularly as we continue our confirmatory Phase 3 clinical trials of Translarna for the treatment of nmDMD and nmCF and our Phase 2 proof-of-concept study of Translarna in nmMPS and our IND-enabling studies under our antibacterial program and prepare to commence our Phase 1 clinical study for PTC596 under our cancer stem cell program. We also expect to initiate proof-of-concept studies for Translarna in at least one additional indication during 2015. Furthermore, since the closing of our initial public offering in June 2013, we have begun to incur additional costs associated with operating as a public company.

We believe that our existing cash and cash equivalents, including the net proceeds from our public offerings of common stock, marketable securities and research funding that we expect to receive under our collaborations, will be sufficient to enable us to fund our operating expenses and capital expenditure requirements through late 2017. 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:

- the progress and results of confirmatory Phase 3 clinical trials of Translarna for nmDMD and nmCF as well as our Phase 2 proof-of-concept study for nmMPS I and our planned Phase 1 clinical study under our cancer stem cell program;
- the scope, costs and timing of the expansion of our commercial infrastructure, including in connection with the growth of our international presence, in Europe and in other territories;
- the scope, costs and timing of our commercialization activities, including product sales, marketing, legal, regulatory, distribution and manufacturing, in the European Economic Area for nmDMD and any of our other product candidates that may receive marketing approval or any additional indications or territories in which we receive authorization to market Translarna;
- the timing and costs related to our rolling NDA submission with the FDA for Translarna for the treatment of nmDMD and our currently anticipated submission of a marketing authorization variation with the EMA to seek to include Translarna for the treatment of nmCF in the second half of 2015;
- 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;
- the number and development requirements of other product candidates that we pursue;

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- the costs, timing and outcome of regulatory review of Translarna and our other product candidates;
- revenue received from commercial sales of Translarna or any of our other product candidates;
- 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 and technologies; and
- our ability to establish and maintain collaborations, including our collaborations 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 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.

We are continuing to engage in significant commercialization efforts for Translarna for nmDMD throughout the EEA. We commenced our commercial launch of Translarna in Germany in December 2014 and we expect to commercially launch in other key countries in the EEA throughout 2015 and beyond, subject to completion of pricing and reimbursement negotiations. In the third quarter of 2014, we began to recognize revenue for payments received under reimbursed early access programs for Translarna for nmDMD patients in selected countries. We expect that our commercial revenue generated in the next several years will be derived exclusively from sales of Translarna for the treatment of nmDMD and other indications, if any, that may receive marketing authorization and that commercial sales will generally be limited to countries in the European Economic Area and other territories in which we have obtained marketing authorization and reimbursement approval or are permitted to initiate treatment under reimbursed early access programs or pursuant to other procedures. Other commercial revenue, if any, would be derived from sales of products that we are not planning to have commercially available for several years, if at all.

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.

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

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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.

We commenced our commercial launch of Translarna in Germany in December 2014 and in the third quarter of 2014 we began to recognize revenue for payments received under reimbursed early access programs for Translarna for nmDMD patients in selected countries. Prior to such time, our operations were limited to organizing and staffing our company, developing and securing our technology, raising capital, undertaking preclinical studies and clinical trials of our product candidates, and preparing for the commercial launch of Translarna for nmDMD in Europe. We are in the process of 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 such a transition. 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 EMA reassessment until we fulfill certain obligations, we have not proven our ability to successfully obtain marketing approvals to sell our product or product candidates. In addition, we have not yet demonstrated our ability to complete development of product candidates, manufacture a commercial scale product or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for a successful full scale product commercialization. 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. 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 rate 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

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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.

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

We depend heavily on the success of our lead product, Translarna, which we are developing for nmDMD, nmCF and nmMPS I. All of our other product candidates 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 European Economic Area, fail to receive regulatory approval in the United States and other territories, fail to maintain or satisfy the conditions of our marketing authorization in the European Economic Area, 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 and are initiating a Phase 2 proof-of-concept study in nmMPS I. Our ability to generate product revenues will depend heavily on the successful development and commercialization of Translarna. In August 2014, Translarna was granted marketing authorization in the EEA for the treatment of nmDMD in ambulatory patients aged 5 years and older, which is subject to annual EMA reassessment and is further conditioned on our ability to complete ACT DMD and submit the final report in 2015. Translarna is still under investigation for the treatment of nmDMD in the United States and has not been approved by the FDA. If we do not successfully 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:

- successful completion of confirmatory Phase 3 clinical trials of Translarna in nmDMD and nmCF and the successful advancement of Translarna in additional indications, in particular, nmMPS I;
- the establishment of an expanded international commercial infrastructure capable of supporting product sales, marketing and distribution of Translarna;
- implementing marketing and distribution relationships with third parties in territories where we do not pursue direct commercialization;
- the continued maintenance of, and satisfaction of the conditions under, the marketing authorization of Translarna for the treatment of nmDMD in the European Economic Area;
- our ability to obtain additional and maintain existing reimbursed named patient and cohort early access programs on adequate terms;
- whether and when we obtain marketing approval of Translarna in additional territories and for additional or expanded indications;
- successful negotiation of adequate pricing and reimbursement terms on a timely basis, or at all, in the countries which require such negotiation and in which we obtain regulatory approval;
- the timing and scope of the commercial launch of Translarna in nmDMD;
- establishing and maintaining commercial manufacturing arrangements with third party manufacturers;

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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 in nmDMD by patients, the medical community and third-party payors;

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 materially harm our business.

The marketing authorization granted by the European Commission for Translarna for the treatment of nmDMD is subject to the satisfaction of specific conditions and is limited to ambulatory patients aged five years and older located in the European Economic Area, which significantly limits an already small treatable patient population, reduces our commercial opportunities, and is subject to an annual reassessment of the risk-benefit balance by the EMA.

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. Overall, we estimate that the potential opportunity for a treatment for nmDMD is approximately 7,000 patients worldwide including 2,000 patients in the United States, 2,500 patients in the European Union and 2,500 patients in the rest-of-world including Latin America, Japan and Australia. We estimate that approximately 40% of nmDMD patients are ambulatory and at least five years old. 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, are based on our beliefs and estimates derived from a variety of sources and may prove to be incorrect. 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.

In addition, the marketing authorization granted by the European Commission is subject to annual review and renewal by the EMA following its reassessment of the risk-benefit balance of the authorization, which we refer to as the annul EMA reassessment, and is further conditioned on our ability to complete ACT DMD and submit the final report, which must include additional efficacy and safety data from the trial in 2015, and implement measures, including pharmacovigilance plans, that are detailed in the risk management plan. We submitted a marketing authorization renewal request to the

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EMA in February 2015. We plan to seek to renew the marketing authorization on an annual basis until we have satisfied the conditions of the marketing authorization and a full marketing authorization is granted. If we fail to satisfy such requirements, or if it is determined that the balance of risks and benefits of using Translarna changes materially, the European Commission could, at the EMA's recommendation, vary, suspend, withdraw or refuse to renew the marketing authorization for Translarna or require additional clinical trials, any of which would negatively impact our anticipated revenue from Translarna and materially harm our business. See "Business Regulation in the European Union on page 40" and "Risk Factors Risks Related to Regulatory Approval of our Product Candidates on page 77" for further detail regarding the EMA's approval process, including a description of the risk-benefit balance.

If clinical trials of our product or product candidates, such as our confirmatory Phase 3 clinical trials of Translarna, fail to demonstrate safety and efficacy to the satisfaction of the EMA or FDA, 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 approval 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 approval of their products.

For example, we did not achieve the primary efficacy endpoint with the pre-specified level of statistical significance in a Phase 2b clinical trial of Translarna for the treatment of nmDMD that we completed in 2010 or in a Phase 3 clinical trial of Translarna for the treatment of nmCF that we completed in 2011. Although we believe that the collective data from these trials, including retrospective and subgroup analyses that we have performed, provide strong support for concluding that Translarna was active and showed clinically meaningful improvements over placebo in these trials, we may similarly fail to achieve the primary efficacy endpoint in ACT DMD and ACT CF, our confirmatory Phase 3 clinical trials of Translarna for these indications. If the results of our confirmatory Phase 3 clinical trials are not favorable, we may need to conduct additional clinical trials at significant cost or altogether abandon development of Translarna for either or both of nmDMD and nmCF. We also did not achieve the primary objective in one of four prior Phase 2 clinical trials that we conducted for Translarna for the treatment of nmCF in which we measured change in chloride conductance in nasal cells over the course of treatment.

Further, the marketing authorization granted by the European Commission is subject to an annual EMA reassessment and is further conditioned on our ability to complete ACT DMD and submit the final report, including additional efficacy and safety data from the trial, during 2015. If the results of ACT DMD are not favorable, if we fail to satisfy the conditions of the marketing authorization, or if it is determined that the balance of risks and benefits of using Translarna changes materially, the European Commission could, at the EMA's recommendation, vary, suspend, withdraw or refuse to renew the marketing authorization for Translarna or require additional clinical trials. See "Business Regulation in the European Union on page 40" and "Risk Factors Risks Related to Regulatory Approval of our Product Candidates on page 77" for further detail regarding the EMA's approval process, including a description of the risk-benefit balance. We also sell Translarna under reimbursed early access programs in a limited number of countries and there is no assurance that such sales will

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continue to be authorized in any particular country. If any of these events were to occur, they would negatively impact our anticipated revenue from Translarna and could materially harm our business.

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:

- be unable to successfully renew our marketing authorization in the EEA for Translarna for the treatment of nmDMD;
- be delayed in obtaining marketing approval for our product candidates or additional authorizations for our product;
- not obtain marketing approval at all;
- 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; or
- have the product removed from the market after obtaining marketing approval.

If we experience any of a number of possible unforeseen events in connection with our clinical trials, potential marketing approval or commercialization of our product or product candidates could be delayed or prevented.

We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing approval 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 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 trials to ensure adequate statistical power to detect any statistically significant treatment effects;
- 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;

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;

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- 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.

Our product development costs will increase if we experience delays in testing or marketing approvals. 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 and results of operations.

Our conclusions regarding the activity and potential efficacy of Translarna in our completed Phase 2b clinical trial of Translarna for the treatment of nmDMD and in our completed Phase 3 clinical trial of Translarna for nmCF are based on retrospective analyses of the results of these trials and nominal p-values, which are generally considered less reliable indicators of efficacy than pre-specified analyses and adjusted p-values.

After determining that we did not achieve the primary efficacy endpoint with the pre-specified level of statistical significance in our completed Phase 2b clinical trial of Translarna for the treatment of nmDMD and in our completed Phase 3 clinical trial of Translarna for nmCF, 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, such as when two active treatments are compared to placebo or when two or more subgroups are analyzed. Nominal p-values cannot be compared to the benchmark p-value of 0.05 to 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 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. This diminishes the likelihood that the EMA will approve our request of a variation to our marketing authorization for Translarna to include Translarna for nmCF on a conditional basis, and, even if we successfully complete our confirmatory Phase 3 clinical trials, could negatively impact the evaluation by the EMA or the FDA of our anticipated applications for full marketing approval for Translarna for the applicable indication.

Our confirmatory Phase 3 clinical trials of Translarna for nmDMD and nmCF, even if successfully completed, may not be sufficient for approval of Translarna for the applicable indication.

It is possible that the EMA or the FDA may not consider the results of our confirmatory Phase 3 clinical trials of Translarna for nmDMD or nmCF, once completed and even if successful, to be sufficient for approval of Translarna for such indication. The FDA typically requires two adequate and well-controlled pivotal clinical trials to support marketing approval of a product candidate for a particular indication. The EMA or the FDA could determine that the results of our trials are not sufficiently robust, are subject to confounding factors or are not adequately supported by other trial endpoints. In addition, although we have had discussions with the FDA regarding our confirmatory Phase 3 clinical trial of Translarna for the treatment of nmCF, the FDA may not consider our proposed trial design acceptable. For example, in 2012, the FDA indicated that in its view the data from our

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completed Phase 3 clinical trial and other data from our development program in cystic fibrosis do not by themselves support an NDA submission and, consequently, the FDA informed us that additional clinical data would be required to establish the evidence necessary to support eventual filing of an NDA for the use of Translarna to treat nmCF. We had additional interactions with the FDA in 2013 regarding the clinical development design which would have the potential to support an NDA, but we did not achieve a consensus between the EMA and FDA views. While we have incorporated feedback from the FDA into our ACT CF trial design, we believe that certain key recommendations from the FDA are not appropriate. Two of the key recommendations that we are in disagreement with are the designation of FEV_1, CF pulmonary exacerbations and body mass index as three co-primary endpoints for the trial and a suggested three-year trial duration. FEV_1 is the primary endpoint in ACT CF, with CF pulmonary exacerbations and body mass index key secondary endpoints, which is consistent with other clinical trials currently ongoing in cystic fibrosis and FDA's earlier recommendation. Additionally, we believe that extending the study duration to three years would result in a number of complications that would ultimately limit the robustness of the data and conclusions that could be drawn from the results. Based on these interactions, we nonetheless initiated ACT CF in the first half of 2014 consistent with feedback from the EMA on our trial design. If the FDA does not consider our trial designs acceptable, we may need to conduct more than one confirmatory clinical trial and our ability to receive marketing approval for this indication could be delayed or prevented.

Because we are developing our product and 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 or nmCF. In addition, there has been limited historical clinical trial experience generally for the development of drugs to treat either of these diseases. 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.

Prior to our conducting the Phase 2b clinical trial of Translarna for nmDMD, there was no established precedent for an appropriate trial design to evaluate the efficacy of Translarna for nmDMD, and little clinical experience in the methodologies used to analyze the resulting data. Although we believe that we now understand the issues of concern with the pre-specified statistical analyses of our Phase 2b clinical trial results, and that we have designed our confirmatory Phase 3 ACT DMD clinical trial of Translarna in an appropriate fashion, we may nonetheless experience similar or other unknown complications with ACT DMD because of the limited clinical experience in this indication. As a result, we may not achieve the pre-specified endpoint with statistical significance in ACT DMD, which would make approval of Translarna for this indication unlikely. Among other endpoints in ACT DMD, the trial protocol includes two secondary endpoints that have not been used previously as outcome measures in published therapeutic clinical trials of nmDMD. These endpoints, in particular, may produce results that are unpredictable or inconsistent with other trial results.

With regard to nmCF, we believe that we now understand subgroup effects that we observed in our completed Phase 3 clinical trial and that we have designed our confirmatory Phase 3 ACT CF clinical trial of Translarna to take these effects into account. However, we may nonetheless experience unknown complications with ACT CF. As a result, we may not achieve the pre-specified endpoint with statistical significance in ACT CF, which would make approval of Translarna for this indication unlikely.

We are faced with similar challenges in connection with the design of our Phase 2 proof-of-concept study of Translarna in nmMPS I because there is also limited historical clinical trial experience for the development of drugs to treat the underlying cause of this disorder. While clinical trials of enzyme replacement therapies conducted by third parties have provided some insight into the disorder, enzyme replacement therapies do not sufficiently address the central nervous system, skeletal or cardiac

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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 our confirmatory Phase 3 ACT CF clinical trial of Translarna or our Phase 2 proof-of-concept study of Translarna in nmMPS I, if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials. For example, nmCF and nmMPS I are characterized by relatively small patient populations, which could result in slow enrollment of clinical trial participants. 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 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 risks and benefits 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 our confirmatory Phase 3 clinical trial of Translarna in nmCF, our Phase 2 proof-of-concept study of Translarna in nmMPS I or any of our other clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether. In addition, we intend to submit a variation to our marketing authorization for Translarna in the EEA in the second half of 2015 to seek approval for the treatment of nmCF. Although we plan to submit the variation with the clinical results achieved in our prior Phase 3 clinical trial in nmCF, we believe that the CHMP will consider it important that ACT CF be well underway prior to our submission. As a result, enrollment delays in ACT CF could also delay the timeline for our planned submission with the EMA. In addition, we expect that even if the EMA approves a variance to include Translarna for nmCF, any such approval will be subject to the same types of conditions that apply to our marketing authorization in nmDMD, including our ability to provide comprehensive clinical data from a confirmatory Phase 3 clinical trial. As a result, ACT CF enrollment delays could have a negative impact on our ability to obtain and maintain any marketing authorization for nmCF that may be granted in the future, if any.

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.

All of our products and 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

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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 risk-benefit 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 our completed 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. If patients in the Translarna arm of a confirmatory Phase 3 clinical trial for the treatment of nmCF exhibit clinically meaningful creatinine elevations, the EMA or the FDA might not approve Translarna for this indication or could require that we instruct physicians to frequently monitor patients for these abnormalities or impose other conditions, which may be an impediment to the use of Translarna because of concerns related to its safety and convenience.

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 any products of 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-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. 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 annual EMA reassessment, and is further conditioned on our ability to complete ACT DMD and submit the final report, including additional efficacy and safety data from the trial, in 2015. We may not be successful in developing and receiving full regulatory approval for such use and we may not receive regulatory approval for additional indications for Translarna or 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.

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Translarna for the treatment of nmDMD, or any other product candidate that receives marketing approval, 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, Translarna and any of our other product candidates that may receive marketing approval 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 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 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, such as a restriction that nmCF patients taking Translarna not also use chronic inhaled aminoglycoside antibiotics.

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

If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell our 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.

We have limited experience in the sale and marketing of pharmaceutical products, and we may be unable to successfully execute our commercial strategy in the EEA or, if approved, in the U.S. or other territories. Our commercial strategy for Translarna involves the development of a commercial infrastructure that spans multiple jurisdictions. In preparation for a potential U.S. launch in the first half of 2016, we are evaluating our commercial strategy and have begun building out our commercial team and infrastructure in the U.S. Our ability to successfully commercialize Translarna for the treatment of nmDMD in the EEA and other territories, including the U.S., if approved, 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

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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 in the EEA and in other 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 inhibit our efforts to commercialize our products on our own include:

- our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- our inability to implement third party marketing and distribution relationships in territories where we do not pursue direct commercialization;
- the inability of our commercial team to obtain access to or persuade adequate numbers of physicians to prescribe Translarna or any future products;
- 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.

We plan to develop our commercial strategy for additional indications for Translarna or other product candidates, if and when such drugs are approved in the applicable region.

We expect that during 2015 all of our sales of Translarna for the treatment of nmDMD will occur in territories outside of the U.S., which subjects us to additional business risks that could adversely affect our revenue and results of operations.

We expect that for at least the next year, all of our revenue from sales of Translarna will be generated from countries other than the United States. Additionally, we have operations in several European countries and other territories. We expect that we will continue to expand our international

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operations in the future. International operations inherently subject us to a number of risks and uncertainties, including:

- changes in international regulatory and compliance requirements 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;
- diminished protection of intellectual property in some countries outside of the U.S.;
- 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.

Any of these factors may, individually or as a group, have a material adverse effect on our business and results of operations. As we continue to expand our existing international operations, we may encounter new risks.

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 Duchenne muscular dystrophy. Other currently available treatments for Duchenne muscular dystrophy are only palliative. However, there are other biopharmaceutical companies, including BioMarin Pharmaceutical Inc. (following its acquisition of Prosensa Therapeutic in early 2015) and Sarepta Therapeutics, that are developing treatments for Duchenne muscular dystrophy based on a different scientific approach known as exon-skipping. Summit Corporation also has a product candidate in early clinical development designed to increase the production of the protein utrophin, which is functionally similar to dystrophin, to treat Duchenne muscular dystrophy. Nobelpharma, a Japanese company, is currently sponsoring a Phase 2 clinical trial in Japan of its product candidate NPC-14 (arbekacin sulfate), which is a generically available aminoglycoside antibiotic, in boys with nmDMD.

There are a number of large pharmaceutical and biotechnology companies that currently market and sell products to manage the symptoms and side effects of cystic fibrosis. These products include Chiron Corporation's TOBI and Genentech, Inc.'s Pulmozyme. Although there are currently no marketed products approved to treat the underlying cause of nmCF, Vertex Pharmaceuticals' CFTR potentiator drug Kalydeco is approved by the FDA and in other territories as a treatment for cystic fibrosis in patients six years of age and older who have a type of mutation in the CFTR gene known as

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a gating mutation. Vertex Pharmaceuticals also is developing two other product candidates for the treatment of cystic fibrosis in patients who have a type of mutation in the CFTR gene known as a process block mutation. We believe that Translarna is the only product candidate in clinical trials that is designed to treat the underlying cause of nmCF by restoring CFTR activity.

In addition, Aldurazyme, which is manufactured by BioMarin Pharmaceutical Inc. and sold by Genzyme Corporation, is an enzyme replacement therapy for the treatment of mucopolysaccharidosis I.

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 approval 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 currently expect that Translarna will be priced at levels consistent with the pricing for other therapies for the treatment of rare disorders where high unmet medical need exists.

The regulations and practices that govern marketing approvals, 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 European Economic Area, 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 approval 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 approval.

Our ability to commercialize Translarna or any other product candidate successfully also will depend in part on the extent to which 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

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reimbursement levels. A primary trend in the E.U. 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 we or our customers seek reimbursement for our products 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 predetermined discounts from list prices and are challenging the prices charged for medical products. We cannot be sure that coverage and reimbursement will be available for Translarna or any other product that we commercialize and, if coverage and reimbursement are available, the level of reimbursement. Reimbursement may impact the demand for, or the price of, any product candidate for which we obtain marketing approval. Obtaining reimbursement for Translarna may be particularly difficult because of the higher prices typically associated with drugs directed at smaller populations of patients. In addition, third-party payors are likely to impose strict requirements for reimbursement of a higher priced drug. If reimbursement is not available or is available only to limited levels, we may not be able to successfully commercialize any product candidate for which we obtain marketing approval.

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. 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 often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. 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 any approved products that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our overall financial condition. In addition, in the European Union, for medicines authorized by the centralized authorization procedure, an authorized trader, such as a wholesaler, can purchase a medicine in one European Union 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 European Union 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 testing of our product candidates in human clinical trials for 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;

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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 early access 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 begin commercializing Translarna or as and when we begin commercializing any other product candidate that receives marketing approval. 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 policy excludes pollution and has a coverage limit of $10.0 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 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. 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.

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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 GEMS and our alternative splicing technology, which we use in the discovery of these molecules, to date we have only been granted marketing authorization to treat nmDMD under a restricted label, and subject to the fulfillment of certain conditions, in the European Economic Area. We may not be able to satisfy the conditions of our current marketing authorization for nmDMD, including the completion of ACT DMD, 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 our Dependence on Third Parties

We contract with third parties for the manufacture and distribution of our product and 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 have a contract with a pharmacy and hospital distributor in the EU that distributes Translarna for both commercial and clinical programs. We are finalizing our business relationship with a third party logistics provider in the EU, which we expect to be in place in the first half of 2015.

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 antibacterial and oncology programs through another third-party manufacturer. We engage a separate manufacturer to provide bulk drug product and expect to finalize our validation of another bulk drug manufacturer in mid-2015. We engage a separate manufacturer to provide fill and finish services for our finished commercial and clinical product and are in the process of completing arrangements with two additional providers to provide these services, initially for our clinical product in early to mid-2015, with commercial product services expected to commence for at least one provider in late 2015. 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.

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.

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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;
- 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 product candidates and any 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 growth 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

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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 MAA 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 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 approvals 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 approvals.

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 approvals of our product or product candidates or commercialization of our products, producing additional losses and depriving us of potential product revenue.

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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 collaborator(s) 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 abilities 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;
- 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;

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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 collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's 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.

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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.

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.

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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 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 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 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.

Moreover, we may be subject to a third party submission of prior art to a patent office or become involved in opposition, derivation, 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 current or future product candidates.

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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 submitted as part of an MAA becoming publicly available. Such developments could enable other companies to circumvent our intellectual property rights and use our clinical trial data to obtain marketing authorizations in the European Union and in other jurisdictions. Such developments may also require us to allocate significant resources 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.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged 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. 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 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 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

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aware of all such intellectual property rights potentially relating to our product candidates. For example, we have not conducted a recent freedom-to-operate search or analysis for Translarna (brand name of ataluren). Any freedom-to-operate search or analysis previously conducted may not have uncovered all relevant patents and patent applications, and there may be pending or future patent applications that, if issued, would block us from commercializing Translarna. Thus, we do not know with certainty whether Translarna, any other product candidate, or our commercialization thereof, does not and will 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 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 Translarna, even though neither the issued U.S. patent nor any of the international patent applications specifically discloses Translarna. In order to successfully challenge the validity of any issued U.S. patent, we would need to overcome a presumption of validity. This burden is a high one requiring us to present clear and convincing evidence as to the invalidity of these claims. There is no assurance that a court would find these claims to be invalid. In addition, we believe that our testing of Translarna 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 a statutory exemption. However, there can be no assurance that our interpretation of the statutory exemption would be upheld, and the statutory exemption would only cover our preclinical research activities, and not the commercialization of Translarna.

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 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.

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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 not be allowed for registration, and our registered trademarks may not be maintained or enforced. During trademark registration proceedings, we may receive rejections. Although we are given an opportunity to respond to those rejections, we may be unable to overcome such rejections. In addition, in the U.S. Patent and Trademark Office and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such

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proceedings. If we do not secure registrations for our trademarks, we may encounter more difficulty in enforcing them against third parties than we otherwise would.

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.

Any trademark we intend to use for our product candidates, including Translarna, will require that we seek trademark registration worldwide. Trademark registration is a territory-specific and we must apply for registration in the US as well as any other country where we intend to commercialize product. Failure to obtain the appropriate registrations may place our use of the trademark at risk or make if subject to legal challenges, which could force us to choose an alternative name for our product candidates. In addition, the FDA, and other regulatory authorities outside the United States, typically conduct a separate review of proposed product names for pharmaceuticals, including an evaluation of potential for confusion with other product names or medication or prescribing errors. These regulatory authorities may also object to any product name we submit if they believe the name inappropriately implies medical claims. If the FDA or other competent regulatory authority outside the United States objects to any of our proposed product names, we may be required to adopt an alternative name for our product candidates. If we adopt an alternative name, either because of our inability to obtain a trademark registration or approval or related legal challenges or because of objections from regulatory authorities, we would lose the benefit of our existing trademark applications for such product candidate, and may be required to expend significant additional resources in an effort to identify a suitable product name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA or applicable other regulatory authority, which could cause delays in getting our products to market and substantially increase our costs. We may be unable 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 candidates.

Risks Related to Regulatory Approval of our Product and Product Candidates

If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to continue to commercialize Translarna for nmDMD or other indications or commercialize our other product candidates, and our ability to generate revenue will be materially impaired.

Translarna and our other 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 marketing approval for a product candidate will prevent us from commercializing the product candidate.

We have received marketing authorization to market Translarna for nmDMD in the European Economic Area, which is subject to annual EMA reassessment and is further conditioned on our ability to complete ACT DMD and submit the final report, including additional efficacy and safety data from the trial, during 2015. We have not otherwise received marketing approval for Translarna or any of our other product candidates from regulatory authorities in any jurisdiction. We intend to submit a variation to our marketing authorization application with the EMA to seek to include Translarna for the treatment of nmCF in the second half of 2015. There is substantial risk that the EMA will not grant us approval of Translarna for the treatment of nmCF. We expect that even if the EMA approves a variance to include Translarna for nmCF, any such approval will be subject to the same types of conditions that apply to our marketing authorization in nmDMD, including our ability to provide comprehensive clinical data from a confirmatory Phase 3 clinical trial, such as ACT CF.

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We have begun seeking and intend to continue to seek marketing approval for Translarna for the treatment of nmDMD in territories outside of the EEA. In December 2014, we commenced a rolling basis submission of a new drug application, or NDA, to the FDA for approval of Translarna for the treatment of nmDMD. We may not receive necessary approvals from the FDA or other regulators to further commercialize Translarna or any product candidate in any market.

We have only limited experience in filing and supporting the applications necessary to obtain marketing approvals for product candidates and expect to continue to rely on third-party contract research organizations to assist us in this process. Securing marketing approval requires the 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. Securing marketing approval 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 approval or that prevent or limit commercial use.

The process of obtaining marketing approvals 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 approval 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 approval of a product candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

For example, our ability to obtain and maintain marketing authorizations granted on a conditional basis in the European Union is limited to specific circumstances and subject to several conditions and obligations. Conditional marketing authorizations based on incomplete clinical data may be granted for a limited number of listed medicinal products for human use, including products designated as orphan medicinal products under E.U. law, if (1) the risk-benefit 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, 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 EMA after an assessment of the risk-benefit balance and need for additional or modified conditions.

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

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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 that are the same drug as our product candidates, or can be classified as a similar medicinal product within the meaning of E.U. 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, and nmMPS I. Generally, if a product with an orphan drug designation subsequently receives the first marketing approval 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 ten years in the European Union and seven years in the United States. The E.U. 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.

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. 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, 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 product candidates.

The fast track designation for Translarna may not actually lead to a faster development or regulatory review or approval process.

If a drug is intended for the treatment of a serious or life-threatening condition and the drug demonstrates the potential to address unmet medical needs for this condition, the drug sponsor may apply for FDA fast track designation. We have obtained a fast track designation from the FDA for Translarna for the treatment of nmDMD. However, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw our fast track designation if the FDA believes that the designation is no longer supported by data from our clinical development program. Our fast track designation does not guarantee that we will qualify for or be able to take advantage of the FDA's expedited review procedures, nor does it increase the likelihood of FDA approval.

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Marketed pharmaceutical products, including Translarna for the treatment of nmDMD, 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.

The company, 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 approval. Any regulatory approval of any of our products or product candidates, once obtained, may be withdrawn. For example, our marketing authorization in the EEA is subject to annual EMA reassessment and is further conditioned on our ability to complete ACT DMD and submit the final report, including additional efficacy and safety data from the trial, during 2015. 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.

We are required to submit safety and other post-market information and reports, implement pharmacovigilance plans, and comply with 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.

Even if marketing approval 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 manufacturers' 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 action for off-label promotion. 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.

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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 approvals;
- 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 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. Similarly, failure to comply with the European Union's 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, if any. Failure to obtain and maintain acceptable pricing and reimbursement terms for Translarna in the European Economic Area and other jurisdictions would prevent us from marketing our products in such regions.

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 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

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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.

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. Since December 2014, Translarna for the treatment of nmDMD has been commercially available in Germany, but we are still in the process of finalizing our pricing negotiations with relevant German authorities. 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 key EEA countries, we have not received both pricing and reimbursement approval in any country, and there is no assurance that we will receive such approval or, if we do, that the price, level of reimbursement and other terms will be acceptable to us. In addition, the price that is approved by local governmental authorities pursuant to commercial pricing and reimbursement processes may be significantly lower than the price we are able to charge for sales under our reimbursed early access programs. In some instances, reimbursement may be subject to challenge, reduction or denial by the government and other payers. In some countries, such as 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, the company 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.

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, during the fourth quarter of 2014, the publicly funded health care system in the UK determined to reconsider how it assesses certain new treatments and postponed certain pricing and reimbursement meetings, including meetings related to Translarna.

Reference pricing used by various E.U. member states and parallel distribution, or arbitrage between low-priced and high-priced member states, can further reduce prices. 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 anticipated revenue and growth prospects could be negatively affected and our business could be adversely affected.

Our relationships with customers, healthcare providers and professionals 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. 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 approval.

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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 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 federal and state healthcare laws and regulations, and equivalent laws and regulations in the European Union, include, and are not limited to, the following:

Anti-corruption and anti-bribery statutes, including the U.S. Foreign Corrupt Practices Act, or FCPA, and the UK Bribery Act of 2010, or Bribery Act. These statutes are generally broad in scope and will require us 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 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.

Anti-kickback statutes, 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 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 commercial payors. Several other countries, including the United Kingdom, have enacted similar anti-kickback, fraud and abuse, and healthcare laws and regulations.

The Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010 (collectively the Affordable Care Act), amended the intent requirement of the federal anti-kickback statute such that a person no longer needs to have actual knowledge of the statue or specific intent to violate it.

Laws and regulations, including the U.S. False Claims Act, which impose civil and criminal liability on individuals and entities who submit, or cause to be submitted, false or fraudulent claims for payment to the government. The U.S. government has brought False Claims Act actions against pharmaceutical companies on the theory that their practices have caused false claims to be submitted to the government. The U.S. Attorneys' Offices and the main Department of Justice have taken broad interpretations of what constitutes falsity or false claims. A wide range of pharmaceutical manufacturers' commercial activity, marketing practices and price reporting practices have been scrutinized as potential violations of the False Claims Act.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program and also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information. In addition,

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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 outside of the U.S. 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 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 regulating off-label promotion. 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 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. The FDA does not, however, restrict physicians from prescribing products for off-label uses in the practice of medicine. 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. In addition, failure to follow FDA rules and guidelines relating to promotion and advertising can result in, among other things, the FDA's refusal to approve a product, the suspension or withdrawal of an approved product from the market, product recalls, fines, disgorgement of money, operating restrictions, injunctions or criminal prosecutions.

Statutory requirements to disclose publicly payments made to physicians, including in certain European Union member states and the U.S. For example, under federal Physician 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, and physician ownership and investment interests in such manufacturers. A number of states have enacted their own transparency requirements that obligate manufacturers to report different types of spending related to physicians and other covered recipients.

Laws 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.

Analogous state laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, and some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures.

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In addition, interactions between pharmaceutical companies and physicians are also governed by industry self- regulation codes of conduct and physicians' codes of professional conduct. 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 EU. 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 will involve substantial costs. We cannot guarantee that we, our employees, our consultants or our third-party contractors are or will be in compliance with all federal, state and foreign regulations and codes. It is possible that governmental authorities will 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 significantly impact our ability to commercialize, sell or distribute any drug. Even if we are 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. If any of the physicians or other providers or entities with whom we expect to do business are found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

Recently enacted and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and affect the prices we may obtain.

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 approval 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 approval.

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. The legislation expanded Medicare coverage for drug purchases by the elderly and introduced a new reimbursement methodology based on average sales prices for physician administered drugs. In addition, this legislation provided authority for limiting the number of drugs that will be covered in any therapeutic class. Cost reduction initiatives and other provisions of this legislation could decrease the coverage and price 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 reimbursement rates. Therefore, any reduction in reimbursement that results from the Medicare Modernization Act may result in a similar reduction in payments from private payors.

In March 2010, President Obama signed into law the Affordable Care Act, a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending,

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enhance remedies against fraud and abuse, add new transparency requirements for health care and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. Effective October 1, 2010, the Affordable Care Act revised the definition of "average manufacturer price" for reporting purposes, which could increase the amount of Medicaid drug rebates to states. Further, the new law imposes a significant annual fee on companies that manufacture or import branded prescription drug products.

While the U.S. Supreme Court upheld the constitutionality of most elements of the Affordable Care Act in June 2012, other legal challenges are still pending final adjudication in several jurisdictions. In addition, Congress has in the past proposed and likely will continue to propose a number of legislative initiatives challenging various aspects of the Affordable Care Act. At this time, it remains unclear whether there will be any changes made to the Affordable Care Act, whether to certain provisions or its entirety. 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.

In addition, other legislative changes have been proposed and adopted since the Affordable Care Act was enacted. For example, the Budget Control Act of 2011, among other things, created the Joint Select Committee on Deficit Reduction to recommend proposals in spending reductions to Congress. The Joint Select Committee did not achieve a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, which triggered the legislation's automatic reduction to several government programs, including aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, starting in 2013. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, or the ATRA, which delayed for another two months the budget cuts mandated by the sequestration provisions of the Budget Control Act of 2011. The ATRA, among other things, also reduced Medicare payments to several providers, including hospitals, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. In March 2013, the President signed an executive order implementing sequestration, and in April 2013, the 2% Medicare reductions went into effect. In December 2013, Congress amended the Budget Control Act to provide greater discretionary spending in 2014 and 2015 than originally budgeted and provide relief from the FDA user fee for two years; this legislation also extended the prohibition against reducing payments to Medicare providers by more than 2% for two years (i.e., until 2023). In December 2014, Congress passed an omnibus funding bill (the Consolidated and Further Continuing Appropriations Act, 2015) and a tax extenders bill, both of which may negatively impact coverage and reimbursement of healthcare items and services.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements.

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.

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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, we have experienced and plan 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 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. 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

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

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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.

An active trading market for our common stock may not be sustained.

Our shares of common stock began trading on The NASDAQ Global Select Market on June 20, 2013. Given the limited trading history of our common stock, there is a risk that an active trading market for our common stock will not be sustained, which could put downward pressure on the market price of our common stock and thereby affect the ability of our stockholders to sell their shares.

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

Our stock price may 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:

- our ability to advance the commercialization of Translarna for the treatment of nmDMD;
- the success of competitive products or technologies;

results of clinical trials of Translarna and any other product candidate that we develop;

results of clinical trials of product candidates of our competitors;

regulatory or legal developments in the United States and other countries;

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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.

We are an "emerging growth company," and the reduced disclosure requirements applicable to emerging growth companies may make our common stock less attractive to investors.

We are an "emerging growth company", as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, and may remain an emerging growth company until December 31, 2018, provided that, if the market value of our common stock that is held by non-affiliates exceeds $700 million as of any June 30 before that time or if we have annual gross revenues of $1 billion or more in any fiscal year, we would cease to be an emerging growth company as of December 31 of the applicable year. We also would cease to be an emerging growth company if we issue more than $1 billion of non-convertible debt over a three-year period. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include: not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting; not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements; reduced disclosure obligations regarding executive compensation; and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved.

We may choose to take advantage of some, but not all, of the available exemptions. We cannot predict whether investors will find our common stock less attractive if we rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

In addition, the JOBS Act also provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have elected to delay such adoption of new or revised accounting standards, and as a result, we may not comply with new or revised accounting standards on the relevant dates on which adoption of such standards is required for public companies that are not emerging growth companies. As a result of such election, our financial statements may not be comparable to the financial statements of other public companies.

If the market value of our common stock that is held by non-affiliates exceeds $700 million as of June 30, 2015, we will cease to be an emerging growth company as of December 31, 2015.

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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, and our management is and will continue to be required to devote substantial time to new compliance initiatives.

As a public company, and particularly after we are no longer an "emerging growth 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 will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance.

However, for as long as we remain an emerging growth company, we may take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies as described in the preceding risk factor. Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, we will be required to furnish a report by our management on our internal control over financial reporting. However, as an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm until we are no longer an emerging growth company. To achieve compliance with Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude within the prescribed timeframe that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

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. A significant number of our shares are currently "restricted" securities as a result of securities laws, but are able to be sold, subject to any applicable volume limitations under federal laws with respect to affiliate sales. Moreover, certain holders of an aggregate of 1,894,327 shares of our common stock have rights, subject to some conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders.

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We have a significant number of restricted stock awards and shares that are subject to outstanding options under our equity compensation plans or as inducement grants to new hire employees pursuant to Nasdaq rules. These 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 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. As of February 27, 2015, an aggregate of approximately 184,000 shares of our common stock, including shares of our common stock underlying stock option awards, held by nine of our directors and executive officers were subject to sale under Rule 10b5-1 plans.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

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 also lease space in Ireland and other European countries to support our operations as a global organization, but these leases are not material to us.

Item 3. Legal Proceedings

From time to time in the ordinary course of our business, we are subject to claims, legal proceedings and disputes as a result of patients seeking to participate in our clinical trials or otherwise gain access to our product candidates. We are not currently subject to any material legal proceedings.

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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, 2013		
Second quarter (beginning June 20, 2013)	$ 17.92	$ 13.03
Third quarter	$ 24.38	$ 13.88
Fourth quarter	$ 22.42	$ 13.15
Year ended December 31, 2014		
First quarter	$ 34.65	$ 16.21
Second quarter	$ 28.75	$ 14.51
Third quarter	$ 47.20	$ 22.70
Fourth quarter	$ 57.50	$ 33.02

Holders

As of February 25, 2015, there were 50 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

Set forth below is information regarding securities sold by us during 2014 that were not registered under the Securities Act of 1933, as amended, or the Securities Act. Also included is the consideration, if any, received by us for the securities and information relating to the section of the Securities Act, or rule of the Securities and Exchange Commission, under which exemption from registration was claimed.

Inducement stock option awards

Pursuant to the NASDAQ inducement grant exception, during the year ended December 31, 2014, we issued options to purchase an aggregate of 595,300 shares of common stock to certain new hire employees at a weighted-average exercise price of $37.15 per share. An aggregate of 5,900 of these options were forfeited during the year ended December 31, 2014 in connection with employee separations from the company. The shares underlying these option awards will be registered on a Form S-8 registration statement prior to the first vesting event applicable to each such award.

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.

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Use of Proceeds from Registered Securities

On June 25, 2013, we closed our initial public offering of 9,627,800 shares of our common stock, including 1,255,800 shares of our common stock pursuant to the exercise by the underwriters of an over-allotment option, at a public offering price of $15.00 per share for an aggregate offering price of approximately $144.4 million. The offer and sale of all of the shares in the offering were registered under the Securities Act pursuant to a registration statement on Form S-1 (File No. 333-188657), which was declared effective by the SEC on June 19, 2013.

We received aggregate net proceeds from the offering of approximately $131.6 million, after deducting underwriting discounts and commissions and other offering expenses payable by us. None of the underwriting discounts and commissions or other offering expenses were incurred or paid to directors or officers of ours or their associates or to persons owning 10 percent or more of our common stock or to any affiliates of ours.

As of December 31, 2014, we have used approximately $70.6 million of the net offering proceeds primarily to fund the clinical development of Translarna for the treatment of nmDMD, nmCF and nmMPS I, to seek marketing approval in the European Union, the United States and other territories for Translarna for nmDMD, for commercial efforts for Translarna, to fund research and development of Translarna for additional indications and for our earlier stage programs, and for working capital and other general corporate purposes. We are holding a significant portion of the balance of the net proceeds from the offering in a variety of capital preservation investments, including short-term, investment grade, interest bearing instruments and U.S. government securities. There has been no material change in our planned use of the net proceeds from the offering as described in our final prospectus filed with the SEC pursuant to Rule 424(b) under the Securities Act.

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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.

	Year ended December 31,		
	2014	2013	2012
Revenues:			
Net product revenue	$ 717	$	$
Collaboration revenue	22,246	31,326	28,779
Grant revenue	2,282	3,370	5,167
Total revenues	25,245	34,696	33,946
Operating expenses:			
Research and development	79,838	54,875	46,139
Selling, general and administrative	44,820	25,219	14,615
Total operating expenses	124,658	80,094	60,754
Loss from operations	(99,413)	(45,398)	(26,808)
Interest income (expense), net	1,180	(6,084)	(1,210)
Loss on extinguishment of debt		(130)	
Other income (expense), net	(213)	38	1,783
Loss from operations before tax benefit	(98,446)	(51,574)	(26,235)
Net tax benefit	4,693		
Net loss	(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	$ (93,753)	$ (66,432)	$ 133,341
Net (loss) income attributable to common stockholders per share:			
Basic	$ (2.97)	$ (5.18)	$ 219.76
Diluted	$ (2.97)	$ (5.18)	$ 42.50
Weighted-average shares outstanding:			
Basic	31,565,310	12,829,411	3,328
Diluted	31,565,310	12,829,411	17,205

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

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 orally administered, small molecule therapeutics targeting an area of RNA biology we refer to as post-transcriptional control. 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, oncology and infectious diseases.

Our lead product, Translarna (ataluren) received marketing authorization from the European Commission, or EC, 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. Our marketing authorization in the EEA is subject to an annual reassessment of the risk-benefit balance by the European Medicines Agency, or EMA, and is further conditioned on our ability to complete our global, confirmatory Phase 3 clinical trial in nmDMD, which we refer to as ACT DMD, and submit the final report, including additional efficacy and safety data from the trial, during 2015. We completed enrollment for ACT DMD in September 2014 and we expect to receive top-line data in the fourth quarter of 2015.

In December 2014, we began submitting a rolling New Drug Application to the FDA for the approval of Translarna in nmDMD. Assuming positive data from the ACT DMD trial, we intend to complete our NDA submission in late 2015 and, if granted priority review and approval by the FDA, believe we have the potential to begin commercialization in the U.S. shortly thereafter. In preparation for the potential U.S. launch, we have begun building out our commercial team and infrastructure in the U.S.

We hold worldwide commercialization rights to Translarna for all indications in all territories. During 2014 we initiated significant commercialization efforts to support the launch of Translarna in the EEA, including the establishment of our international headquarters in Ireland and additional offices in Europe and other territories, the hiring of country managers and other field-based commercial support employees, the submission of pricing and reimbursement dossiers, and the engagement of local consultants and, in select counties, third-party distributor/marketing partners. In many countries outside the U.S., including almost all countries in the EEA, a product must receive pricing and reimbursement approval before it can be commercialized. This market access process varies from country to country and can take over 18 months in certain circumstances.

We initiated our global, confirmatory Phase 3 ACT CF trial in nmCF patients in June 2014. We intend to file a variation to our marketing authorization for Translarna in the EEA to seek approval for the treatment of nmCF in the second half of 2015. If approved, such variation will likely be subject to annual review and renewal by the EMA and conditioned upon our ability to provide comprehensive clinical data from ACT CF in a similar manner as our marketing authorization for Translarna in nmDMD.

Our spinal muscular atrophy collaboration with F. Hoffman-La Roche Ltd and Hoffman-La Roche Inc., or Roche, and the Spinal Muscular Atrophy Foundation, or SMA Foundation, is advancing through clinical development. This is a program that was discovered internally at PTC with initial

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funding by the SMA Foundation. Roche is responsible for pursuing clinical development of the SMA program and commercialization consistent with a governance structure that includes representation from PTC and the SMA Foundation.

In addition, we have a pipeline of product candidates that are in early clinical and preclinical development.

Funding

During 2015, we expect that our revenues will be primarily generated from sales of Translarna in counties in the EEA where we are able to obtain pricing and reimbursement approval at acceptable levels and in other territories where we are permitted to distribute Translarna under our early access programs, or EAP.

Historically, we have financed our operations primarily through 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, 2014, we had an accumulated deficit of $422.6 million. We had a net loss of $93.8 million for the fiscal year ended December 31, 2014 and a net loss of $51.6 million for the fiscal year ended December 31, 2013.

We anticipate that our expenses will increase substantially in connection with the expansion of our commercial infrastructure as we continue to establish an international presence, particularly throughout Europe and in the U.S., and our efforts to commercialize Translarna for the treatment of nmDMD, including significant sales and marketing, legal and regulatory, and distribution and manufacturing expenses. In addition, we expect to continue to incur significant costs in connection with our ongoing ACT DMD and ACT CF trials as well as our Phase 2 proof-of-concept study for nmMPS I. We also expect to incur ongoing research and development expenses for our other product candidates, including in our initiation of a Phase 1 clinical study under our cancer stem cell program in the first half of 2015. In addition, we may incur substantial costs in connection with our ongoing rolling NDA submission with the FDA for Translarna for the treatment of nmDMD and our currently anticipated submission of a marketing authorization variation with the EMA to seek to include Translarna for the treatment of nmCF in the second half of 2015. We have begun seeking and intend to continue to seek marketing approval for Translarna for the treatment of nmDMD in territories outside of the EEA and we may also seek marketing approval for Translarna for other indications, and these efforts may significantly impact the timing and extent of our commercialization expenses.

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. 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. We will need to generate significant revenues to achieve and sustain profitability, and we may never do so.

Financial operations overview

To date, we have not generated significant product sale revenues. In the third quarter of 2014, we began to recognize revenue for payments received under the reimbursed early access programs for

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Translarna for nmDMD patients in selected countries. Once we establish a pattern of collectability, revenue will be recorded upon shipment assuming all other revenue recognition criteria are met.

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 team, 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. 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, 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 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

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 as we continue our confirmatory Phase 3 clinical trials of Translarna for the treatment of nmDMD and nmCF, our Phase 2 proof-of-concept study of Translarna in nmMPS I, and our IND-enabling studies under our antibacterial program, and as we prepare to commence our Phase 1 clinical study for PTC596 under our cancer stem cell program. We also expect to initiate

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proof-of-concept studies for Translarna in at least one additional indication during 2015. 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 candidates and the related expansion of our research and development organization, regulatory requirements, advancement of our preclinical programs and product candidate manufacturing costs.

The following table provides research and development expense for our most advanced principal product development programs, for the year ended December 31, 2014 and December 31, 2013.

	Year ended December 31,	
	2014	2013
	(in thousands)	
Translarna (nmDMD, nmCF and nmMPS I)	$ 47,098	$ 30,270
Antibacterial	6,538	5,906
Cancer stem cell	2,681	1,172
Spinal muscular atrophy	2,523	2,776
Next generation nonsense readthrough	5,683	3,282
Other research and preclinical	15,315	11,469
Total research and development	$ 79,838	$ 54,875

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 products and product candidate over other therapies;
- our ability to market, commercialize and achieve market acceptance for any of our product candidates that we are developing or may develop in the future;
- 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 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, 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

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shows; and professional fees for legal services, including patent-related expenses, and accounting services.

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 income, net

Interest income, net consists of interest related to our secured debt facility and interest income earned on investments. In July 2013, we paid in full the outstanding principal and interest related to our secured debt facility.

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.

As an emerging growth company under the Jumpstart Our Business Startups Act of 2012, we have elected to delay the adoption of new or revised accounting standards until those standards would otherwise apply to private companies. As a result of this election, our financial statements may not be comparable to the financial statements of other public companies.

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 apply the revenue recognition guidance in accordance with Financial Accounting Standards Board ("FASB") Accounting Standards Codification ("ASC") Subtopic 605-15, Revenue Recognition Products. 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.

We have recorded revenue on sales where Translarna is available on a reimbursed early access program and typically paid for by a government authority or institution. We generally recognize revenue for these reimbursed early access programs on a cash basis if all other revenue recognition criteria have been met. Once we established a pattern of collectability, revenue will be recognized upon shipment assuming all other revenue recognition criteria are met.

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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. Allowances for government and other third-party rebates and discounts are established at the time of delivery. These allowances are adjusted to reflect known changes in factors and may impact such allowances in the quarter those changes are known.

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. In addition, 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 Financial Accounting Standards Board, or 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, or EC, granted marketing authorization for Translarna for the treatment of Duchenne muscular dystrophy caused by nonsense mutations, or nmDMD, in ambulatory patients aged five years and older. This marketing authorization is subject to annual review and renewal by the EMA following its reassessment of the risk-benefit balance of the authorization, which we refer to as the annual EMA reassessment, and is further conditioned on our ability to complete ACT DMD and submit the final report, including additional efficacy and safety data from the trial, in 2015 and implement measures, including pharmacovigilance plans, that are detailed in the risk management plan for Translarna that was submitted to EMA. We submitted a marketing authorization renewal request to the EMA in February 2015. We plan to seek to renew the approval on an annual basis until their obligations have been fulfilled and the approval is converted from a conditional approval into a full approval. The conditional marketing authorization allows the Company

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to market Translarna in the 31 member states of European Economic Area. Our launch in these countries is on a country by country basis.

We do not have sufficient history or experience from which to accurately forecast product sales or demand generation. As such, we have not capitalized inventory and will not capitalize inventory until full approval has been obtained or until the Company can reasonably predict future product sales and demand generation. The costs incurred related to Translarna have been recorded as research and development expense in the statements of operations. We do not separately present a cost of product revenues in our statement of operations since the cost of product sales for 2014 was insignificant.

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 2014, we issued a total of 1,639,996 stock options to various employees. Of those, 595,300 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 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. We calculate expected volatility based on reported data for similar publicly traded companies for which historical information is available and will continue to do so until the historical volatility of our common stock is sufficient to measure expected volatility for future option grants.

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The fair value of grants made in the year ended December 31, 2014 was contemporaneously estimated on the date of grant using the following assumptions:

	2014	2013	2012
Risk-free interest rate	0.11 - 2.04%	0.85 - 1.90%	1.14%
Expected volatility	70 - 91%	87 - 89%	87%
Expected term	5.50 - 6.25 years	6.00 - 6.25 years	6.00 - 6.25 years

We assumed no expected dividends for all grants. The weighted average grant date fair value of options granted during the year ended December 31, 2014 was $22.39 per share.

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 expected volatility of share options was estimated 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. 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.

The following table summarizes information on our restricted stock:

	Restricted Stock	
	Number of Shares	Weighted Average Grant Date Fair Value
January 1, 2014	1,110,226	$ 10.68
Granted		
Vested	(373,200)	$ 10.59
Forfeited	(18,626)	$ 10.75
Unvested at December 31, 2014	718,400	$ 10.72

We recorded share-based compensation expense in the statement of operations as follows:

(in thousands)	2014	2013	2012
Research and development	$ 9,739	$ 4,312	$ 1,269
Selling, general and administrative	9,571	4,115	1,020
Total	$ 19,310	$ 8,427	$ 2,289

As of December 31, 2014, 2013 and 2012 there was approximately $38.4 million, $21.6 million and $2.2 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 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 2.66 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

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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.

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. As of December 31, 2014, we had approximately $226.3 million and $154.6 million of federal and state net operating loss carryforwards, respectively. As of December 31, 2014, credit carryforwards for federal and state purposes are approximately $6.5 million and $1.7 million, respectively. In addition the Orphan Drug Credit Carryover available as of December 31, 2013 is approximately $11.4 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 begin to expire in 2015. Sections 382 and 383 of the Internal Revenue Code of 1986 subject the future utilization of net operating losses, or NOLs, 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 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 NOL 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 NOL's 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 $226.1 million of NOLs available, out of which $169.2 million are limited by IRC Section 382. At December 31, 2014 there were $81.9 million in NOLs available for immediate use and an additional $16.7 million will free up in 2015.

Year ended December 31, 2014 compared to year ended December 31, 2013

The following table summarizes revenues and selected expense and other income data for the year ended December 31, 2014 and 2013.

(in thousands)	Year ended December 31, 2014	2013	Change 2014 vs. 2013
Revenues	$ 25,245	$ 34,696	$ (9,451)
Research and development expense	79,838	54,875	24,963
Selling, general and administrative expense	44,820	25,219	19,601
Net tax benefit	4,693		4,693
Interest income (expense), net	1,180	(6,084)	7,264

Revenues. Revenues were $25.2 million for the year ended December 31, 2014, a decrease of $9.5 million, or 27%, from $34.7 million for the year ended December 31, 2013. Net product sales were $0.7 million for the year ended December 31, 2014. In the third quarter of 2014, we began to recognize revenue for payments received under the reimbursed early access programs for Translarna for nmDMD patients in selected countries on a cash basis until we establish a pattern of collectability with our product. Total invoiced revenue in 2014 was $2.5 million, which approximately $1.7 million has been booked as deferred revenue. Collaboration revenue was $22.2 million for the year ended December 31, 2014, a decrease of $9.1 million, or 29%, from collaboration revenues of $31.3 million for the year ended December 31, 2013. The decrease was primarily due to a decrease in the recognition of the deferred revenue balance related to the amortization of approximately $16.8 million of upfront payments from grants and collaborations partially offset by milestone payments received from Roche

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for program achievements in the SMA program. Grant revenue was $2.3 million for the year ended December 31, 2014, a decrease of $1.1 million, or 32%, from grant revenue of $3.4 million for the year ended December 31, 2013.

Research and development expense. Research and development expense was $79.8 million for the year ended December 31, 2014, an increase of $24.9 million, or 45%, from $54.9 million for the year ended December 31, 2013. The increase resulted primarily from increased clinical trial expenses including the initiation of our ACT CF clinical trial, manufacturing of drug product and increase in non-cash, stock-based compensation expense of $5.4 million.

Selling, general and administrative expense. Selling, general and administrative expense was $44.8 million for the year ended December 31, 2014, an increase $19.6 million or 78% from $25.2 million for the year ended December 31, 2013. The increase resulted primarily from increased non-cash stock-based compensation expense of $5.5 million and increased costs related to our commercial launch activities and costs associated with establishing our international infrastructure.

Net tax benefit. 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, 2013.

Interest income (expense),net. Net interest income was $1.2 million for the year ended December 31, 2014, an increase of $7.3 million from net interest expense of $6.1 million for the year ended December 31, 2013. The increase was primarily due to interest income related to investments offset by lower interest expense resulting from the payoff of debt in July 2013. Interest expense for the year ended December 31, 2013 was due to interest related to the debt discount associated with the convertible debt issued in 2013.

Year ended December 31, 2013 compared to year ended December 31, 2012

(in thousands)	2013	2012	Change 2013 vs. 2012
Revenue	$ 34,696	$ 33,946	$ 750
Research and development expenses	54,875	46,139	8,736
Selling, general and administrative expenses	25,219	14,615	10,604
Interest expense, net	6,084	1,210	4,874
Loss on extinguishment of debt	130		130
Other income, net	38	1,783	(1,745)

Revenues. Revenues were $34.7 million for the year ended December 31, 2013, an increase of $0.8 million from revenues of $33.9 million for the year ended December 31, 2012. Collaboration revenue was $31.3 million for the year ended December 31, 2013, an increase of $2.5 million from collaboration revenues of $28.8 million for the year ended December 31, 2012. The increase primarily resulted from the achievement of a $10.0 million milestone related to the Roche agreement in July 2013, partially offset by a decrease in the recognition of the deferred revenue balance related to the value of the remaining performance obligations under our restructured agreement with Genzyme in 2012. Grant revenue was $3.4 million for the year ended December 31, 2013, a decrease of $1.8 million from grant revenue of $5.2 million for the year ended December 31, 2012.

Research and development expense. Research and development expense was $54.9 million for the year ended December 31, 2013, an increase of $8.8 million, or 19%, from $46.1 million for the year ended December 31, 2012. The increase resulted primarily from increased costs for clinical trials of $8.5 million related to the initiation of the Phase 3 clinical trial of Translarna for the treatment of nmDMD and an increase in share-based compensation of $1.2 million partially offset by a decrease in

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personnel costs of $2.1 million as a result of a reduction in force that we implemented in the second quarter of 2012.

Selling, general and administrative expense. Selling, general and administrative expense was $25.2 million for the year ended December 31, 2013, an increase of $10.6 million, or 72%, from $14.6 million for the year ended December 31, 2012. The increase resulted primarily from an increase in share-based compensation of $4.9 million and increases in public company related expenses and pre-commercial activities.

Interest expense, net. Interest expense was $6.1 million for the year ended December 31, 2013, an increase of $4.9 million from $1.2 million for the year ended December 31, 2012. The increase was due to interest expense related to the amortization of the debt discount associated with the convertible debt that we issued in 2013 partially offset by interest income related to investments.

Loss on extinguishment of debt. In July 2013, we paid in full the outstanding principal and interest of $2.6 million due under promissory notes issued related to a $25 million secured debt facility with a syndicate of two lenders. In connection with the repayment, we incurred a loss on extinguishment of debt of $0.1 million, primarily related to the write off of deferred financing costs, the acceleration of recognition of debt extinguishment fees and the prepayment premium payable. The notes were secured by substantially all our assets except for intellectual property and carried a fixed interest rate of 13.65%.

Other income, net. Other income, net was $0.04 million for the year ended December 31, 2013, a decrease of $1.8 million as compared to the year ended December 31, 2012. The decrease was due to the change in fair value related to our warrant liability.

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. 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 over-allotment 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.

Cash flows

As of December 31, 2014, we had cash and cash equivalents and marketable securities of $315.2 million.

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The following table provides information regarding our cash flows and our capital expenditures for the periods indicated.

(in thousands)	Years ended December 31, 2014	2013

In accordance with SFAS 123R, we recognize tax benefit upon expensing certain share-based awards associated with our share-based compensation plans, including nonqualified stock options and deferred stock unit awards, but under current accounting standards we cannot recognize tax benefit currently for share-based compensation expenses associated with incentive stock options and employee stock purchase plan shares (qualified stock options). For qualified stock options that vested after our adoption of SFAS 123R, we recognize

tax benefit only in the period when disqualifying dispositions of the underlying stock occur, and for qualified stock options that vested prior to our adoption of SFAS 123R, the tax benefit is recorded directly to additional paid-in capital. For the fiscal ended June 30, 2006, we realized tax benefit from non-qualified stock option exercises and disqualifying dispositions of qualified stock options totaling $6.6 million, of which $210,000 of the tax benefit was recognized as a reduction of the provision for income taxes, $233,000 reduced deferred tax assets established after our adoption of SFAS 123R, and the remaining tax benefit was recorded

directly to additional paid-in capital.

Our pre-tax income, net income, and basic and diluted net income per share for the year ended June 30, 2006 were reduced by $13.1 million, $10.2 million, and $0.42 and $0.34 per share, respectively, under SFAS 123R more than they would have been had we continued to account for our share-based awards in accordance with APB 25.

Application of SFAS 123R had no impact on our cash position, but did result in a change in presentation on our consolidated statements of cash flows by classifying excess tax benefit on share-based awards from cash flows from operating

activities to cash flows from financing activities. To determine excess tax benefit, we use the long-haul method in which we compare the actual tax benefit associated with the tax deduction from share-based award activity to the hypothetical tax benefit on the grant date fair values of the corresponding share-based awards. Actual tax benefit related to the tax deduction for share-based awards exceeded the hypothetical tax benefit on the grant date fair values of the corresponding share-based awards resulting in excess tax benefit of $5.2 million for the year ended June 30, 2006.

Historically, we have issued new shares in connection with our share-based compensation plans; however, 2,306,100 treasury shares are also available for issuance as of the end of fiscal 2006. As of June 30, 2006, we have $40 million remaining under our stock repurchase program, which expires in October 2007. Any incremental shares repurchased under the stock repurchase program would be available for issuance.

Deferred Stock Units

Our 2001 Incentive Compensation Plan (2001 Plan) provides for the grant of deferred stock unit awards (DSUs) to our employees,

consultants, and directors. A DSU is a promise to deliver shares of our common stock at a future date in accordance with the terms of the DSU grant agreement. We began granting DSU awards in January 2006.

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DSUs granted under the 2001 Plan generally vest 25% at the end of 12 months from the vesting commencement date and at a rate of approximately 2% each month thereafter until fully vested at the end of 48 months from the vesting commencement date. Delivery of shares under the plan takes place quarterly for all DSUs vested as of the scheduled delivery dates. Until delivery of shares, the grantee has no rights as a stockholder.

An election to defer delivery of the underlying shares for unvested DSU awards can be made provided the deferral election is made at least one year before vesting and the deferral period is at least five years from the scheduled delivery date.

The following table summarizes DSU activity including DSUs granted, delivered, and forfeited during fiscal 2006 and the balance and aggregate intrinsic value of DSUs as of June 30, 2006:

	Deferred Stock Unit Awards Outstanding	Aggregate Intrinsic Value (thousands)	Weighted Average Grant Date Fair Value
Balance at June 30, 2005			
Granted	38,680		$29.69
Delivered			
Forfeited	(400)		$30.71
Balance at June 30, 2006	38,280	$834	$29.68

Unrecognized share-based compensation costs for DSUs granted under the 2001 Plan are approximately $891,000 as of June 30, 2006, to be recognized over a weighted average period of approximately four years.

Stock Options

Our current share-based compensation plans that provide for the grant of stock options include our 1996 Stock Option Plan, our 2000 Nonstatutory Stock Option Plan, and our 2001 Incentive Compensation Plan (the Plans). Under the Plans, employees, consultants, and directors may be granted incentive stock options or nonqualified stock options to purchase shares of our common stock at not less than 100% or 85% of the fair value, respectively, on the date of grant.

Options issued under the Plans generally vest 25% at the end of 12 months from the vesting commencement date and approximately 2% each month thereafter until fully vested at the end of 48 months from the vesting commencement date. Options not exercised ten years after the date of grant are cancelled.

In October 2002, we granted 200,000 options to a consultant that at the time were to vest over four years; however, in December 2002 we hired the consultant as an employee. In accordance with FIN 44, Accounting for Certain Transactions Involving Stock Compensation, we remeasured the intrinsic value of the option grant on the date the consultant became an employee and recorded deferred stock compensation that we were amortizing over the remaining vesting period of the options. With the adoption of SFAS 123R, we ceased amortizing deferred stock compensation, reclassified the remaining balance of deferred stock compensation on our balance sheet to additional paid-in capital, and began expensing the remaining fair value, as previously determined under SFAS 123, of the underlying options over their remaining vesting periods.

In August 2002, our board approved an option regrant offer to several employees who had received option grants under the 2001 Incentive Compensation Plan having option exercise prices of $12.98 and $18.70. The option exercise prices were substantially higher than the price of our stock at the time of the regrant offer. Under the terms of the regrant, the employees were allowed to elect to have their option cancelled and in consideration thereof to receive a new option for the same number of shares as cancelled six months and one day after the date of cancellation. On March 3, 2003, new options to acquire a total of 106,500 shares were granted pursuant to the regrant offer with a new exercise price of $6.56 per share. The vesting period and schedule for the new options remained the same as the vesting period and schedule of the cancelled options.

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The following table summarizes stock option activity and weighted average exercise prices for stock options granted, exercised, and forfeited during fiscal 2006 and the balance of outstanding and exercisable stock options as of June 30, 2006:

	Stock Option Awards Outstanding	Weighted Average Exercise Price
Balance at June 30, 2005	5,426,266	$ 10.94
Granted	1,585,184	22.88
Exercised	(949,658)	7.19
Forfeited	(253,781)	17.04
Balance at June 30, 2006	5,808,011	14.55
Exercisable at June 30, 2006	3,130,138	8.92

As of June 30, 2006, the number of stock options outstanding and exercisable by range of exercise prices, the weighted average exercise prices, the intrinsic value and for options outstanding the weighted average remaining contractual life are as follows:

	Options Outstanding				Options Exercisable		
Range of Exercise Prices	Number Outstanding	Weighted Average Remaining Contractual Term	Weighted Average Exercise Price	Intrinsic Value (thousands)	Number Exercisable	Weighted Average Exercise Price	Intrinsic Value (thousands)
$1.00 - $3.00	1,008,977	3.50	$ 2.37	$ 19,594	1,008,977	$ 2.37	$ 19,594
$3.50 - $7.37	734,346	6.17	6.34	11,346	633,647	6.24	9,853
$8.19 - $9.96	882,598	6.11	9.25	11,068	744,759	9.13	9,429
$10.91 - $16.40	509,684	7.52	15.05	3,435	263,527	14.93	1,808
$18.26 - $18.70	559,033	8.05	18.26	1,973	259,120	18.27	912
$19.56 - $20.33	267,959	9.16	19.81	531	24,213	20.33	35
$21.50	822,500	9.09	21.50	239	16,029	21.50	5
$21.88 - 25.78	363,520	9.43	22.90		34,346	24.93	
$30.26	406,582	8.57	30.26		145,520	30.26	
$30.71	252,812	9.56	30.71				
	5,808,011	7.07	14.55	$ 48,186	3,130,138	8.92	$ 41,636

At June 30, 2006, we estimate fully vested options and options expected to vest to be 5,583,202 with an aggregate intrinsic value of $47.9 million having a weighted average exercise price and a weighted average remaining contractual term of $14.23 per share and seven years, respectively.

The following table summarizes cash received and the aggregate intrinsic value for stock options exercised during the years ended June 30, 2004, 2005, and 2006 (in thousands):

	Years ended June 30,		
	2004	2005	2006
Cash received	$ 4,271	$ 7,014	$ 6,832
Aggregate intrinsic value	$12,383	$29,086	$17,707

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The fair value of each award granted from our Plans during the year ended June 30, 2006 was estimated at the date of grant using the Black-Scholes option pricing model, assuming no expected dividends and the following assumptions:

Expected volatility	71.4% - 73.9%
Expected life in years	5.0
Risk-free interest rate	4.1% - 4.9%
Fair value per award	$12.38-$19.14

The expected volatility is based on historical volatility; the expected life is based on historical option exercise trends; and the risk free interest rate is based on U. S. Treasury yields in effect at the time of grant for the expected life of the option.

Unrecognized share-based compensation costs for stock options granted under the Plans are approximately $29.1 million as of June 30, 2006, to be recognized over a weighted average period of approximately three years.

Employee Stock Purchase Plan

Our 2001 Employee Stock Purchase Plan (ESPP) became effective on January 29, 2002, the effective date of the registration statement for our initial public offering. The ESPP allows employees to designate up to 15% of their base compensation, subject to legal restrictions and limitations, to purchase shares of common stock at 85% of the lesser of the fair market value (FMV) at the beginning of the offering period or the exercise date. The offering period extends for up to two years and includes four exercise dates occurring at six month intervals. Under the terms of the plan, if the FMV at an exercise date is less than the FMV at the beginning of the offering period, the current offering period will terminate and a new two-year offering period will commence.

The following table summarizes shares purchased, weighted average purchase price, cash received, and the aggregate intrinsic value for ESPP purchases during the years ended June 30, 2004, 2005, and 2006 (in thousands, except for shares purchased and weighted average purchase price):

	Years ended June 30,		
	2004	2005	2006
Shares purchased	165,833	198,251	93,020
Weighted average purchase price	$ 6.63	$ 7.02	$ 17.69
Cash received	$ 1,099	$ 1,391	$ 1,645
Aggregate intrinsic value	$ 1,253	$ 3,636	$ 488

Under the terms of our ESPP, the offering period that commenced on January 1, 2005 was terminated on June 30, 2005 and a new offering period commenced on July 1, 2005. In accordance with Technical Bulletin No. FTB 97-1, Accounting under Statement 123 for Certain Employee Stock Purchase Plans with a Look-Back Option, the early termination of an offering period followed by the commencement of a new offering period represents a modification to the terms of the related awards. This modification affected 169 employees participating in the ESPP as of June 30, 2005 and resulted in incremental compensation costs that will be recognized on a straight-line basis over the two-year period ending June 30, 2007.

The fair value of each award granted under our ESPP during the year ended June 30, 2006 was estimated using the Black-Scholes option pricing model, assuming no expected dividends and the following weighted average assumptions:

Expected volatility	49.3% - 75.7%
Expected life in years	0.5 - 2.0
Risk-free interest rate	3.3% - 4.4%
Fair value per award	$7.40-$11.86

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The expected volatility is based on implied and historical volatility; the expected life is based on each period that begins with the enrollment date until each purchase date remaining in the offering period at the date of enrollment in the plan; and the risk free interest rate is based on U. S. Treasury yields or yield curve in effect for each expected life.

Unrecognized share-based compensation costs for awards granted under our ESPP are approximately $1.2 million as of June 30, 2006, to be recognized over a weighted average period of approximately one year.

Pre-SFAS 123R Pro Forma Accounting Disclosures

The fair value of each share-based award granted during the years ended June 30, 2004 and 2005 was estimated at the date of grant using the Black-Scholes option pricing model, assuming no expected dividends and the following weighted average assumptions:

	Stock Option Plan		Employee Stock Purchase Plan	
	Years ended June 30,		Years ended June 30,	
	2004	2005	2004	2005
Expected volatility	74.5%	68.4%	65.0%	58.9%
Expected life in years	5	5	0.5	1.1
Risk-free interest rate	3.0%	3.5%	1.0%	2.6%
Fair value per award	$7.97	$13.71	$2.57	$10.31

During the years ended June 30, 2004 and 2005, had compensation expense for stock options been determined based on the fair value of the options at dates of grant consistent with the provisions of SFAS 123, net income and net income per share would have been reduced to the pro forma amounts indicated in the following table (in thousands, except per share amounts):

	Years ended June 30,	
	2004	2005
Net income as reported	$ 12,992	$ 37,985
Add: Total stock-based compensation included in reported net income, net of tax	320	213
Deduct: Total stock-based compensation determined under fair value based method for all awards, net of tax	(4,045)	(6,506)
Net income pro forma	$ 9,267	$ 31,692
Net income per share basic:		
As reported	$ 0.53	$ 1.48
Pro forma	$ 0.38	$ 1.23
Net income per share diluted:		
As reported	$ 0.48	$ 1.30
Pro forma	$ 0.34	$ 1.09

10. Employee benefit plans

401(k) Plan

We have a 401(k) Retirement Savings Plan for full-time employees. Under the plan, eligible employees may contribute a maximum of 25% of their net compensation or the annual limit of $15,000. The annual limit for employees who are 50 years or older is $20,000. We provide matching funds of 20% of the employee s contribution up to a maximum of $3,000. We made matching contributions of $49,000, $183,000, and $305,000 in fiscal 2004, 2005,

and 2006, respectively.

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11. Income Taxes

Income before provision for income taxes consisted of the following (in thousands):

	Years ended June 30,		
	2004	2005	2006
U.S	$ 20,340	$ 35,148	$ 18,949
Foreign	586	23,184	6,574
Income before provision for income taxes	$ 20,926	$ 58,332	$ 25,523

The provision for income taxes consists of the following (in thousands):

	Years ended June 30,		
	2004	2005	2006
Current tax expense			
Federal	$ 7,230	$ 12,317	$ 5,192
State	1,188	1,778	1,602
Foreign	35	4,421	3,524
	8,453	18,516	10,318
Deferred tax expense			
Federal	(427)	1,611	1,144
State	(115)	554	125
Foreign	23	(334)	235
	(519)	1,831	1,504
Provision for income taxes	$ 7,934	$ 20,347	$ 11,822

The provision for income taxes differs from the federal statutory rate as follows (in thousands):

	Years ended June 30,		
	2004	2005	2006
Provision at U.S. federal statutory rate	$ 7,324	$ 20,416	$ 8,933
State income taxes	657	665	1,437
Foreign withholding taxes		3,728	3,130
Unrecognized tax benefit on share-based compensation, net			2,432
Research and development credit	(328)	(226)	(2,129)
Foreign tax rate differential		(4,081)	(844)
Tax exempt interest	(261)	(436)	(1,065)
Other differences	542	281	(72)
Provision for income taxes	$ 7,934	$ 20,347	$ 11,822

The American Jobs Creation Act of 2004 (the Act) was signed into law in October 2004. The Act created a temporary incentive for U.S. corporations to repatriate accumulated income earned abroad by providing an 85% dividends received deduction for certain dividends from controlled foreign corporations resulting in an approximate 5.25% federal tax rate on the repatriated earnings. We did not repatriate any foreign accumulated income under the

Act.

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As of June 30, 2005 and 2006, significant components of our deferred tax assets (liabilities) are as follows (in thousands):

	2005	2006
Deferred tax assets:		
Investment writedowns	$ 1,105	$ 1,102
Inventory writedowns	74	129
Warranty reserve	15	7
Depreciation and amortization	629	875
Accrued compensation	618	742
Accruals not currently deductible	838	258
Share-based compensation		2,491
Foreign loss carryforwards	280	
	3,559	5,604
Valuation allowance	(1,105)	(1,102)
	2,454	4,502
Deferred tax liabilities:		
Interest deduction	(1,878)	(5,450)
Other	(20)	
	(1,898)	(5,450)
Net deferred tax assets (liabilities)	$ 556	$ (948)

Realization of deferred tax assets depends on our generating sufficient U.S. and certain foreign taxable income in future years to obtain benefit from the reversal of deferred tax assets. Accordingly, the amount of deferred tax assets considered realizable may increase or decrease when we reevaluate the underlying basis for our estimates of future U.S. and foreign taxable income. As of June 30, 2006, a valuation allowance of $1.1 million had been established to reduce deferred tax assets to levels that we believe are more likely than not to be realized through future taxable income. The valuation allowance decreased by $332,000, $575,000, and $3,000 during the years ended June 30, 2004, 2005, and 2006, respectively. As of June, 30, 2006, the remaining valuation allowance relates to our investment writedowns. During fiscal 2005 and 2006, we recognized $1.2 million and $2.7 million of tax benefit, respectively, from the release of tax contingency accruals associated with income tax issue settlements and statute expirations. No material tax benefit from the release of tax contingency accruals was realized in fiscal 2004. The tax contingency accruals released in fiscal 2005 and 2006 were established in earlier fiscal years.

As of June 30, 2005and 2006, net deferred tax assets (liabilities) consisted of the following balances (in thousands):

	2005	2006
Current deferred tax assets	$ 1,182	$ 1,036
Non-current deferred tax assets	280	
Non-current deferred tax liabilities	(906)	(1,984)
Net deferred tax assets (liabilities)	$ 556	$ (948)

Current deferred tax assets, non-current deferred tax assets, and non-current deferred tax liabilities are included in prepaid expenses and other current assets, other assets, and other liabilities, respectively, in the accompanying consolidated balance sheets.

Included in other assets as of June 30, 2006 is $13.1 million of non-current prepaid tax. The non-current prepaid tax is associated with an intercompany royalty arrangement on the licensing of intangibles in connection with our international operating structure. The non-current prepaid tax will be charged to tax expense over the weighted average life of the licensed intangibles or approximately four years.

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12. Segment, Customers, and Geographic Information

We operate in one segment: the development, marketing, and sale of interactive user interface solutions for electronic devices and products. We generate our revenue from two broad product categories: the PC market and digital lifestyle product markets. The PC market accounted for 84%, 59%, and 85% of our net revenue in the years ended June 30, 2004, 2005, and 2006, respectively.

The following is a summary of net revenue within geographic areas based on our customers location (in thousands):

	Years ended June 30,		
	2004	2005	2006
China	$ 75,899	$ 157,661	$ 141,958
Taiwan	37,211	23,370	23,558
Japan	3,698	3,294	4,873
Singapore	340	13,680	4,541
United States	5,693	4,007	3,242
Korea	4,307	1,498	2,176
Other	6,128	4,629	4,209
	$ 133,276	$ 208,139	$ 184,557

As of June 30, 2005 and 2006, long-lived assets within geographic areas consisted of the following (in thousands):

	2005	2006
United States	$ 14,339	$ 14,642
Asia/Pacific	66	1,149
United Kingdom	210	247
	$ 14,615	$ 16,038

Major customers as a percentage of net revenue:

	Years ended June 30,		
	2004	2005	2,006
Customer A	25%	34%	14%
Customer B	3%	2%	10%
Customer C	10%	6%	9%

13. Subsequent Events

Subsequent to June 30, 2006, we repurchased 215,000 shares for $4.6 million, or an average cost of $21.45 per share.

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SCHEDULE II
SYNAPTICS INCORPORATED AND SUBSIDIARIES
VALUATION AND QUALIFYING ACCOUNTS
Years Ending June 30, 2004, 2005, and 2006
(in thousands)

	Balance at beginning of year	Additions charged to expense	Adjustments to reserve	Balance at end of year
Reserve deducted from assets				
Allowance for doubtful accounts:				
2004	$160		(30)	130
2005	130	44	(9)	165
2006	165	52	(28)	189

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INDEX TO EXHIBITS

Exhibit Number	Exhibit
3.1	Certificate of Incorporation (1)
3.2	Bylaws (1)
3.3	Certificate of Amendment of Certificate of Incorporation of the registrant (6)
4	Form of Common Stock Certificate (2)
4.1	Indenture dated December 7, 2004 by and between the registrant and American Stock Transfer & Trust Company (6)
4.2	Registration Rights Agreement dated December 7, 2004 by and among the registrant, Bear, Stearns & Co. Inc., and Credit Suisse First Boston LLC (6)
10.1	1986 Incentive Stock Option Plan and form of grant agreement (3)
10.2	1986 Supplemental Stock Option Plan and form of grant agreement (3)
10.3(a)	1996 Stock Option Plan (3)
10.3(b)	Form of grant agreements for 1996 Stock Option Plan (2)
10.4	2000 U.K. Approved Sub-Plan to the 1996 Stock Option Plan and form of grant agreement (3)
10.5	2000 Nonstatutory Stock Option Plan and form of grant agreement (3)
10.6(a)	Amended and Restated 2001 Incentive Compensation Plan (4)
10.6(b)	Form of grant agreements for Amended and Restated 2001 Incentive Compensation Plan (4)
10.6(c)	Form of deferred stock award agreement for Amended and Restated 2001 Incentive Compensation Plan *
10.7(a)	Corrected Amended and Restated 2001 Employee Stock Purchase Plan (as amended through February 20, 2002) (2)
10.7(b)	2001 Employee Stock Purchase Sub-Plan for U.K. Employees (2)
10.8	401(k) Profit Sharing Plan (3)
10.12	Subordinated Secured Non-Recourse Promissory Note dated August 12, 1997 executed by the registrant in favor of National Semiconductor Corporation (3)
10.13	Form of Stock Option Grant and Stock Option Agreement between the registrant and Federico Faggin (3)
10.14	Form of Stock Option Grant and Stock Option Agreement between the registrant and Francis F. Lee (3)

10.15 Form of Stock Option Grant and Stock Option Agreement between the registrant and Russell J. Knittel (3)

10.16 Loan and Security Agreement dated as of August 30, 2001 between Silicon Valley Bank and the registrant as amended through November 30, 2004 (7)

10.17 Form of Indemnification Agreement entered into as of January 28, 2002 with the following directors and executive officers: Federico Faggin, Francis F. Lee, Donald E. Kirby, Russell J. Knittel, Shawn P. Day, David T. McKinnon, Thomas D. Spade, William T. Stacy, Keith B. Geeslin, and Richard L. Sanquini, as of April 23, 2002 with W. Ronald Van Dell, as of June 26, 2004 with Clark F. Foy as of September 29, 2005 with Jeffrey D. Buchanan, and as of March 28, 2006 with Thomas J. Tiernan (1)

10.18 Severance Policy for Principal Executive Officers (5)

10.19 Change of Control and Severance Agreement entered into by Francis F. Lee as of April 22, 2003 (5)

10.20 Form of Change of Control and Severance Agreement entered into by Donald E. Kirby and Russell J. Knittel as of April 22, 2003 (5)

10.21 Purchase Agreement dated December 1, 2004 by and among the registrant, Bear, Stearns & Co. Inc., and Credit Suisse First Boston LLC (6)

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Exhibit Number	Exhibit
10.22	Settlement Agreement dated March 31, 2005 by and among the registrant, Alps Electric Co. Ltd., and Cirque Corporation (8) **
10.23	Change of Control Severance Agreement entered into by Thomas Tiernan as of April 3, 2006 (10)
12.1	Ratio of Earnings to Fixed Charges
21	List of Subsidiaries
23.1	Consent of KPMG LLP, independent registered public accounting firm
31.1	Certification of Chief Executive Officer pursuant to Rule 13a-14(a)/15d-14(a)
31.2	Certification of Chief Financial Officer pursuant to Rule 13a-14(a)/15d-14(a)
32.1	Section 1350 Certification of Chief Executive Officer
32.2	Section 1350 Certification of Chief Financial Officer

(1) Incorporated by reference to the registrant s Form 10-Q for the quarter ended December 29, 2001, as filed with the SEC on February 21, 2002.

(2) Incorporated by reference to the registrant s Form 10-K for the fiscal year ended June 30, 2002, as filed with the SEC on September 12, 2002.

(3) Incorporated by reference to the registrant s registration statement on

Form S-1 (Registration No. 333-56026) as filed with the SEC January 22, 2002 and declared effective January 28, 2002.

(4) Incorporated by reference to the registrant s Form 10-Q for the quarter ended December 28, 2002, as filed with SEC on February 6, 2003.

(5) Incorporated by reference to the regis trant s Form 10-K for the fiscal year ended June 30, 2002, as filed with the SEC on September 12, 2003.

(6) Incorporated by reference to the registrant s Current Report on Form 8-K as filed with the SEC on December 7, 2004.

(7) Incorporated by reference to the registrant s Current Report on Form 8-K as filed with the SEC on December 3,

2004.

(8) Incorporated by reference to the registrant s Current Report on Form 8-K as filed with the SEC on April 1, 2005.

(9) Incorporated by reference to the registrant s Current Report on Form 8-K as filed with the SEC on January 23, 2006.

(10) Incorporated by reference to the registrant s Current Report on Form 8-K as filed with the SEC on April 3, 2006.

* Filed herewith.

** Portions of this exhibit have been omitted pursuant to a confidential treatment request that was granted by the Securities and Exchange Commission pursuant to Rule 24b-2 of the Exchange Act.