PTC THERAPEUTICS, INC.
Form 424B4
June 20, 2013

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Filed Pursuant to Rule 424(b)(4)
Registration Statement No. 333-188657

Prospectus

8,372,000 shares

Common stock

This is an initial public offering of common stock by PTC Therapeutics, Inc. We are selling 8,372,000 shares of our common stock. The initial public offering price is $15.00 per share.

Prior to this offering, there has been no public market for our common stock. Our common stock has been approved for listing on The NASDAQ Global Select Market under the symbol "PTCT".

We are an emerging growth company as that term is used in the Jumpstart Our Business Startups Act of 2012, and as such, have elected to comply with certain reduced public company reporting requirements.

Investing in our common stock involves a high degree of risk. See "Risk factors" beginning on page 11.

	Per share	Total
Initial public offering price	$ 15.00	$ 125,580,000
Underwriting discounts and commissions(1)	$ 1.05	$ 8,790,600
Proceeds to PTC Therapeutics, Inc., before expenses	$ 13.95	$ 116,789,400

(1) The underwriters will receive compensation in addition to the underwriting discount. See "Underwriting" on page 183.

Certain of our existing principal stockholders or their affiliates and entities affiliated with certain of our directors have agreed to purchase an aggregate of 3,250,000 shares of our common stock in this offering at the initial public offering price. The underwriters will receive the same underwriting discount on any shares purchased by these entities as they will on any other shares sold to the public in this offering.

We have granted the underwriters an option for a period of 30 days to purchase up to 1,255,800 additional shares of common stock to cover any over-allotments. The underwriters can exercise this right at any time within 30 days after the date of this prospectus.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed on the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

The underwriters expect to deliver the shares of common stock to investors on or about June 25, 2013.

J.P. Morgan **Credit Suisse**

Cowen and Company

Wedbush PacGrow Life Sciences

The date of this prospectus is June 19, 2013

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We have not authorized anyone to provide you with information other than that contained in this prospectus or in any free writing prospectus prepared by or on behalf of us or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give to you. We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The information contained in this prospectus is accurate only as of the date of this prospectus, regardless of the time of delivery of this prospectus or any sale of our common stock. Our business, financial conditions, results of operations and prospects may have changed since that date.

No action is being taken in any jurisdiction outside the United States to permit a public offering of our common stock or possession or distribution of this prospectus in that jurisdiction. Persons who come into possession of this prospectus in jurisdictions outside the United States are required to inform themselves about and to observe any restrictions as to this offering and the distribution of this prospectus applicable to that jurisdiction.

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Prospectus summary

This summary highlights information contained elsewhere in this prospectus. This summary does not contain all of the information you should consider before investing in our common stock. You should read this entire prospectus carefully, especially the "Risk factors" section and our financial statements and the related notes appearing at the end of this prospectus, before making an investment decision.

Our company overview

We are a biopharmaceutical company focused on the discovery and development of orally administered, proprietary small-molecule drugs that target post-transcriptional control processes. While our discovery programs are directed at targets in multiple therapeutic areas, we are focusing particularly on the development and commercialization of treatments for orphan and ultra-orphan disorders. Our lead product candidate is ataluren for the treatment of patients with genetic disorders that arise from a type of genetic mutation known as a nonsense mutation. We have retained worldwide commercialization rights to ataluren for all indications in all territories. Ataluren is in late stage clinical development for the treatment of Duchenne muscular dystrophy caused by nonsense mutations, or nmDMD, and cystic fibrosis caused by nonsense mutations, or nmCF. There are currently no marketed therapies approved to treat the underlying cause of nmDMD or nmCF. The European Medicines Agency, or EMA, has designated ataluren as an orphan medicinal product and the U.S. Food and Drug Administration, or FDA, has granted orphan drug designation to ataluren for the treatment of both nmDMD and nmCF.

We have initiated a confirmatory Phase 3 clinical trial of ataluren for the treatment of nmDMD. We dosed the first patient in this trial in April 2013. In October 2012, we submitted a marketing authorization application, or MAA, to the EMA for conditional approval of ataluren for the treatment of nmDMD. We are also planning a confirmatory Phase 3 clinical trial of ataluren for the treatment of nmCF. We plan to begin enrolling trial sites for this trial in the second half of 2013, and we expect to dose the first patient in this trial in the first half of 2014, subject to the conclusion of our ongoing discussions with regulatory authorities regarding our proposed trial design. We have completed a Phase 2b clinical trial of ataluren for the treatment of nmDMD and a Phase 3 clinical trial of ataluren for the treatment of nmCF. We did not achieve the primary efficacy endpoint in either trial with the pre-specified level of statistical significance. However, we believe that the collective data from these trials, including retrospective and subgroup analyses that we have performed, provide strong support for concluding that ataluren was active and showed clinically meaningful improvements over placebo in these trials. In addition, we believe that our experience in these completed clinical trials has allowed us to enhance the designs of our confirmatory Phase 3 clinical trials and improve our likelihood of success in these trials. Ataluren has been generally well tolerated in all of our clinical trials to date.

The letters "PTC" in our corporate name are an acronym for post-transcriptional control processes, which are the regulatory events that occur in cells after a messenger RNA, or mRNA, molecule is copied, or transcribed, from DNA. Post-transcriptional control processes regulate the rate and timing of protein production and are essential to proper cellular function. 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. The absence or overproduction of specific proteins can cause disease. We apply proprietary technologies and our extensive knowledge of post-transcriptional control processes in our drug discovery and development activities. We discovered ataluren by applying our technologies to identify molecules that promote or enhance the suppression of nonsense mutations.

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In addition to ataluren, we have a pipeline of product candidates that are in preclinical development. 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 develop these compounds both on our own and through selective collaboration arrangements with leading pharmaceutical and biotechnology companies. For example, we currently are collaborating with F. Hoffman-La Roche Ltd and Hoffman-La Roche, Inc. and the Spinal Muscular Atrophy Foundation for the development and commercialization of compounds for the treatment of spinal muscular atrophy.

Ataluren

Ataluren is a novel, orally administered small-molecule compound that targets nonsense mutations. We are developing ataluren for the treatment of genetic disorders in which a nonsense mutation is the cause of the disease. Genetic tests are available for many genetic disorders, including Duchenne muscular dystrophy and cystic fibrosis, to determine if the underlying cause is a nonsense mutation.

We believe that ataluren interacts with the ribosome, which is the component of the cell that decodes the mRNA molecule and manufactures proteins, to enable the ribosome to read through premature nonsense stop signals on mRNA and allow the cell to produce a full-length, functional protein. We believe that a drug with a mechanism of action that allows the ribosome to read through premature stop signals without affecting the normal termination of protein synthesis may be able to overcome the effects of nonsense mutations.

Ataluren is administered orally as granules mixed with permitted liquids or semi-solid foods, such as milk, water, applesauce or yogurt. We designed this formulation because children comprise a significant portion of the patient population for ataluren and often have difficulty swallowing pills or capsules. Ataluren is manufactured in reliable and reproducible synthetic processes from readily available starting materials.

Ataluren for 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. Based on information from the American Journal of Medical Genetics, we estimate that a nonsense mutation is the cause of Duchenne muscular dystrophy in approximately 13% of patients, or approximately 2,000 patients in the United States and 2,500 patients in the European Union. There is currently no marketed therapy approved for the treatment of the underlying cause of Duchenne muscular dystrophy. Currently available treatments for Duchenne muscular dystrophy are only palliative.

We have initiated a multicenter, randomized, double-blind, placebo controlled Phase 3 clinical trial to evaluate the efficacy and safety of ataluren in patients with nmDMD. We plan to conduct this trial in approximately 220 patients at investigational sites worldwide. The primary objective of this trial is to evaluate the effect of ataluren on ambulation as measured by mean change in distance walked during a 6-minute walk test, which we refer to as 6-minute walk distance. Based on our estimates regarding patient enrollment, we expect to complete this trial and have initial, top-line data available in mid-2015.

The trial protocol specifies the following key inclusion criteria for patients enrolling in this trial:

- the patient must be seven through 16 years of age;

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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 study population and outcome measures that we are using in our confirmatory Phase 3 clinical trial 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, and a post-hoc, retrospective subgroup analysis of patients who would meet the enrollment criteria for our confirmatory Phase 3 clinical trial. This retrospective subgroup analysis showed a much larger treatment effect in mean change in 6-minute walk distance between ataluren and placebo in this subgroup than in the overall population included in the Phase 2b clinical trial. In light of this natural history data and retrospective subgroup analysis, our confirmatory Phase 3 clinical trial is focusing 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 ataluren's effect to slow decline in walking ability. In addition, we believe that by only enrolling patients who are treated with systemic corticosteroids, the variability of 6-minute walk distance results will be reduced.

In October 2012, we submitted an MAA to the EMA for conditional approval of ataluren for the treatment of nmDMD. In March 2013, the EMA provided an initial response to our MAA submission for conditional approval of ataluren for the treatment of nmDMD. In this response, referred to as the day 120 list of questions, the EMA informed us of major objections that would preclude a recommendation for marketing authorization unless adequately addressed. These major objections relate to, among other things, the EMA's views regarding insufficient evidence of efficacy based on our single Phase 2b clinical trial, resulting in a negative risk-benefit balance for purposes of conditional approval, uncertainties about the effective dose and questions about whether our confirmatory Phase 3 clinical trial for this indication could be continued if the EMA grants conditional approval.

We expect to submit responses to the day 120 list of questions in July 2013. Although we believe that we have reasonable responses to all of the EMA's major objections, there is substantial risk that the EMA will not grant us this conditional approval. If granted, EMA conditional approval would permit us to market ataluren in the European Union for treatment of nmDMD prior to completion of our confirmatory Phase 3 clinical trial for this indication. We plan to complete our confirmatory Phase 3 clinical trial of ataluren for the treatment of nmDMD before applying for marketing approval from the FDA. In designing our confirmatory Phase 3 clinical trial for the treatment of nmDMD, we have sought to reflect the views expressed by both the EMA and the FDA in our discussions with these regulatory authorities. We expect that these trial results, if favorable, could serve as the basis for full approval by the EMA and the FDA of ataluren for the treatment of nmDMD. If the trial results are favorable, and based on our estimates of patient enrollment and data availability, we expect to be able to submit applications for full marketing approval of ataluren for the treatment of nmDMD in both the European Union and the United States in 2016.

Ataluren for nmCF

Cystic fibrosis is among the most common life-threatening genetic disorders worldwide. Cystic fibrosis is caused by defects in a single gene known as the cystic fibrosis transmembrane conductance regulator, or CFTR. Based on information from the Cystic Fibrosis Foundation, we estimate that nonsense mutations are

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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. 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.

We are planning a multicenter, randomized, double-blind, placebo controlled Phase 3 clinical trial to evaluate the efficacy and safety of ataluren in approximately 210 patients with cystic fibrosis caused by a nonsense mutation as confirmed by gene sequencing. We expect that the primary objective of this trial will be to evaluate the effect of ataluren on pulmonary function as measured by relative change in percent of predicted forced expiratory volume in one second, or FEV_1. FEV_1 is a measure of the volume of air that has been exhaled at the end of the first second of forced expiration. Percent of predicted FEV_1, or %-predicted FEV_1, is based on a comparison to healthy individuals matched for age, height and gender. Based on our estimates regarding initiation of the trial and patient enrollment, we expect to complete this trial and have initial, top-line data available in 2016.

We expect to require that patients in this trial be at least six years of age and have %-predicted FEV_1 within a specified range, sweat chloride in excess of a specified level as evidence of the severity of the disease and documentation of a nonsense mutation in at least one copy of the CFTR gene. We expect to exclude patients from the trial if, among other reasons, they are receiving chronic inhaled aminoglycoside antibiotics.

We selected the enrollment criteria for our confirmatory Phase 3 clinical trial in part based on a subgroup analysis of patients not receiving inhaled aminoglycoside antibiotics in our completed Phase 3 clinical trial for the treatment of nmCF. We believe that the inhaled antibiotic tobramycin interfered with ataluren's mechanism of action. For the subgroup of patients not receiving chronic inhaled aminoglycoside antibiotics, there was a substantial difference in mean relative changes from baseline in %-predicted FEV_1 at the end of the trial favoring ataluren in comparison with placebo. In contrast, patients that received chronic inhaled aminoglycoside antibiotics and ataluren did not exhibit a difference compared to patients that received chronic inhaled aminoglycoside antibiotics and placebo.

We have received scientific advice from the EMA regarding the possibility of submitting an MAA for conditional approval of ataluren for the treatment of nmCF and the protocol design of a post-approval confirmatory trial. There also is substantial risk that the EMA will not grant us conditional approval of ataluren for the treatment of nmCF. In addition, we have begun discussions with the FDA regarding the clinical development design options which would have the potential to support the submission of a new drug application with the FDA. Our goal in these continuing discussions is to achieve consensus between the EMA and the FDA that a single placebo controlled Phase 3 clinical trial can serve as the basis for full approval of ataluren to treat nmCF in both the European Union and the United States.

Our strategy

Our goal is to become a leading biopharmaceutical company focused on discovering, developing and commercializing small-molecule therapeutics that target post-transcriptional control processes and address disorders, particularly in the orphan and ultra-orphan areas, with high unmet medical needs. To achieve our goal, we are pursuing the following strategies:

Complete clinical development and seek marketing approvals for ataluren for the treatment of nmDMD and nmCF.

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Commercialize ataluren through our own focused, specialized sales force initially in the European Union and the United States and, eventually, in other key territories.

Explore additional, strategically attractive indications for ataluren based on the large number of genetic disorders caused by nonsense mutations.

Advance the development of our preclinical product candidates and discover and develop additional small molecules that alter post-transcriptional control processes in a broad range of indications.

Seek third party grants and support and selectively establish strategic alliances.

Risks associated with our business

Our business is subject to a number of risks of which you should be aware before making an investment decision. These risks are discussed more fully in the "Risk factors" section of this prospectus immediately following this prospectus summary. These risks include the following:

We currently depend heavily on the success of ataluren. Our ability to generate product revenues, which may not occur for several years, if ever, will depend heavily on the successful development and commercialization of ataluren for either or both of nmDMD and nmCF. There is substantial risk that the EMA will not grant us conditional approval of ataluren for the treatment of either nmDMD or nmCF.

Clinical trials of ataluren or any of our other product candidates may not be successful. 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 ataluren for the treatment of nmDMD that we completed in 2009 or in a Phase 3 clinical trial of ataluren for the treatment of nmCF that we completed in 2011. If we are unable to obtain required marketing approvals for, commercialize, obtain and maintain patent protection for or gain market acceptance by physicians, patients and third-party payors of ataluren or any of our other product candidates, or experience significant delays in doing so, our business will be materially harmed and our ability to generate revenue will be materially impaired.

Our scientific approach focusing on the discovery and development of product candidates that target post-transcriptional control processes is unproven and may not result in the development of commercially viable drugs that safely and effectively treat genetic disorders or other diseases.

Our current and any future collaborations with third parties for the development and commercialization of our product candidates may not be successful.

We have a limited operating history. We currently have no commercial products and we have not received marketing approval for any product candidate.

We have incurred significant operating losses since inception and may need substantial additional funding. We expect to incur significant expenses and increasing operating losses for at least the next several years. As of March 31, 2013, we had an accumulated deficit of $291.9 million.

Our corporate information

Our executive offices are located at 100 Corporate Court, South Plainfield, New Jersey 07080, and our telephone number is (908) 222-7000. Our website address is www.ptcbio.com. The information contained on, or that can be accessed through, our website is not a part of this prospectus. We have included our website address in this prospectus solely as an inactive textual reference.

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In this prospectus, 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 consolidated subsidiaries. The trademarks, trade names and service marks appearing in this prospectus are the property of their respective owners.

Implications of being an emerging growth company

As a company with less than $1 billion in revenue during our last fiscal year, we qualify as an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, and we may remain an emerging growth company for up to five years. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from certain disclosure and other requirements that are applicable to other public companies that are not emerging growth companies. In particular, in this prospectus, we have provided only two years of audited financial statements and have not included all of the executive compensation related information that would be required if we were not an emerging growth company. Accordingly, the information contained herein may be different than the information you receive from other public companies in which you hold stock.

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The offering

Common stock offered by us	8,372,000 shares
Common stock to be outstanding after this offering	23,678,190 shares
Over-allotment option	The underwriters have an option for a period of 30 days to purchase up to 1,255,800 additional shares of our common stock to cover over-allotments.
Use of proceeds	We intend to use the net proceeds from this offering to fund the clinical development of ataluren for the treatment of nmDMD and nmCF, to seek marketing approval in the European Union and the United States for ataluren for these indications, for pre-approval commercial efforts for ataluren, to fund research and development of ataluren for additional indications and for our earlier stage programs, and for working capital and other general corporate purposes. See "Use of proceeds" for more information.
Risk factors	You should read the "Risk factors" section of this prospectus for a discussion of factors to consider carefully before deciding to invest in shares of our common stock.
Directed share program	At our request, the underwriters have reserved up to 345,000 shares of our common stock offered by this prospectus for sale, at the initial public offering price, to our directors and officers and certain employees and other parties related to us. Shares purchased by our directors and officers will be subject to the 180-day lock-up restriction described in the "Underwriting" section of this prospectus. The number of shares of common stock available for sale to the general public will be reduced to the extent these individuals purchase such reserved shares. Any reserved shares that are not so purchased will be offered by the underwriters to the general public on the same basis as the other shares offered by this prospectus.
NASDAQ Global Select Market symbol	"PTCT"

The number of shares of our common stock to be outstanding after this offering is based on 1,135,234 shares of our common stock outstanding as of May 31, 2013 and 14,170,956 additional shares of our common stock issuable upon the automatic conversion of all outstanding shares of our preferred stock upon the closing of this offering.

The number of shares of our common stock to be outstanding after this offering excludes:

- 2,049,737 shares of our common stock issuable upon the exercise of stock options outstanding as of May 31, 2013, at a weighted-average exercise price of $20.26 per share;

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122,296 additional shares of our common stock available for future issuance as of May 31, 2013 under our 2009 equity and long term incentive plan and 2013 stock incentive plan, which shares, upon the closing of this offering, will be available for future issuance under our 2013 long term incentive plan; and

17,013 shares of our common stock issuable upon the exercise of warrants outstanding as of May 31, 2013, at a weighted-average exercise price of $218.69 per share.

Unless otherwise indicated, all information in this prospectus assumes:

no exercise of the outstanding options or warrants described above;

no exercise by the underwriters of their option to purchase up to 1,255,800 additional shares of our common stock to cover over-allotments;

the automatic conversion of all outstanding shares of our preferred stock into an aggregate of 14,170,956 shares of our common stock upon the closing of this offering;

the warrants outstanding as of May 31, 2013 to purchase an aggregate of 16,368 shares of our series five junior preferred stock, at an exercise price of $128 per share, automatically become warrants to purchase 16,368 shares of our common stock at an exercise price of $128 per share upon the closing of this offering; and

the restatement of our certificate of incorporation and the amendment and restatement of our bylaws upon the closing of this offering.

In addition, unless otherwise indicated, all information in this prospectus gives effect to a one-for-120 reverse stock split of our common stock that was effected on March 7, 2013.

Brookside Capital Partners Fund, L.P., HBM Healthcare Investments (Cayman) Ltd., Section Six Partners, L.P., Longwood Fund, L.P. and Vulcan Ventures Incorporated, which are existing principal stockholders of ours or their affiliates and entities affiliated with certain of our directors, have agreed to purchase an aggregate of 3,250,000 shares of our common stock in this offering at the initial public offering price in the following amounts: Brookside Capital Partners Fund, L.P.: 1,250,000 shares; HBM Healthcare Investments (Cayman) Ltd.: 666,667 shares; Section Six Partners, L.P.: 533,333 shares; Longwood Fund, L.P.: 466,667 shares; and Vulcan Ventures Incorporated: 333,333 shares.

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Summary financial data

You should read the following summary financial data together with our financial statements and the related notes appearing at the end of this prospectus and the "Selected financial data" and "Management's discussion and analysis of financial condition and results of operations" sections of this prospectus. We have derived the statements of operations data for the years ended December 31, 2011 and 2012 from our audited financial statements included in this prospectus. We have derived the statements of operations data for the three months ended March 31, 2012 and 2013 and the balance sheet data as of March 31, 2013 from our unaudited financial statements included in this prospectus. The unaudited financial data include, in the opinion of our management, all adjustments, consisting of normal recurring adjustments, that are necessary for a fair statement of our financial position and results of operations for these periods. Our historical results for any prior period are not necessarily indicative of results to be expected in any future period, and our results for any interim period are not necessarily indicative of results to be expected for a full fiscal year.

	Year ended December 31,		Three months ended March 31,	
	2011	2012	2012	2013
			(in thousands, except share and per share data)	
Statement of operations data				
Revenues:				
Collaboration revenue	$ 98,961	$ 28,779	$ 10,754	$ 6,072
Grant revenue	6,451	5,167	1,772	1,070
Total revenues	105,412	33,946	12,526	7,142
Operating expenses:				
Research and development	58,677	46,139	14,303	11,257
General and administrative	16,153	14,615	4,443	4,461
Total operating expenses	74,830	60,754	18,746	15,718
Income (loss) from operations	30,582	(26,808)	(6,220)	(8,576)
Interest expense, net	(2,444)	(1,210)	(425)	(6,162)
Other income, net	461	1,783	47	53
Income (loss) before tax benefit	28,599	(26,235)	(6,598)	(14,685)
Income tax benefit	2,306			
Net income (loss)	30,905	(26,235)	(6,598)	(14,685)
Deemed dividend				(18,249)
Gain on exchange of convertible preferred stock in connection with recapitalization		159,954		3,391
Less beneficial conversion charge		(378)		
Net income (loss) attributable to common stockholders	$ 30,905	$ 133,341	$ (6,598)	$ (29,543)
Net income (loss) per share(1)				
Basic	$ 23.95	$ 219.76	$ (5,992.61)	$ (6,527.30)
Diluted	$ 4.55	$ 42.50	$ (5,992.61)	$ (6,527.30)
Weighted-average shares outstanding:				
Basic	1,089	3,328	1,101	4,526
Diluted	5,729	17,205	1,101	4,526

(1) See Note 8 to our audited financial statements appearing at the end of this prospectus regarding the calculation of net income per share.

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As of March 31, 2013	Actual	Pro forma(1)	Pro forma as adjusted(2)
		(in thousands)	
Balance sheet data			
Cash, cash equivalents and short-term investments	$ 50,247	$ 54,747	$ 168,911
Working capital	24,745	29,245	143,410
Total assets	59,906	64,406	178,570
Long-term debt, including current portion	3,835	3,835	3,835
Convertible preferred stock	158,140		
Accumulated deficit	(291,909)	(291,909)	(291,909)
Total stockholders' (deficit) equity	(128,562)	34,077	148,242

(1) The pro forma balance sheet data give effect to our issuance of an additional 375,000 shares of our series four senior preferred stock in May 2013 and the automatic conversion of all outstanding shares of our preferred stock, including shares of our series four senior preferred stock that we issued in May 2013, into an aggregate of 14,170,956 shares of our common stock upon the closing of this offering.

(2) The pro forma as adjusted balance sheet data give further effect to our issuance and sale of 8,372,000 shares of our common stock in this offering at the initial public offering price of $15.00 per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

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Risk factors

Investing in our common stock involves a high degree of risk. Before investing in our common stock, you should consider carefully the risks described below, together with the other information contained in this prospectus, including our financial statements and the related notes appearing at the end of this prospectus. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected. In these circumstances, the market price of our common stock could decline, and you may lose all or part of your investment.

Risks related to our financial position and need for additional capital

We have incurred significant losses since our inception. We expect to incur 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 March 31, 2013, we had an accumulated deficit of $291.9 million. To date, we have financed our operations primarily through 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. We have devoted substantially all of our efforts to research and development, including clinical trials. We have not completed development of any drugs. We expect to continue to incur significant expenses and increasing operating losses for at least the next several years. The net losses we incur may fluctuate significantly from quarter to quarter.

We anticipate that our expenses will increase substantially in connection with initiating and completing confirmatory Phase 3 clinical trials for our lead product candidate, ataluren, for the treatment of patients with Duchenne muscular dystrophy caused by nonsense mutations, or nmDMD, and patients with cystic fibrosis caused by nonsense mutations, or nmCF, commencing early access programs for ataluren for nmDMD patients in selected territories and seeking marketing approval for ataluren for these indications in the European Union and the United States. We have submitted a marketing authorization application, or MAA, to the European Medicines Agency, or EMA, for conditional approval of ataluren for the treatment of nmDMD. Subject to the conclusion of our ongoing discussions with regulatory authorities regarding the proposed design of our planned Phase 3 clinical trial, we also plan to pursue conditional approval of ataluren for the treatment of nmCF in the European Union. EMA conditional approval would permit us to market ataluren in the European Union for treatment of the applicable indication prior to completion of the confirmatory Phase 3 clinical trial for that indication. If we obtain marketing approval of ataluren for either nmDMD or nmCF, we also expect to incur significant sales, marketing, distribution and manufacturing expenses. The timing of commercialization expenses for ataluren depends in part on whether we receive conditional approval for ataluren for either or both of nmDMD and nmCF.

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

- initiate or continue the research and development of ataluren 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 planned future commercialization efforts.

Our ability to generate profits from operations and remain profitable depends on our ability to successfully develop and commercialize drugs that generate significant revenue. Based on our current plans, we do not expect to generate significant revenue unless and until we obtain marketing approval for, and

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commercialize, ataluren for the treatment of nmDMD or nmCF. This will require us to be successful in a range of challenging activities, including:

- obtaining approval to market ataluren for the treatment of either or both of nmDMD and nmCF;
- successfully initiating and completing confirmatory Phase 3 clinical trials of ataluren for the treatment of either or both of nmDMD and nmCF;
- protecting our rights to our intellectual property portfolio related to ataluren;
- contracting for the manufacture of commercial quantities of ataluren;
- negotiating and securing adequate reimbursement from third-party payors for ataluren; and
- establishing sales, marketing and distribution capabilities to effectively market and sell ataluren in the European Union and the United States.

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 you to lose all or part of your investment.

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 our research and development expenses to increase in connection with our ongoing activities, particularly as we initiate and continue confirmatory Phase 3 clinical trials of ataluren for the treatment of nmDMD and nmCF, continue our research activities in our preclinical programs and initiate clinical development of other product candidates. In addition, if we obtain regulatory approval for ataluren or any of our other product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, distribution and manufacturing. We also expect to incur expenses in connection with commencing early access programs for ataluren for nmDMD patients in selected territories. Furthermore, upon the closing of this offering, we expect to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. 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 any future commercialization efforts.

We believe that the net proceeds from this offering, together with our existing cash and cash equivalents, short-term investments and research funding that we expect to receive under our collaborations, will be sufficient to enable us to fund our operating expenses, debt service obligations and capital expenditure requirements into the fourth quarter of 2015. 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. This estimate assumes, among other things, that we do not receive conditional approval to market ataluren for nmDMD or nmCF in the European Union prior to completing a confirmatory Phase 3 clinical trial for the applicable indication and, as a result, that we do not incur significant related commercialization expenses prior to such time. Our future capital requirements will depend on many factors, including:

- the progress and results of confirmatory Phase 3 clinical trials of ataluren for nmDMD and nmCF;
- the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials for ataluren 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 ataluren and our other product candidates;
- the costs and timing of commercialization activities, including product sales, marketing, distribution and manufacturing, for any of our product candidates that receive marketing approval;
- subject to receipt of marketing approval, revenue received from commercial sales of ataluren 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.

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. In addition, our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will 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 to achieve our business objectives. In addition, we may seek additional capital due to favorable market conditions or 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.

Raising additional capital may cause dilution to our stockholders, including purchasers of common stock in this offering, 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, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or to grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, 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 you to evaluate the success of our business to date and to assess our future viability.

Our operations to date have been limited to organizing and staffing our company, developing and securing our technology, raising capital and undertaking preclinical studies and clinical trials of our product candidates. We have not yet demonstrated our ability to successfully complete development of any product candidates, obtain marketing approvals, 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 successful product

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commercialization. Consequently, any predictions you 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. We will need to transition from a company with a research and development focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

Risks related to the development and commercialization of our product candidates

We depend heavily on the success of our lead product candidate, ataluren, which we are developing for nmDMD and nmCF. All of our other product candidates are still in preclinical development. If we are unable to commercialize ataluren, or experience significant delays in doing so, our business will be materially harmed.

We have invested a significant portion of our efforts and financial resources in the development of ataluren for nmDMD and nmCF. Our ability to generate product revenues, which may not occur for several years, if ever, will depend heavily on the successful development and commercialization of ataluren. The success of ataluren will depend on a number of factors, including the following:

- successful completion of confirmatory Phase 3 clinical trials of ataluren;
- receipt of marketing approvals for ataluren in the European Union and the United States, including possible receipt of conditional approval to market ataluren in the European Union prior to completion of confirmatory Phase 3 clinical trials;
- establishing commercial manufacturing arrangements with third-party manufacturers;
- launching commercial sales of ataluren, if and when approved, whether alone or in collaboration with others;
- acceptance of ataluren, if and when approved, by patients, the medical community and third-party payors;
- effectively competing with other therapies;
- a continued acceptable safety profile of ataluren following approval;
- 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 successfully commercialize ataluren, which would materially harm our business.

If clinical trials of our product candidates, such as our confirmatory Phase 3 clinical trials of ataluren, fail to demonstrate safety and efficacy to the satisfaction of the EMA or the U.S. Food and Drug Administration, 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 ataluren or any other product candidate.

In connection with obtaining 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

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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 ataluren for the treatment of nmDMD that we completed in 2009 or in a Phase 3 clinical trial of ataluren 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 ataluren was active and showed clinically meaningful improvements over placebo in these trials, we may similarly fail to achieve the primary efficacy endpoint in confirmatory Phase 3 clinical trials of ataluren 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 ataluren 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 ataluren for the treatment of nmCF in which we measured change in chloride conductance in nasal cells over the course of treatment.

If we are required to conduct additional clinical trials or other testing of ataluren 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 delayed in obtaining marketing approval for our product candidates;
- 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 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 candidates, including:

- clinical trials of our 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;

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- 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 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 candidates may be greater than we anticipate;

- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate; and

- our 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 candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

Our conclusions regarding the activity and potential efficacy of ataluren in our completed Phase 2b clinical trial of ataluren for the treatment of nmDMD and in our completed Phase 3 clinical trial of ataluren 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 ataluren for the treatment of nmDMD and in our completed Phase 3 clinical trial of ataluren for nmCF, we performed retrospective and subgroup analyses that we believe provide strong support for concluding that ataluren 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.

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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. This diminishes the likelihood that the EMA will grant conditional approval of ataluren for either of these indications 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 ataluren for the applicable indication.

If the EMA does not grant conditional approval of ataluren for the treatment of nmDMD or nmCF, our potential commercialization of this product candidate and receipt of related revenues will be delayed.

In March 2013, the EMA provided an initial response to our MAA submission for conditional approval of ataluren for the treatment of nmDMD. In this response, referred to as the day 120 list of questions, the EMA informed us of major objections that would preclude a recommendation for marketing authorization unless adequately addressed. These major objections relate to, among other things, the EMA's views regarding insufficient evidence of efficacy based on our single Phase 2b clinical trial, resulting in a negative risk-benefit balance for purposes of conditional approval, uncertainties about the effective dose and questions about whether our confirmatory Phase 3 clinical trial for this indication could be continued if the EMA grants conditional approval. In May 2012, in connection with our preparation to apply for conditional approval of ataluren for the treatment of nmDMD, the EMA also informed us in scientific advice that although ataluren falls within the scope of the regulation for conditional approval for this indication, it appeared unlikely that a positive risk-benefit ratio for ataluren can be concluded primarily based on the results of our completed Phase 2b clinical trial.

As a result, there is substantial risk that the EMA will not grant us the conditional approval for which we have applied and will not consider approval of ataluren for the treatment of nmDMD until we have completed a confirmatory Phase 3 clinical trial for this indication, which would delay the potential commercialization of this product candidate and our receipt of related revenues. We expect to face similar risks if we apply for conditional approval of ataluren for the treatment of nmCF prior to completing a confirmatory Phase 3 clinical trial for this indication. In particular, conditional approval of ataluren for the treatment of nmCF 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.

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

It is possible that the EMA or the FDA may not consider the results of our confirmatory Phase 3 clinical trial of ataluren for nmDMD or nmCF, once completed and even if successful, to be sufficient for approval of ataluren 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 proposed confirmatory Phase 3 clinical trial of ataluren for the treatment of nmCF, the FDA may not consider our proposed trial design acceptable. This could cause us to conduct more than one confirmatory clinical trial or could delay or prevent our ability to receive marketing approval for this indication.

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

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 clinical trials of ataluren, if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials. For example, both nmDMD and nmCF 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, 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;

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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, which would cause the value of the company to decline and limit our ability to obtain additional financing. Our inability to enroll a sufficient number of patients in our confirmatory Phase 3 clinical trials of ataluren or any of our other clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether.

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

All of our product candidates are in clinical or preclinical development and their risk of failure is high. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive regulatory approval. If our product 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 ataluren, 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 ataluren 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 ataluren for the treatment of nmCF, five adverse events in the ataluren arm of the trial that involved the renal system led to discontinuation. As compared to the placebo group, the ataluren treatment arm also had a higher incidence of adverse events of creatinine elevations, which can be an indication of impaired kidney function. In the ataluren 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 ataluren and these antibiotics, which was successful in addressing this issue in the clinical trial. If patients in the ataluren 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 ataluren 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 ataluren because of concerns related to its safety and convenience.

Further, in 2011, we suspended development of our oncology product candidate PTC299, an inhibitor of production of vascular endothelial growth factor, or VEGF, in part because of two cases of severe liver toxicity that occurred in our clinical trials of PTC299 and in part because of our limited resources available at that time.

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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 ataluren 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, even if we are successful in developing and receiving regulatory approval for a commercially viable drug that treats an approved indication by targeting a particular post-transcriptional control process, we may not receive regulatory approval for additional indications. 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.

Even if ataluren or any other product candidate receives marketing approval, it 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.

If ataluren or any of our other product candidates receive marketing approval, they 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 ataluren 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 ataluren or any of our other product candidates that receive marketing approval.

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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 commercializing ataluren or any other product candidate if and when they are approved.

We do not have a sales or marketing infrastructure and have no experience in the sale or marketing of pharmaceutical products. To achieve commercial success for any approved product, we must either develop a sales and marketing organization or outsource these functions to third parties. We plan to establish our own sales and marketing capabilities and promote ataluren in the European Union and the United States with a targeted sales force if and when it is approved. 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 a sales force is expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force 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 our sales and marketing personnel.

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;
- the inability of sales personnel to obtain access to or persuade adequate numbers of physicians to prescribe any future products;
- the lack of complementary products to be offered by sales personnel, 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 sales and marketing organization.

If we enter into arrangements with third parties to perform sales and marketing services, our product revenues or the profitability of these product revenues to us are likely to be lower 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 likely will 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.

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.

Currently available treatments for Duchenne muscular dystrophy are only palliative. Although there are currently no marketed therapeutics approved to treat the underlying cause of nmDMD, there are other biopharmaceutical companies, including Prosensa Therapeutics 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. We believe that ataluren is the only product candidate in clinical trials that is designed to treat the underlying cause of nmDMD by restoring dystrophin activity.

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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 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 believe that ataluren is the only product candidate in clinical trials that is designed to treat the underlying cause of nmCF by restoring CFTR activity.

Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization. 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 ataluren 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.

The regulations 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 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, 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.

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Our ability to commercialize ataluren 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 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. 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 ataluren 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 ataluren 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.

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 testing of our product candidates in human clinical trials and will face an even greater risk if we commercially sell any products 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;

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withdrawal of clinical trial participants;

significant costs to defend the related litigation;

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 clinical trials up to a $5.0 million annual aggregate limit and subject to a per claim deductible. The amount of insurance that we currently hold may not be adequate to cover all liabilities that we may incur. We will need to increase our insurance coverage when and if we begin commercializing ataluren or any other product candidate that receives marketing approval. Insurance coverage 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 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 $5.0 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 ataluren 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 ataluren 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, we have not yet developed, and may never successfully develop, any marketed drugs using this 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

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

We do not own or operate manufacturing facilities for the production 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 our product candidates. Our strategy is to outsource all manufacturing of our product candidates and products to third parties.

We do not currently have any agreements with third-party manufacturers for the long-term commercial supply of any of our product candidates. We obtain our supply of the bulk drug substance for ataluren from a single third-party manufacturer. We engage a separate manufacturer to provide fill and finish services for the finished product that we are using in our clinical trials of ataluren. We may be unable to conclude agreements for commercial supply with third-party manufacturers, or may be unable to do so on acceptable terms.

Even if we are able to establish and maintain arrangements with third-party manufacturers, reliance on third-party manufacturers 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; and
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

Third-party manufacturers may not be able to comply with current good manufacturing practice, or cGMP, regulations or similar regulatory requirements outside the United States. Our failure, or the failure of our third-party manufacturers, 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

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revocation, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates.

Our 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 preclinical tests and clinical trials should cease to continue to do so for any reason, we likely would experience delays in advancing these 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 our product candidates or the drug substances used to manufacture them, 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 of our product candidates may adversely affect our future profit margins and our ability to develop product candidates and commercialize any 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 candidates. We rely on third parties, such as contract research organizations, clinical data management organizations, medical institutions and clinical investigators, to perform this function. Any of these third parties may terminate their engagements with us at any time. If we need to enter into alternative arrangements, it would delay our product development activities.

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

For example, inspectors acting at the request of the EMA recently conducted GCP inspections of selected clinical sites from our completed Phase 2b clinical trial of ataluren for the treatment of nmDMD and our clinical trial site relating to our pending MAA for conditional approval of ataluren for the treatment of nmDMD. Following these inspections, we received inspection reports containing a combination of critical and major findings. These findings relate to waivers we granted to admit patients to our Phase 2b clinical trial of ataluren 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 intend to describe 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 ataluren for the treatment of nmDMD. In addition, we intend to propose corrective action plans to address the inspectors' specific findings. If our responses and proposed corrective actions are not deemed sufficient

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by 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 obtain EMA approval of ataluren for the treatment of nmDMD.

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

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

For each of our product candidates, we plan to evaluate the merits of retaining commercialization rights for ourselves or entering into selective collaboration arrangements with leading pharmaceutical or biotechnology companies, such as our collaborations with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., which we refer to collectively as Roche, and the Spinal Muscular Atrophy Foundation, or SMA Foundation, for our spinal muscular atrophy program. We generally plan to seek collaborators for the development and commercialization of product candidates that have high anticipated development costs or that are directed at indications for which a potential collaborator has a particular expertise or markets that require a large sales and marketing organization to serve effectively. Our likely collaborators for any marketing, distribution, development, licensing or broader collaboration arrangements include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and 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' 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 and whether Roche pursues clinical development of any compounds identified under our collaboration with the SMA Foundation.

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;

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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;

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 ataluren under which we granted to Genzyme rights to commercialize ataluren in all countries other than the United States and Canada. In 2011, we restructured the collaboration and regained worldwide rights to ataluren, with Genzyme obtaining an option to commercialize ataluren 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

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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.

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

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because we fail to achieve practical application of the U.S. government-funded technology, because action is necessary to alleviate health or safety needs, to meet requirements of federal regulations or to give preference to U.S. industry. In addition, U.S. government-funded inventions must be reported to the government and U.S. government funding must be disclosed in any resulting patent applications. Furthermore, our rights in such inventions are subject to government license rights and certain restrictions on manufacturing products outside the United States.

Risks related to our intellectual property

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

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary technology and products. We seek to protect our proprietary position by filing patent applications in the United States and in certain foreign jurisdictions related to our novel technologies 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, European patent law 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 preissuance submission of prior art to the U.S. Patent and Trademark 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

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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.

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

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intellectual property litigation in the biotechnology and pharmaceutical industries, and we may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our products and technology, including interference, derivation, inter partes review or post-grant review proceedings before the U.S. Patent and Trademark Office. The risks of being involved in such litigation and proceedings may also increase as our product candidates approach commercialization, and as we gain greater visibility as a public company. Third parties may assert infringement claims against us based on existing or future intellectual property rights. We may not be aware of all such intellectual property rights potentially relating to our product candidates. For example, we have not conducted a recent freedom-to-operate search or analysis for 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 ataluren. Thus, we do not know with certainty whether ataluren, 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 ataluren. We are aware of an issued U.S. patent and international patent applications that purport to disclose or contain claims to chemical scaffolds that are sufficiently broad that they could be read to encompass ataluren, even though neither the issued U.S. patent nor any of the international patent applications specifically discloses ataluren. 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 ataluren in clinical trials for the purpose of seeking FDA approval would be a valid defense against any infringement claims in the United States based on the availability of 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 ataluren.

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

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

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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.

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.

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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 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.

Risks related to regulatory approval of our 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 commercialize our product candidates, and our ability to generate revenue will be materially impaired.

Our product candidates, including ataluren, 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 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 not received approval to market ataluren or any of our other product candidates from regulatory authorities in any jurisdiction. In 2011, we submitted a new drug application, or NDA, to the FDA for approval of ataluren for the treatment of nmDMD. The FDA refused to file this NDA on the grounds that the NDA did not contain substantial evidence of effectiveness based on the single placebo controlled Phase 2b clinical trial conducted to date.

We have only limited experience in filing and supporting the applications necessary to obtain marketing approvals for product candidates and expect 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 ataluren 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

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obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

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 Europe 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 ataluren for the treatment of nmDMD and nmCF. 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 ataluren, 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 ataluren for these indications, both in Europe 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 ataluren 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 ataluren 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 our product candidate 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 our product candidate 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 fast track designation for ataluren 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 ataluren 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.

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Any product candidate for which we obtain marketing approval 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.

Any product for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such product, will be subject to continual requirements of and review by the FDA and other regulatory authorities. The FDA's requirements include submissions of safety and other post-marketing information and reports, registration requirements, cGMP requirements relating to manufacturing, quality control, quality assurance and complaints and corresponding maintenance of records and documents, requirements regarding the distribution of samples to healthcare professionals and recordkeeping. 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. The FDA also may impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product. The FDA closely regulates 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. The FDA imposes 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.

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, 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; or

the imposition of civil or criminal penalties.

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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.

Failure to obtain or maintain regulatory approval in international jurisdictions would prevent us from marketing our products abroad.

In order to market and sell ataluren and our other products in the European Union and many other jurisdictions, we must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, some countries outside the United States require approval of the sales price of a drug before it can be marketed. In many countries, separate procedures must be followed to obtain reimbursement. We may not obtain marketing, pricing or reimbursement approvals outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market. Regulatory approvals in countries outside the United States do not ensure pricing approvals in those countries or in any other countries, and regulatory approvals and pricing approvals do not ensure that reimbursement will be obtained.

Our ability to obtain and maintain conditional marketing authorizations 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. 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. Even if we obtain conditional approval for ataluren for the treatment of either or both of nmDMD and nmCF, we may not be able to renew such conditional approval. A failure to renew any conditional approval that we obtain prior to full approval for the applicable indication would prevent us from continuing to market ataluren for such indication.

Governments outside the United States tend to impose strict price controls, which may adversely affect our revenues, if any.

In some countries, particularly the member states of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing 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. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after

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reimbursement has been obtained. 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. 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 or maintain reimbursement or pricing approval. 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 reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be adversely affected.

Our relationships with customers, healthcare providers and professionals and third-party payors will be subject to applicable anti-kickback, fraud and abuse 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 product candidates, including ataluren, for which we obtain marketing approval. Our future arrangements with customers, healthcare providers and professionals and third-party payors may expose us to broadly applicable fraud and abuse 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. Restrictions under applicable federal and state healthcare laws and regulations, include, and are not limited to, the following:

The federal healthcare anti-kickback statute prohibits, 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 federally funded 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. Several other countries, including the United Kingdom, have enacted similar anti-kickback, fraud and abuse, and healthcare laws and regulations.

The federal False Claims Act imposes civil penalties, including 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. The government and *qui tam* relators have brought False Claims Act actions against pharmaceutical companies on the theory that their practices have caused false claims to be submitted to the government. There is also a separate false claims provision imposing criminal penalties.

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.

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.

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The federal Physician Sunshine Act requirements 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, 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 or at the request of covered recipients, such as physicians and teaching hospitals, and physician ownership and investment interests in such manufacturers. Payments made to physicians and research institutions for clinical trials are included within the ambit of this law.

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.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. 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, 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. 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 ataluren or any of our other product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product candidates, including ataluren, 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.

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More recently, 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, 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. Substantial new provisions affecting compliance have also been enacted, which may affect our business practices with health care practitioners. We will not know the full effects of the Affordable Care Act until applicable federal and state agencies issue regulations or guidance under the new law. Although it is too early to determine the full effect of the Affordable Care Act, the new law appears likely to continue the pressure on pharmaceutical pricing, especially under the Medicare program, and may also increase our regulatory burdens and operating costs.

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 our products. 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.

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.

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We expect to expand 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.

We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of drug development, regulatory affairs and sales and marketing. To manage our 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 anticipated 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 and this offering

After this offering, our executive officers, directors and principal stockholders will maintain the ability to control or significantly influence all matters submitted to stockholders for approval.

Upon the closing of this offering, our executive officers, directors and principal stockholders will, in the aggregate, beneficially own shares representing approximately 43.8% of our capital stock. Assuming the purchase in this offering of an aggregate of 3,250,000 shares of our common stock by certain of our principal stockholders or their affiliates and entities associated with certain of our directors, the number of shares of our common stock beneficially owned by our executive officers, directors and principal stockholders will, in the aggregate, increase to 57.5% of our capital stock. As a result, if these stockholders were to choose to act together, they would be able to control or significantly influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would control or significantly influence the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of voting power could delay or prevent an acquisition of our company on terms that other stockholders may desire.

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

- provide for a classified board of directors such that not all members of the board are elected at one time;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from the board;

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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.

If you purchase shares of common stock in this offering, you will suffer immediate dilution of your investment.

The initial public offering price of our common stock is substantially higher than the net tangible book value per share of our common stock. Therefore, if you purchase shares of our common stock in this offering, you will pay a price per share that substantially exceeds our net tangible book value per share after this offering. At the initial public offering price of $15.00 per share, you will experience immediate dilution of $8.74 per share, representing the difference between our pro forma net tangible book value per share after giving effect to this offering and the initial public offering price. If the underwriters exercise their over-allotment option, you will experience further dilution.

An active trading market for our common stock may not develop.

Prior to this offering, there was no public market for our common stock. The initial public offering price for our common stock was determined through negotiations with the underwriters. Although our common stock has been approved for listing on the NASDAQ Global Select Market, an active trading market for our shares may never develop or be sustained following this offering. If an active market for our common stock does not develop, it may be difficult for you to sell shares you purchase in this offering without depressing the market price for the shares or at all.

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

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, you may not be able to sell your common stock at or above the initial public offering price. The market price for our common stock may be influenced by many factors, including:

the success of competitive products or technologies;

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

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results of clinical trials of product candidates of our competitors;

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

developments or disputes concerning patent applications, issued patents or other proprietary rights;

the recruitment or departure of key personnel;

the level of expenses related to any of our product candidates or clinical development programs;

actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;

variations in our financial results or those of companies that are perceived to be similar to us;

changes in the structure of healthcare payment systems;

market conditions in the pharmaceutical and biotechnology sectors;

general economic, industry and market conditions; and

the other factors described in this "Risk factors" section.

We have broad discretion in the use of the net proceeds from this offering and may not use them effectively.

Our management will have broad discretion in the application of the net proceeds from this offering and could spend the proceeds in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our common stock to decline and delay the development of our product candidates. Pending their use, we may invest the net proceeds from this offering in a manner that does not produce income or that loses value.

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 for up to five years. 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:

providing only two years of audited financial statements, in addition to any required unaudited interim financial statements, with correspondingly reduced "Management's discussion and analysis of financial condition and results of operations" disclosure;

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

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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 have taken advantage of reduced reporting burdens in this prospectus. In particular, in this prospectus, we have provided only two years of audited financial statements and have not included all of the executive compensation related information that would be required if we were not an emerging growth company. 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.

We will incur increased costs as a result of operating as a public company, and our management will 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 will 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. We may remain an emerging growth company until the end of the fiscal year in which the fifth anniversary of this offering occurs, although 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.

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

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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 your 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 existing or any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future.

A significant portion of our total outstanding shares are restricted from immediate resale but may be sold into the market in the near future. This could cause the market price of our common stock to drop significantly, even if our business is doing well.

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. After this offering, we will have outstanding 23,678,190 shares of common stock based on the number of shares outstanding as of May 31, 2013. This includes the shares that we are selling in this offering, which may be resold in the public market immediately without restriction, unless purchased by our affiliates. Of the remaining shares, 15,306,190 shares are currently restricted as a result of securities laws or lock-up agreements but will be able to be sold after the offering as described in the "Shares eligible for future sale" section of this prospectus. Moreover, after this offering, holders of an aggregate of 14,183,589 shares of our common stock will 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. We also intend to register all shares of common stock that we may issue under our equity compensation plans. Once we register these shares, they can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates and the lock-up agreements described in the "Underwriting" section of this prospectus.

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Special note regarding forward-looking statements

This prospectus contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this prospectus, 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 prospectus include, among other things, statements about:

- the timing and conduct of our clinical trials of ataluren for the treatment of Duchenne muscular dystrophy and cystic fibrosis caused by nonsense mutations, including statements regarding the timing of initiation and completion of the trials and the period during which the results of the trials will become available;
- the timing of and our ability to obtain marketing approval, including conditional approval in the European Union, of ataluren and our other product candidates, and the ability of ataluren and our other product candidates to meet existing or future regulatory standards;
- the potential receipt of revenues from future sales of ataluren;
- our plans to pursue development of ataluren for additional indications other than Duchenne muscular dystrophy and cystic fibrosis caused by nonsense mutations;
- our plans to pursue research and development of other product candidates;
- the potential advantages of ataluren;
- the rate and degree of market acceptance and clinical utility of ataluren;
- our estimates regarding the potential market opportunity for ataluren;
- our sales, marketing and distribution capabilities and strategy;
- our ability to establish and maintain arrangements for manufacture of ataluren and our other product candidates;
- our intellectual property position;
- our expectations related to the use of proceeds from this offering;
- our estimates regarding expenses, future revenues, capital requirements and needs for additional financing;

the impact of government laws and regulations; and

our competitive position.

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

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statements we make. We have included important factors in the cautionary statements included in this prospectus, particularly in the "Risk factors" section, 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 prospectus and the documents that we reference in this prospectus and have filed as exhibits to the registration statement of which this prospectus is a part completely and with the understanding that our actual future results may be materially different from what we expect. The forward-looking statements contained in this prospectus are made as of the date of this prospectus, and we do not assume any obligation to update any forward-looking statements.

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Use of proceeds

We estimate that the net proceeds from our issuance and sale of 8,372,000 shares of our common stock in this offering will be approximately $114.2 million, based on the initial public offering price of $15.00 per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us. If the underwriters exercise in full their over-allotment option, we estimate that the net proceeds from this offering will be approximately $131.7 million.

As of May 31, 2013, we had cash and cash equivalents of approximately $39.7 million. We currently estimate that we will use the net proceeds from this offering, together with our cash and cash equivalents, as follows:

- approximately $52 million to fund the clinical development of and seek marketing approval for ataluren for the treatment of nmDMD;
- approximately $28 million to fund the clinical development of and seek marketing approval for ataluren for the treatment of nmCF;
- approximately $12 million to fund pre-approval commercial efforts for ataluren;
- approximately $11 million to fund research and development of ataluren for additional indications and for our earlier stage programs; and
- the remainder for working capital and other general corporate purposes.

This expected use of the net proceeds from this offering and our existing cash and cash equivalents represents our intentions based upon our current plans and business conditions. The amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our development and commercialization efforts, the status of and results from clinical trials, as well as any collaborations that we may enter into with third parties for our product candidates, and any unforeseen cash needs. As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering. We have no current agreements, commitments or understandings for any material acquisitions or licenses of any products, businesses or technologies.

Based on our planned use of the net proceeds from this offering and our existing cash and cash equivalents described above, we estimate that such funds will be sufficient to enable us to complete the confirmatory Phase 3 clinical trial of ataluren for the treatment of nmDMD and initiate a confirmatory Phase 3 clinical trial of ataluren for the treatment of nmCF. We have based this estimate on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. This estimate assumes, among other things, that we do not receive conditional approval to market ataluren for nmDMD or nmCF prior to completing a Phase 3 clinical trial for the applicable indication and, as a result, that we do not incur significant related commercialization expenses prior to such time.

Pending our use of the net proceeds from this offering, we intend to invest the net proceeds in a variety of capital preservation investments, including short-term, investment-grade, interest-bearing instruments and U.S. government securities.

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Dividend policy

We have never declared or paid cash dividends on our common stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. We do not intend to pay cash dividends to holders of our common stock in the foreseeable future. Additionally, our ability to pay dividends on our common stock is limited by restrictions under the terms of the agreements governing our debt facility.

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Capitalization

The following table sets forth our cash and cash equivalents and capitalization as of March 31, 2013:

- on an actual basis;
- on a pro forma basis to give effect to our issuance of an additional 375,000 shares of our series four senior preferred stock and 396,200 shares of restricted common stock in May 2013 and the automatic conversion of all outstanding shares of our preferred stock, including shares of our series four senior preferred stock that we issued in May 2013, into an aggregate of 14,170,956 shares of our common stock upon the closing of this offering; and
- on a pro forma as adjusted basis to give further effect to our issuance and sale of 8,372,000 shares of our common stock in this offering at the initial public offering price of $15.00 per share, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

You should read this table together with our financial statements and the related notes appearing at the end of this prospectus and the "Management's discussion and analysis of financial condition and results of operations" section of this prospectus.

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As of March 31, 2013	Actual	Pro forma	Pro forma as adjusted
Cash and cash equivalents	$ 50,246,512	$ 54,746,512	$ 168,910,912
Series four convertible preferred stock, $0.001 par value per share, designated 5,050,000 shares actual, 5,425,000 shares pro forma and no shares pro forma as adjusted; issued and outstanding 4,999,954 shares actual and no shares pro forma and pro forma as adjusted	$ 56,457,840	$	$
Series five convertible preferred stock, $0.001 par value per share, designated 9,640,000 shares actual, 9,640,000 shares pro forma and no shares pro forma as adjusted; issued and outstanding 8,796,002 shares actual and no shares pro forma and pro forma as adjusted	101,681,783		
Debt obligations	3,835,328	3,835,328	3,835,328
Stockholders' deficit:			
Common stock, $0.001 par value per share, authorized 17,000,000 shares actual, 125,000,000 shares pro forma and 125,000,000 shares pro forma as adjusted; issued and outstanding 739,850(1) shares actual, 15,306,190(2) shares pro forma and 23,678,190 shares pro forma as adjusted	545	15,306	23,678
Additional paid-in capital	163,346,406	325,971,268	440,127,296
Accumulated deficit	(291,909,253)	(291,909,253)	(291,909,253)
Total capitalization	$ 33,412,649	$ 37,912,649	$ 152,077,049

(1) Includes 735,324 shares of unvested restricted stock issued in March 2013.

(2) Includes 396,200 additional shares of unvested restricted stock issued in May 2013.

The table above does not include:

46,642 shares of our common stock issuable upon the exercise of stock options outstanding as of March 31, 2013, at a weighted-average exercise price of $424.42 per share;

20,775 additional shares of our common stock available for future issuance as of March 31, 2013 under our 2009 equity and long term incentive plan and our 2013 stock incentive plan, which shares, upon the closing of this offering, will be available for future issuance under our 2013 long term incentive plan; and

17,013 shares of our common stock issuable upon the exercise of warrants outstanding as of March 31, 2013, at a weighted-average exercise price of $218.69 per share.

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Dilution

If you invest in our common stock in this offering, your ownership interest will be diluted immediately to the extent of the difference between the public offering price per share of our common stock and the pro forma net tangible book value per share of our common stock after this offering.

Our historical net tangible book value as of March 31, 2013 was $(128.6) million, or $(173.77) per share of our common stock. Historical net tangible book value per share represents the amount of our total tangible assets less total liabilities, divided by the number of shares of our common stock outstanding.

Our pro forma net tangible book value as of March 31, 2013 was $34.1 million, or $2.23 per share of our common stock. Pro forma net tangible book value per share represents the amount of our total tangible assets less our total liabilities, divided by the pro forma number of shares of our common stock outstanding after giving effect to our issuance of an additional 375,000 shares of our series four senior preferred stock and 396,200 shares of restricted common stock in May 2013 and the automatic conversion of all outstanding shares of our preferred stock, including shares of our series four senior preferred stock that we issued in May 2013, into an aggregate of 14,170,956 shares of our common stock.

After giving effect to our issuance and sale of 8,372,000 shares of our common stock in this offering at the initial public offering price of $15.00 per share, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us, our pro forma net tangible book value as of March 31, 2013 would have been $148.2 million, or $6.26 per share. This represents an immediate increase in pro forma net tangible book value per share of $4.03 to existing stockholders and immediate dilution of $8.74 in pro forma net tangible book value per share to new investors purchasing common stock in this offering. Dilution per share to new investors is determined by subtracting pro forma net tangible book value per share after this offering from the initial public offering price per share paid by new investors. The following table illustrates this dilution on a per share basis:

Initial public offering price per share		$ 15.00
Historical net tangible book value per share as of March 31, 2013	$ (173.77)	
Increase per share attributable to the conversion of outstanding preferred stock	176.00	
Pro forma net tangible book value per share as of March 31, 2013	2.23	
Increase in net tangible book value per share attributable to new investors	4.03	
Pro forma net tangible book value per share after this offering		6.26
Dilution per share to new investors		$ 8.74

If the underwriters exercise their over-allotment option, you will experience further dilution.

The following table summarizes, on a pro forma basis as of March 31, 2013, the total number of shares purchased from us, the total consideration paid, or to be paid, and the average price per share paid, or to be paid, by existing stockholders and by new investors in this offering at the initial public offering price of

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$15.00 per share, before deducting underwriting discounts and commissions and estimated offering expenses payable by us.

	Shares purchased		Total consideration		Average price per share
	Number	Percent	Amount	Percent	
Existing stockholders	15,306,190	65%	$ 326,451,336	72%	$ 21.33
New investors	8,372,000	35	125,580,000	28	15.00
Total	23,678,190	100%	452,031,336	100%	

The table above is based on actual shares of our common stock outstanding as of March 31, 2013 and 14,170,956 additional shares of our common stock issuable upon the automatic conversion of all outstanding shares of our preferred stock upon the closing of this offering.

The table above does not include:

- 46,642 shares of our common stock issuable upon the exercise of stock options outstanding as of March 31, 2013, at a weighted-average exercise price of $424.42 per share;
- 20,775 additional shares of our common stock available for future issuance as of March 31, 2013 under our 2009 equity and long term incentive plan, which shares, upon the closing of this offering, will be available for future issuance under our 2013 long term incentive plan; and
- 17,013 shares of our common stock issuable upon the exercise of warrants outstanding as of March 31, 2013, at a weighted-average exercise price of $218.69 per share.

If the underwriters exercise in full their over-allotment option, the following will occur:

- the percentage of shares of our common stock held by existing stockholders will decrease to approximately 61% of the total number of shares of our common stock outstanding after this offering; and
- the number of shares of our common stock held by new investors will increase to 9,627,800, or approximately 39% of the total number of shares of our common stock outstanding after this offering.

Certain of our existing principal stockholders or their affiliates and entities affiliated with certain of our directors have agreed to purchase an aggregate of 3,250,000 shares of our common stock in this offering at the initial public offering price. The foregoing discussion and table do not reflect any potential purchases by these stockholders and entities.

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Selected financial data

You should read the following selected financial data together with our financial statements and the related notes appearing at the end of this prospectus and the "Management's discussion and analysis of financial condition and results of operations" section of this prospectus. We have derived the consolidated statements of operations data for the years ended December 31, 2011 and 2012 and the consolidated balance sheet data as of December 31, 2011 and 2012 from our audited financial statements included in this prospectus. We have derived the statements of operations data for the three months ended March 31, 2012 and 2013 and the balance sheet data as of March 31, 2013 from our unaudited financial statements included in this prospectus. The unaudited financial data include, in the opinion of our management, all adjustments, consisting of normal recurring adjustments, that are necessary for a fair statement of our financial position and results of operations for these periods. Our historical results for any prior period are not necessarily indicative of results to be expected in any future period, and our results for any interim period are not necessarily indicative of results to be expected for a full fiscal year.

	Year ended December 31,		Three months ended March 31,	
Statement of operations data	**2011**	**2012**	**2012**	**2013**
	(in thousands, except share and per share data)			
Revenues:				
Collaboration revenue	$ 98,961	$ 28,779	$ 10,754	$ 6,072
Grant revenue	6,451	5,167	1,772	1,070
Total revenues	105,412	33,946	12,526	7,142
Operating expenses:				
Research and development	58,677	46,139	14,303	11,257
General and administrative	16,153	14,615	4,443	4,461
Total operating expenses	74,830	60,754	18,746	15,718
Income (loss) from operations	30,582	(26,808)	(6,220)	(8,576)
Interest expense, net	(2,444)	(1,210)	(425)	(6,162)
Other income, net	461	1,783	47	53
Income (loss) before tax benefit	28,599	(26,235)	(6,598)	(14,685)
Income tax benefit	2,306			
Net income (loss)	30,905	(26,235)	(6,598)	(14,685)
Deemed dividend				(18,249)
Gain on exchange of convertible preferred stock in connection with recapitalization		159,954		3,391
Less beneficial conversion charge		(378)		
Net income (loss) attributable to common stockholders	$ 30,905	$ 133,341	$ (6,598)	$ (29,543)
Net income (loss) per share(1)				
Basic	$ 23.95	$ 219.76	$ (5,992.61)	$ (6,527.30)
Diluted	$ 4.55	$ 42.50	$ (5,992.61)	$ (6,527.30)
Weighted-average shares outstanding:				
Basic	1,089	3,328	1,101	4,526
Diluted	5,729	17,205	1,101	4,526

(1) See Note 8 to our audited financial statements appearing at the end of this prospectus regarding the calculation of net income per share.

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Balance sheet data	As of December 31, 2011	2012	As of March 31, 2013
		(in thousands)	
Cash, cash equivalents and short-term investments	$ 28,431	$ 2,726	$ 50,247
Working capital	(10,091)	(23,564)	24,745
Total assets	44,148	13,072	59,906
Long-term debt, including current portion	11,689	4,883	3,835
Convertible preferred stock	214,380	80,824	158,140
Accumulated deficit	(250,612)	(277,225)	(291,909)
Total stockholders' deficit	(238,605)	(99,641)	(128,562)

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Management's discussion and analysis of financial condition and results of operations

You should read the following discussion and analysis of our financial condition and results of operations together with our financial statements and the related notes appearing at the end of this prospectus. Some of the information contained in this discussion and analysis or set forth elsewhere in this prospectus, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. You should read the "Risk factors" section of this prospectus for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a biopharmaceutical company focused on the discovery and development of orally administered, proprietary small-molecule drugs that target post-transcriptional control processes. Our lead product candidate is ataluren for the treatment of patients with genetic disorders that arise from a type of genetic mutation known as a nonsense mutation. In addition to ataluren, we have a pipeline of product candidates that are in preclinical development. 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 initiated a Phase 3 clinical trial of ataluren for the treatment of Duchenne muscular dystrophy caused by nonsense mutations, or nmDMD. We dosed the first patient in this trial in April 2013. In October 2012, we submitted a marketing authorization application, or MAA, to the European Medicines Agency, or EMA, for conditional approval of ataluren for the treatment of nmDMD. We plan to complete our confirmatory Phase 3 clinical trial of ataluren for the treatment of nmDMD before applying for marketing approval from the U.S. Food and Drug Administration, or FDA. We are also planning a Phase 3 clinical trial of ataluren for the treatment of cystic fibrosis caused by nonsense mutations, or nmCF. We plan to begin enrolling trial sites for this trial in the second half of 2013, and we expect to dose the first patient in this trial in the first half of 2014, subject to the conclusion of our ongoing discussions with regulatory authorities regarding our proposed trial design. Our goal in these continuing discussions is to achieve consensus between the EMA and the FDA that a single placebo controlled Phase 3 clinical trial can serve as the basis for full approval of ataluren to treat nmCF in both the European Union and the United States. In addition, we plan to pursue early access programs for ataluren for nmDMD patients in selected territories that support reimbursement for such programs in the second half of 2013.

To date, we have financed our operations primarily through 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 March 31, 2013, we had an accumulated deficit of $291.9 million. We had net income of $30.9 million for the year ended December 31, 2011, including a $79 million revenue adjustment due to the termination of a collaboration with Genzyme Corporation, or Genzyme, a net loss of $26.2 million for the year ended December 31, 2012 and a net loss of $14.7 million for the three months ended March 31, 2013.

We anticipate that our expenses will increase substantially in connection with initiating and continuing confirmatory Phase 3 clinical trials for ataluren for the treatment of nmDMD and nmCF, commencing early

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access programs for ataluren for nmDMD patients in selected territories and seeking marketing approval for ataluren for these indications in the European Union and the United States. If we obtain marketing approval of ataluren for either nmDMD or nmCF, we also expect to incur significant sales, marketing, distribution and manufacturing expenses, as well as ongoing research and development expenses for our other product candidates. The timing of commercialization expenses for ataluren depends in part on whether we receive conditional approval for ataluren for either or both of nmDMD and nmCF. Furthermore, upon the closing of this offering, we expect to incur additional costs associated with operating as a public company. Although we cannot reasonably estimate the amount of these additional public company costs, we expect that these costs will include significant legal, accounting, investor relations and other expenses that we did not incur as a private company. Accordingly, we will 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 any future commercialization efforts. We will need to generate significant revenues to achieve and sustain profitability, and we may never do so.

Financial operations overview

Revenues

To date, we have not generated any product sale revenues. Based on our current plans, we do not expect to generate significant product revenues unless and until we obtain marketing approval for, and commercialize, ataluren for the treatment of nmDMD or nmCF. The timing of any product revenues depends in part on whether we receive conditional approval for ataluren for either or both of nmDMD and nmCF. Our revenues to date have consisted of collaborative agreements revenues and grant revenues. We had revenues of $105.4 million for the year ended December 31, 2011, including a $79 million revenue adjustment due to the modification of a collaboration with Genzyme in 2011, $33.9 million for the year ended December 31, 2012 and $7.1 million for the three months ended March 31, 2013.

We have ongoing collaborations 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, for our spinal muscular atrophy program and early stage discovery arrangements with other institutions. During 2011, our collaboration with Genzyme was modified and later terminated.

Genzyme. In July 2008, we entered into an exclusive global collaboration with Genzyme to develop and commercialize ataluren for the treatment of genetic disorders due to nonsense mutations. Under the terms of this agreement, we granted Genzyme rights to commercialize ataluren in all countries except the United States and Canada, which rights we retained. Genzyme made a nonrefundable, upfront payment to us of $100,000,000 in July 2008, which we then began recognizing over the estimated period of performance under the arrangement.

In August 2011, we announced a restructuring of the agreement with Genzyme. Under the terms of the restructuring, we regained worldwide rights to ataluren and Genzyme made an additional payment of $7.5 million to us in exchange for an option to commercialize ataluren in indications other than nmDMD outside the United States and Canada. In March 2012, Genzyme declined to exercise the option, the option expired and the collaboration terminated.

We evaluated the August 2011 restructuring of the agreement and determined it to be a material modification to the original agreement for financial reporting purposes pursuant to the revised multiple-element revenue recognition guidance. We reevaluated the collaboration arrangement under this revised

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guidance and recorded a one-time adjustment to our deferred revenue balance to reflect the value of the remaining performance obligations under the restructured agreement as represented by the best estimate of selling price. As a result of this reevaluation, we recognized approximately $79 million of existing deferred revenue as of the modification date.

Roche and the SMA Foundation. In November 2011, we entered into a license and collaboration 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 sponsored research program with the SMA Foundation, as described below, and to research, develop and commercialize other small molecule compounds with potential for therapeutic use in patients with spinal muscular atrophy. Pursuant to the license and collaboration agreement, Roche paid us an upfront non-refundable payment of $30.0 million.

Grant revenue. We receive grant funding from various institutions and governmental bodies. The grants are typically for early discovery research, and generally the grant program lasts 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 stock-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 initiate and continue confirmatory Phase 3 clinical trials of ataluren for the treatment of nmDMD and nmCF, continue our research activities in our preclinical programs and initiate clinical development of other product candidates. 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.

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The following table provides research and development expense for our most advanced principal product development programs.

	Year ended December 31,		Three months ended March 31,	
	2011	2012	2012	2013
	(in thousands)			
Ataluren	$ 23,471	$ 15,700	$ 4,686	$ 4,730
Antibacterial	834	1,989	505	486
BMI1	2,422	2,254	885	140
Spinal muscular atrophy	3,718	1,664	522	149
Other research and preclinical	28,232	24,532	7,705	5,752
Total research and development	$ 58,677	$ 46,139	$ 14,303	$ 11,257

We expect that our total external costs through June 2016 for the development of ataluren for nmDMD will be approximately $34.1 million and for nmCF will be approximately $31.3 million.

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

- the scope, rate of progress and expense of our clinical trials and other research and development activities;
- the potential benefits of our product 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 ataluren 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 ataluren or any other product candidate or if we experience significant delays in enrollment in any our clinical trials, we could be required to expend significant additional financial resources and time on the completion of clinical development.

General and administrative expense

General and administrative expense consists primarily of salaries and other related costs for personnel, including stock-based compensation expenses, in our executive, legal, business development, finance, accounting, information technology and human resource functions. Other general and administrative expenses include facility-related costs not otherwise included in research and development expense; advertising and promotional expenses; costs associated with industry and trade shows; and professional fees for legal services, including patent-related expenses, and accounting services.

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We expect that general and administrative expense will increase in 2013 and in future periods as a result of increased payroll, expanded infrastructure, commercial operations, increased consulting, legal, accounting and investor relations expenses associated with being a public company and costs incurred to seek collaborations with respect to any of our product candidates, among other factors.

Interest expense, net

Interest expense, net consists of 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 U.S. generally accepted accounting principles. 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.

While our significant accounting policies are more fully described in the notes to our financial statements appearing at the end of this prospectus, we believe that the following accounting policies are the most critical to aid you in fully understanding and evaluating our financial condition and results of operations.

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.

Our revenue is generated primarily through collaborative research and development and licensing agreements and grants.

The terms of these 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, we generate service revenue through agreements that generally provide for fees for research and development services and may include additional payments upon achievement of specified events.

For existing collaborations entered into prior to the adoption in 2011 of the revised multiple element revenue recognition guidance described below, we recognize revenue consistent with the approach established at the inception of each arrangement. For these existing collaborations, where we have continued involvement, we recorded nonrefundable, upfront fees as deferred revenue and recognize revenue on a straight line basis as collaboration revenue over the expected performance period.

For new collaborations or for material modifications made to existing collaborations, in 2011, we adopted the updated multiple element revenue recognition guidance. Under this new guidance, all non-contingent arrangement consideration is allocated to the identified units of accounting based on their relative selling price at inception of the collaboration arrangement. We derive the selling price using a combination of internal subjective and available external objective information, such as comparable transactions. We recognize revenue commensurate with delivery, such as in the case with delivery of a license, or ratably over the course of a service period, as appropriate, such as in the case of ongoing research and development activities.

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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.

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. Accordingly, we describe below the methodology we have employed to date in measuring such expenses. Following the consummation of this offering, stock option values will be determined based on the market price of our common stock.

We utilized various valuation methodologies in accordance with the framework of the 2004 American Institute of Certified Public Accountants Technical Practice Aid, *Valuation of Privately-Held Company EquitySecurities Issued as Compensation*, or the AICPA Practice Aid, to estimate the fair value of our common

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stock. The methodologies included an option pricing method to estimate our underlying equity value, and a methodology that determined an estimated value under an initial public offering, or IPO, scenario and a sale scenario based upon an assessment of the probability of occurrence of each scenario. Each valuation methodology includes estimates and assumptions that require judgment. These estimates include assumptions regarding future performance, including the completion of clinical trials and the time to complete an IPO or sale of the company. As with any valuation, significant changes to the key assumptions used in the valuations could result in different fair values of common stock at each valuation date. Factors that we considered in determining the fair value of our common stock include:

- pricing of private sales of our preferred stock;
- prior valuations of stock grants and preferred stock sales and the effect of events, including the progression of our product candidates, that have occurred between the time of the grants or sales;
- comparative rights and preferences of the security being granted compared to the rights and preferences of our other outstanding equity;
- comparative values of public companies discounted for the risk and limited liquidity provided for in the shares we are issuing;
- estimates and analysis provided by management and contemporaneous valuations;
- perspective provided by investment banks, including the likelihood of an initial public offering and our potential value in an initial public offering; and
- general economic trends and external market conditions affecting the biopharmaceutical industry.

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. That cost 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.

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 stock price, expected volatility and expected term. Our estimates of these assumptions are primarily based on contemporaneous valuations, historical data, peer company data and judgment regarding future trends and factors. This is a distinct valuation process from that used to determine the fair value of our common stock for purposes of establishing the exercise price of stock options that we grant.

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

The fair value of grants made in the years ended December 31, 2011 and 2012 and in the three months ended March 31, 2012 and 2013 was contemporaneously estimated on the date of grant using the following assumptions:

	Year ended Decmeber 31,		Three months ended March 31,	
	2011	2012	2012	2013
Risk-free interest rate	2.40%	1.135%	1.135%	0.85%
Expected volatility	87%	87%	87%	88%
Expected term	6.00-6.25 years	6.00-6.25 years	6.00-6.25 years	5.00 years

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We assumed no expected dividends for all grants. The weighted average grant date fair value per share was $364.80 for options granted during the year ended December 31, 2011, $160.65 for options granted during the year ended December 31, 2012, $160.65 for options granted during the three months ended March 31, 2012 and $7.22 for options granted during the three months ended March 31, 2013.

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 options 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.

We recognized share-based compensation expense of approximately $2.8 million during the year ended December 31, 2011 and $2.3 million during the year ended December 31, 2012. We recognized share-based compensation expense of approximately $0.7 million for the three months ended March 31, 2012 and $0.6 million for the three months ended March 31, 2013.

We had total unrecognized compensation cost related to unvested share-based compensation arrangements of $4.0 million as of December 31, 2011, $2.2 million as of December 31, 2012 and $8.2 million as of March 31, 2013. We expect to recognize this cost as compensation expense over the weighted average remaining service period of approximately 2.07 years.

The following tables set forth information regarding stock and option awards and equity issuances during the years ended December 31, 2011 and 2012 and through May 31, 2013:

Stock options

Date	Number of options	Exercise price per share	Common stock grant date fair value per share	Black-Scholes fair value per share of options
4/27/2011	8,123	$ 490.80	$ 490.80	$ 364.80
1/10/2012	5,715	$ 218.40	$ 218.40	$ 160.65
3/7/2013	4,613	$ 10.59	$ 10.59	$ 7.22
5/15/2013	1,877,100	$ 10.85	(1)	(1)
5/22/2013	126,000	$ 10.85	(1)	(1)

(1) The fair value per share of the option awards granted on May 15, 2013 and May 22, 2013 will be calculated in connection with the preparation of our unaudited financial statements for the three months ended June 30, 2013.

Restricted common stock

Date	Number of restricted shares	Common stock grant date fair value per share	Black-Scholes fair value per share of common stock
3/7/2013	735,324	$ 10.59	$ 10.59
5/15/2013	382,200	(1)	(1)
5/22/2013	14,000	(1)	(1)

(1) The fair value per share of the restricted stock awards granted on May 15, 2013 and May 22, 2013 will be calculated in connection with the preparation of our unaudited financial statements for the three months ended

June 30, 2013.

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Preferred stock

Date	Number of series one preferred stock	Series one fair value per share	Number of series two preferred stock	Series two fair value per share	Number of series three preferred stock	Series three fair value per share	Common stock fair value per share
5/29/2012	1,483,337	$ 41.98	10,701,405	$ 1.68	2,853,517	$ 0.13	$ 67.20

Date	Number of series four preferred stock	Series four fair value per share	Number of series five preferred stock	Series five fair value per share	Common stock fair value per share
3/7/2013	4,999,954	$ 12.01	8,796,002	$ 11.56	$ 10.59
5/14/2013	375,000	(1)		(1)	(1)

(1) The fair value per share of our series four preferred stock, series five preferred stock and common stock will be calculated in connection with the preparation of our unaudited financial statements for the three months ended June 30, 2013.

Stock option grants made on April 27, 2011. Our board of directors granted options to purchase 8,123 shares of common stock on April 27, 2011, with each option having an exercise price of $490.80 per share. In determining this exercise price, our board of directors considered input from management and a valuation of our common stock. We determined the value of our common stock based on the probability weighted expected return method, or PWERM, described in the AICPA Practice Aid. We considered but did not use the market approach because our early stage of development and the absence of clinical trial data from our lead candidate made comparisons to public companies difficult. Similarly, we did not use the income approach because of the uncertain outcomes of our ongoing and future clinical trials.

Under a PWERM analysis, the value of a company's common stock is estimated based upon an analysis of current and future enterprise values, assuming three possible liquidity scenarios: an IPO, a recapitalization of the company and a sale of the company. We considered two significant value inflection points related to the ataluren program. The first inflection point was related to anticipated FDA action regarding our dispute of the FDA's refusal to file our new drug application, or NDA, that we submitted for ataluren for the treatment of nmDMD. The second inflection point was related to anticipated Phase 3 clinical trial results for ataluren for the treatment of nmCF.

After considering the various potential liquidity scenarios for our company and their likely timing, we used a pre-money enterprise value assigned to each scenario based on recent trends in capital markets. To determine the price per share of our common stock, we divided the resulting enterprise value for each liquidity scenario by the number of common shares that would be outstanding under each scenario. The common stock price for each scenario was then assigned a probability based on management's estimates. The resulting probability-weighted common share values were then discounted to present value at a rate that reflected general industry risks. The result was a value of our common stock on a minority, non-marketable basis of $490.80 per share.

Stock option grants made on January 10, 2012. Our board of directors granted options to purchase 5,715 shares of common stock on January 10, 2012, with each option having an exercise price of $218.40 per share. In determining this exercise price, our board of directors considered input from management and a valuation of our common stock. We determined the value of our common stock based on a PWERM analysis as described in the AICPA Practice Aid. We again considered but did not use the market approach because our early stage of development and the absence of clinical trial data from our lead candidate made comparisons to public companies difficult. Similarly, we did not

use the income approach because of the uncertain outcomes of our ongoing and future clinical trials.

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We considered two significant value inflection points related to the ataluren program. The first inflection point was related to anticipated Phase 3 clinical trial results for ataluren for the treatment of nmCF. The second inflection point was related to U.S. or E.U. regulatory approval of ataluren for the treatment of nmDMD.

After considering the various potential liquidity scenarios for our company and their likely timing, we used a pre-money enterprise value assigned to each scenario based on recent trends in capital markets. To determine the price per share of our common stock, we divided the resulting enterprise value for each liquidity scenario by the number of common shares that would be outstanding under each scenario. The common stock price for each scenario was then assigned a probability based on management's estimates. The resulting probability-weighted common share values were then discounted to present value at a rate that reflected general industry risks. The result was a value of our common stock on a minority, non-marketable basis of $218.40 per share.

The reduction in the value of our common stock from $490.80 to $218.40 between April 2011 and January 2012 primarily reflected the FDA's reaffirmation of its earlier decision to refuse to file our NDA for ataluren for the treatment of nmDMD and the unavailability of results of our Phase 3 clinical trial of ataluren for nmCF by January 2012. Acceptance of our NDA for filing by the FDA could have led to approval of ataluren and a subsequent higher value with respect to the IPO scenario. Given the FDA's reaffirmation of its earlier decision to refuse to file our NDA, the high value IPO scenarios were no longer realistic, resulting in a decrease in the value of our common stock.

Series one preferred stock financing and June 2012 valuation. In May and July 2012, we issued and sold an aggregate of 1,483,337 shares of our series one preferred stock, at a price per share of $20.00, to accredited investors, including entities affiliated with Credit Suisse First Boston Equity Partners, L.P., HBM Healthcare Investments (Cayman) Ltd., Vulcan Ventures Incorporated, Celgene Corporation, Delphi Ventures, The Column Group, LP and Novo A/S, and other of our existing stockholders. In connection with the series one preferred stock financing, we also effected a recapitalization of our previously outstanding preferred stock into an aggregate of 10,701,405 shares of series two preferred stock and 2,853,517 shares of series three preferred stock. Stockholders who participated in the series one preferred stock financing received series two preferred stock following the recapitalization of our previously outstanding preferred stock.

In June 2012, in connection with the series one preferred stock financing, we conducted a valuation analysis. Our value was estimated using a PWERM analysis, as described in the AICPA Practice Aid. We considered but did not use the market approach because our early stage of development made comparisons to public companies difficult. Similarly, we did not use the income approach because of the uncertain outcomes of our ongoing and future clinical trials.

The PWERM considered the most significant near-term driver of value for us to be our ability to file an MAA for conditional approval of ataluren. The remaining scenarios in the PWERM related to funding the completion of the Phase 3 clinical trial for nmDMD. The path to raising this money made up the remaining nodes in the PWERM.

After identifying the various potential liquidity scenarios and their likely timing, a pre-money enterprise value was assigned to each scenario based on a combination of management's guidance and recent trends in the capital markets. The resulting enterprise value for each liquidity event was divided by the total shares that would be outstanding under each scenario to arrive at a price per share for the common and preferred classes of stock. Each scenario was then assigned an outcome probability based on management's estimates. The resulting probability-weighted share values were then discounted to present

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value at a rate that reflects general industry risks (but not company specific risks). The senior series of preferred stock enjoys enhanced economics over the common stock, particularly liquidation preference. The resulting value per share was $41.98 for series one preferred stock, $1.68 for series two preferred stock, $0.13 for series three preferred stock and $67.20 for common stock.

In January and February 2013, we issued convertible promissory notes in an aggregate principal amount of $6 million to certain existing investors, including entities affiliated with Credit Suisse First Boston Equity Partners, HBM Healthcare Investments, Vulcan Ventures, Celgene, Delphi Ventures, The Column Group and Novo A/S. In connection with this bridge financing, we issued to the holders of the promissory notes warrants to purchase an aggregate of 515,186 shares of series one preferred stock, at an exercise price of $0.01 per share, and warrants to purchase an aggregate of 2,012,489 shares of series two preferred stock, at an exercise price of $0.01 per share.

Series four preferred stock financing, March 2013 valuation and March 2013 stock and option grants. In March 2013, we issued and sold an aggregate of 4,497,035 shares of our series four senior preferred stock, at a price per share of $12.00, to new accredited investors, including Brookside Capital Partners Fund, L.P., Adage Capital Partners, LP, Jennison Global Healthcare Master Fund, Ltd. and Longwood Fund LP, and existing investors, including entities affiliated with Credit Suisse First Boston Equity Partners, L.P., HBM Healthcare Investments (Cayman) Ltd., Vulcan Ventures Incorporated, Celgene Corporation, Delphi Ventures, The Column Group, LP and Novo A/S. In connection with the series four preferred stock financing, we issued an aggregate of 502,919 shares of our series four preferred stock upon conversion of the convertible promissory notes described above. In connection with the series four senior preferred stock financing, we effected a one-for-120 reverse stock split of our common stock and a recapitalization of our previously outstanding preferred stock into an aggregate of 6,700,487 shares of series five junior preferred stock. In addition, we issued an aggregate of 2,095,515 shares of our series five junior preferred stock upon the automatic exercise of the preferred stock warrants that we issued in January 2013.

In March 2013, in connection with the series four preferred stock financing, we conducted a valuation analysis. Our value was estimated using the PWERM analysis, as described in the AICPA Practice Aid. We considered but did not use the market approach because our early stage of development made comparisons to public companies difficult. Similarly, we did not use the income approach because of the uncertain outcomes of our ongoing and future clinical trials.

The PWERM considered the most significant near-term driver of value for us to be our ability to complete a Phase 3 clinical trial of ataluren for the treatment of nmDMD. The remaining scenarios in the PWERM related to funding the completion of the Phase 3 clinical trial for nmDMD. The path to raising this money made up the remaining nodes in the PWERM.

After identifying the various potential liquidity scenarios and their likely timing, a pre-money enterprise value was assigned to each scenario based on a combination of management's guidance and recent trends in the capital markets. The resulting enterprise value for each liquidity event was divided by the total shares that would be outstanding under each scenario to arrive at a price per share for the common and preferred classes of stock. Each scenario was then assigned an outcome probability based on management's estimates. The resulting probability-weighted share values were then discounted to present value at a rate that reflects general industry risks (but not company specific risks). The senior series of preferred stock enjoys enhanced economics over the common stock, particularly liquidation preference. The resulting value per share was $12.00 for series four preferred stock, $11.56 for series five preferred stock and $10.59 for common stock.

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On March 7, 2013, we issued 735,324 shares of restricted common stock to our directors and employees, including our executive officers, and we issued options to purchase an aggregate of 4,613 shares of common stock to our directors. The exercise price of each of these options is $10.59 per share.

Additional sale of series four preferred stock and May 2013 stock and option grants. In May 2013, we issued and sold 375,000 shares of our series four senior preferred stock, at a price per share of $12.00, to a new accredited investor.

In May 2013, we conducted a valuation analysis of our common stock. Our value was estimated using the PWERM analysis, as described in the AICPA Practice Aid. We considered but did not use the market approach because our early stage of development made comparisons to public companies difficult. Similarly, we did not use the income approach because of the uncertain outcomes of our ongoing and future clinical trials.

The PWERM considered the most significant near-term driver of value for us to be our ability to complete a Phase 3 clinical trial of ataluren for the treatment of nmDMD. The remaining scenarios in the PWERM related to funding the completion of the Phase 3 clinical trial of ataluren for the treatment of nmDMD. The path to raising this money made up the remaining nodes in the PWERM.

After identifying the various potential liquidity scenarios and their likely timing, a pre-money enterprise value was assigned to each scenario based on a combination of management's guidance and recent trends in the capital markets. The resulting enterprise value for each liquidity event was divided by the total shares that would be outstanding under each scenario to arrive at a price per share for our common stock. Each scenario was then assigned an outcome probability based on management's estimates. The resulting probability-weighted share values were then discounted to present value at a rate that reflects general industry risks (but not company specific risks). The senior series of preferred stock enjoys enhanced economics over the common stock, particularly liquidation preference. The resulting value per share was $10.85 for common stock.

The increase in the value per share of our common stock from $10.59 in March 2013 to $10.85 in May 2013 primarily reflected the increase in the probability of an IPO scenario.

On May 15, 2013, we issued 382,200 shares of restricted common stock and granted options to purchase an aggregate of 1,877,100 shares of our common stock to our directors and employees, including our executive officers. The exercise price of each of these options is $10.85 per share. On May 22, 2013, we issued 14,000 shares of restricted common stock and granted an option to purchase 126,000 shares of our common stock, at an exercise price of $10.85 per share.

On May 31, 2013, we and our underwriters determined the estimated price range for this offering. The midpoint of the price range was $14.50 per share. In comparison, our estimate of the fair value of our common stock was $10.85 per share as of May 15, 2013. As is typical in initial public offerings, the estimated price range for this offering was not derived using a formal determination of fair value, but was determined by negotiation between us and the underwriters. Among the factors that were considered in setting this range were our prospects and the history of and prospects for our industry, the general condition of the securities markets and the recent market prices of, and the demand for, publicly-traded common stock of generally comparable companies. In addition, at the time these awards were made, our underwriters had not yet communicated to us the definitive proposed price range for this offering. Specifically, we believe that the difference between the fair value of our common stock as of May 15, 2013

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and the midpoint of the estimated price range for this offering was primarily the result of the following factors:

- The May 15, 2013 contemporaneous valuation used a probability weighting of 75% that this offering would close by June 30, 2013.

- The estimated price range for this offering necessarily assumes that this offering has closed, a public market for our common stock has been created and that our preferred stock converted into common stock upon the closing of this offering, and therefore excludes any discount for lack of marketability of our common stock, which was factored into the May 15, 2013 valuation.

- Upon the closing of this offering, all outstanding shares of our preferred stock will convert into common stock, thus eliminating the superior rights and preferences of our preferred stock as compared to our common stock.

- The proceeds of a successful offering will substantially strengthen our balance sheet by increasing our cash resources. In addition, the completion of this offering is expected to provide us with access to the public company debt and equity markets. These projected improvements in our financial position influenced the increased common stock valuation indicated by the midpoint of the estimated price range.

Warrant liability

We classify as liabilities warrants to purchase our common stock with nonstandard antidilution provisions and warrants to purchase our preferred stock that include a put feature, regardless of the probability or likelihood that may conditionally obligate us to ultimately transfer assets, and record the estimated fair value of these warrants at each reporting period. We record as gain or loss any change in fair value of these warrants each reporting period in other income 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, 2012, we had federal net operating loss carryforwards of $211.0 million, which expire starting in 2021, and federal research and development credit carryforwards of $5.4 million, which expire starting in 2013. We also had state net operating loss carryforwards of $128.3 million, which expire starting in 2029, and state research and development credit carryforwards of $1.5 million, which expire starting in 2022. The Internal Revenue Code contains provisions that may limit the net operating loss and credit carryforwards available to be used in any given year given certain historical changes in the ownership interests of significant stockholders. At December 31, 2012, we recorded a full valuation allowance against our net deferred tax asset of approximately $106.9 million, as our management believes it cannot at this time conclude that it is more likely than not they will be realized. If we determine in the future that we will be able to realize all or a portion of our net deferred tax asset, an adjustment to the deferred tax valuation allowance would increase net income in the period in which we make such a determination.

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Results of operations

Three months ended March 31, 2012 compared to three months ended March 31, 2013

(in thousands)	2012	2013	Change 2013 vs. 2012
Revenue	$ 12,526	$ 7,142	$ (5,384)
Research and development expenses	14,303	11,257	(3,046)
General and administrative expenses	4,443	4,461	18
Interest expense	425	6,162	5,737

Three months ended March 31, 2012 and 2013

Revenues. Revenues were $7.1 million for the three months ended March 31, 2013, a decrease of $5.4 million from revenues of $12.5 million for the three months ended March 31, 2012. Collaboration revenue was $6.1 million for the three months ended March 31, 2013, a decrease of $4.7 million from collaboration revenues of $10.8 million for the three months ended March 31, 2012. The decrease resulted primarily from our deferred revenue balance related to the value of the remaining performance obligations under our restructured agreement with Genzyme. Grant revenue was $1.1 million for the three months ended March 31, 2013, a decrease of $0.7 million from grant revenue of $1.8 million for the three months ended March 31, 2012.

Research and development expense. Research and development expense was $11.3 million for the three months ended March 31, 2013, a decrease of $3.0 million, or 21%, from $14.3 million for the three months ended March 31, 2012. The decrease resulted primarily from a decrease in personnel costs of $1.5 million as a result of a reduction in force that we implemented in the second quarter of 2012 and a decrease in clinical trial costs and laboratory supplies of $1.3 million.

General and administrative expense. General and administrative expense was $4.5 million for the three months ended March 31, 2013, an increase of 0.4% from $4.4 million for the three months ended March 31, 2012. Decreased personnel costs of $0.4 million as a result of a reduction in force that we implemented in the second quarter of 2012 were offset by an increase to expenses related to our preparation for this offering and operations as a public company.

Interest expense. Interest expense was $6.2 million for the three months ended March 31, 2013, an increase of $5.7 million from $0.4 million for the three months ended March 31, 2012. The increase was due to interest related to the debt discount associated with the convertible debt that we issued in 2013.

Year ended December 31, 2011 compared to year ended December 31, 2012

(in thousands)	2011	2012	Change 2012 vs. 2011
Revenue	$ 105,412	$ 33,946	$ (71,466)
Research and development expenses	58,677	46,139	(12,538)
General and administrative expenses	16,153	14,615	(1,538)
Interest expense	2,444	1,210	(1,234)
Other income, net	461	1,783	1,322
Tax benefit	2,306		(2,306)

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Years ended December 31, 2011 and 2012

Revenues. Revenues were $33.9 million for the year ended December 31, 2012, a decrease of $71.5 million from revenues of $105.4 million for the year ended December 31, 2011. Collaboration revenue was $28.8 million for the year ended December 31, 2012, a decrease of $70.2 million from collaboration revenues of $99.0 million for the year ended December 31, 2011. The decrease resulted primarily from a one-time non cash adjustment in 2011 to our deferred revenue balance to reflect the value of the remaining performance obligations under our restructured agreement with Genzyme. We recognized approximately $79 million of existing deferred revenue under our agreement with Genzyme as of the modification date. Grant revenue was $5.2 million for the year ended December 31, 2012, a decrease of $1.3 million from grant revenue of $6.5 million for the year ended December 31, 2011.

Research and development expense. Research and development expense was $46.1 million for the year ended December 31, 2012, a decrease of $12.6 million, or 21%, from $58.7 million for the year ended December 31, 2011. The decrease resulted primarily from decreased costs for clinical trials of $5.8 million, decrease in manufacturing of clinical trial supplies of $2.3 million and a decrease in personnel costs of $2.3 million as a result of a reduction in force that we implemented in the second quarter of 2012. Clinical trial expense for 2011 reflected costs associated with our Phase 3 clinical trial of ataluren for the treatment of nmCF, which concluded in November 2011, and a related extension trial and a Phase 3 continuation trial for ataluren for the treatment of nmDMD. Clinical trial expense for 2012 reflected costs associated with the ongoing extension trial for patients who had participated in our Phase 3 clinical trial of ataluren for the treatment of nmCF, the ongoing continuation trial for ataluren for the treatment of nmDMD and a second Phase 3 continuation trial that we initiated in 2012 for ataluren for the treatment of nmDMD.

General and administrative expense. General and administrative expense was $14.6 million for the year ended December 31, 2012, a decrease of $1.6 million, or 9.5%, from $16.2 million for the year ended December 31, 2011. The decrease was due principally to decreased personnel costs of $1.6 million as a result of a reduction in force that we implemented in the second quarter of 2012.

Interest expense. Interest expense was $1.2 million for the year ended December 31, 2012, a decrease of $1.2 million from $2.4 million for the year ended December 31, 2011. The increase was due to a smaller loan balance in 2012 as we continued to repay outstanding debt.

Other income, net. Other Income, net was $1.8 million for the year ended December 31, 2012, an increase of $1.3 million from $0.5 million for the year ended December 31, 2011. The increase was due to the change in fair value related to our warrant liability.

Tax benefit. We recognized a tax benefit related to our sale of net operating losses in the New Jersey Technology Business Tax Certificate Transfer Program. For the year ended December 31, 2011, our benefit was $2.3 million. We did not qualify for this program in 2012.

Liquidity and capital resources

Sources of liquidity

Since inception, we have incurred significant operating losses. To date, we have not generated any product sale revenues. We have financed our operations primarily through 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.

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We have engaged in the following preferred stock and convertible debt financings since January 1, 2011.

Series one preferred stock financing. In May and July 2012, we issued and sold an aggregate of 1,483,337 shares of our series one preferred stock, at a price per share of $20.00, for an aggregate purchase price of $29.7 million. In connection with the series one preferred stock financing, we also effected a recapitalization of our previously outstanding preferred stock into an aggregate of 10,701,405 shares of series two preferred stock and 2,853,517 shares of series three preferred stock. Stockholders who participated in the series one preferred stock financing received series two preferred stock following the recapitalization of our outstanding preferred stock.

Bridge financing. In January and February 2013, we issued convertible promissory notes in an aggregate principal amount of $6 million. In connection with this bridge financing, we also issued to the holders of the promissory notes warrants to purchase an aggregate of 515,186 shares of our series one preferred stock, at an exercise price of $0.01 per share, and warrants to purchase an aggregate of 2,012,489 shares of our series two preferred stock, at an exercise price of $0.01 per share.

Series four preferred stock financing. In March 2013, we issued and sold an aggregate of 4,497,035 shares of our series four senior preferred stock, at a price per share of $12.00, for an aggregate purchase price of $54 million. In addition, we issued an aggregate of 502,919 shares of our series four senior preferred stock upon conversion of the convertible promissory notes described above that we originally issued in January and February 2013. In connection with the series four senior preferred stock financing, we effected a one-for-120 reverse stock split of our common stock and a recapitalization of our previously outstanding preferred stock into an aggregate of 6,700,487 shares of series five junior preferred stock. In addition, we issued an aggregate of 2,095,515 shares of our series five junior preferred stock upon the automatic exercise of the preferred stock warrants that we originally issued in January 2013. In May 2013, we issued and sold an additional 375,000 shares of our series four preferred stock, at a price per share of $12.00, for an aggregate purchase price of $4.5 million.

Cash flows

As of March 31, 2013, we had cash and cash equivalents of $50.2 million. In addition, we received aggregate proceeds of $4.5 million in May 2013 from our sale of additional shares of our series four senior preferred stock described above.

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

	Year ended December 31,		Three months ended March 31,	
(in thousands)	**2011**	**2012**	**2012**	**2013**
Cash provided by (used in):				
Operating activities	$ (20,767)	$ (47,928)	$ (16,578)	$ (7,847)
Investing activities	27,703	(189)	(158)	(21)
Financing activities	(7,180)	22,411	(2,330)	55,389

Net cash used in operating activities was $16.6 million for the three months ended March 31, 2012 and $7.8 million for the three months ended March 31, 2013. The net cash used in 2012 primarily reflects decreased personnel costs related to a reduction in force in the second quarter of 2012 and decreased expenditures for laboratory supplies.

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Net cash used in investing activities was $0.2 million for three months ended March 31, 2012 and $0.02 million for the three months ended March 31, 2013. Cash used in investing activities was related to purchases of property and equipment.

Net cash used in financing activities was $2.3 million for three months ended March 31, 2012. Net cash used in financing activities in 2012 was attributable to payments on debt obligations. Net cash provided by financing activities was $55.4 million for the three months ended March 31, 2013. Net cash provided by financing activities in 2013 was primarily attributable to the $56.5 million in proceeds that we received from a preferred stock financing. Partially offsetting these proceeds were payments on debt obligations of $1.1 million in 2013.

Net cash used in operating activities was $20.8 million for the year ended December 31, 2011 and $47.9 million for the year ended December 31, 2012. The net cash used in 2011 and 2012 primarily reflects changes in deferred revenue, including an upfront cash payment of $30 million in 2011 related to the collaboration agreement with Roche for a spinal muscular atrophy program, which is being amortized over the research term, and decreased spending in 2012 on research and development costs due to the completion of our Phase 2b clinical trial of ataluren for nmDMD and our Phase 3 clinical trial of ataluren for nmCF.

Net cash provided by investing activities was $27.7 million for the year ended December 31, 2011. Net cash used in investing activities was $0.2 million for the year ended December 31, 2012. Cash provided by or used in investing activities in 2011 was primarily related to net maturities of investments, and to a lesser extent, purchases of property and equipment.

Net cash used in financing activities was $7.2 million for the year ended December 31, 2011. Net cash used in financing activities in 2011 was attributable to payments on debt obligations. Net cash provided by financing activities was $22.4 million for the year ended December 31, 2012. Net cash provided by financing activities in 2012 was primarily attributable to the $29.3 million in proceeds that we received from a preferred stock financing. Partially offsetting these proceeds were payments on debt obligations of $6.9 million in 2012.

Funding requirements

We anticipate that our expenses will increase substantially in connection with initiating and continuing confirmatory Phase 3 clinical trials for ataluren for the treatment of nmDMD and nmCF, commencing early access programs for ataluren for nmDMD patients in selected territories and seeking marketing approval for ataluren for these indications in the European Union and the United States. If we obtain marketing approval of ataluren for either nmDMD or nmCF, we also expect to incur significant selling, marketing, distribution and manufacturing expenses. The timing of commercialization expenses for ataluren depends in part on whether we receive conditional approval for ataluren for either or both of nmDMD and nmCF.

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

- initiate or continue the research and development of ataluren for additional indications and of our other product candidates;
- seek to discover and develop additional product candidates;

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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 planned future commercialization efforts.

We believe that the net proceeds from this offering, together with our existing cash and cash equivalents, short-term investments and research funding that we expect to receive under our collaborations, will be sufficient to enable us to fund our operating expenses, debt service obligations and capital expenditure requirements into the fourth quarter of 2015. 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. This estimate assumes, among other things, that we do not receive conditional approval to market ataluren for nmDMD or nmCF in the European Union prior to completing a confirmatory Phase 3 clinical trial for the applicable indication and, as a result, that we do not incur significant related commercialization expenses prior to such time. Our future capital requirements will depend on many factors, including:

the progress and results of confirmatory Phase 3 clinical trials of ataluren for nmDMD and nmCF;

the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials for ataluren for additional indications and for our other product candidates;

the number and development requirements of other product candidates that we pursue;

the costs, timing and outcome of regulatory review of ataluren and our other product candidates;

the costs and timing of commercialization activities, including product sales, marketing, distribution and manufacturing, for any of our product candidates that receive marketing approval;

subject to receipt of marketing approval, revenue received from commercial sales of ataluren 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.

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, the ownership interest of our existing stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or to grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our

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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.

Contractual obligations

The following table summarizes our significant contractual obligations and commercial commitments as of March 31, 2013.

(in thousands)	Total	Less than 1 year	1-3 years	4-5 years	More than 5 years
Debt obligations	$ 3,835	$ 3,823	$ 12	$	$
Operating and equipment lease obligations(1)	5,168	872	2,546	1,750	
Total fixed contractual obligations	9,003	4,695	2,558	1,750	

(1) We lease office space under a noncancelable operating lease with a term that extends through February 2019. We also lease certain office equipment under operating leases.

In September 2009, we entered into a $25 million secured debt facility with a syndicate of two lenders. We borrowed $12.5 million under the debt facility in September 2009 and an additional $10 million under the facility in December 2010 and issued the lenders promissory notes. The notes are secured by substantially all our assets except for intellectual property. The notes carry a fixed interest rate of 13.65%. As of March 31, 2013, the outstanding principal balance on the notes was $3,717,000. The notes are scheduled to be repaid in full in January 2014. The debt facility contains negative covenants restricting our activities, including limitations on dispositions, mergers or acquisitions, incurring indebtedness or liens, paying dividends or making investments and certain other business transactions. There are no financial covenants associated with the debt facility. The debt facility contains certain events of default. The obligations under the debt facility and the other loan documents may at the lenders' option be accelerated upon the occurrence of certain events of default, and are automatically accelerated upon certain bankruptcy and insolvency related events of default.

The preceding table excludes contingent contractual payments that we may become obligated to make. Under various agreements, we will be required to pay royalties and milestone payments upon the successful development and commercialization of products, including the following agreements with The Wellcome Trust Limited, or Wellcome Trust, and SMA Foundation.

We have entered into funding agreements with Wellcome Trust for the research and development of small molecule compounds in connection with our BMI1 and antibacterial programs. To the extent that we develop and commercialize program intellectual property on a for-profit basis, we may become obligated to pay to Wellcome Trust development and regulatory milestone payments of up to an aggregate of $68.9 million and single-digit royalties on sales of any research program product. Our obligation to pay such royalties would continue on a country-by-country basis until the longer of the expiration of the last patent in the program intellectual property in such country covering the research program product and the expiration of market exclusivity of such product in such country.

We have also entered into a sponsored research agreement with the SMA Foundation in connection with our spinal muscular atrophy program. We may become obligated to pay the SMA Foundation single-digit royalties on worldwide net product sales of any collaboration product that we successfully develop and subsequently commercialize or, with respect to collaboration products we outlicense, a specified percentage of certain payments we receive from our licensee. We are not obligated to make such payments unless and

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until annual sales of a collaboration product exceed a designated threshold. Our obligation to make such payments would end upon our payment to the SMA Foundation of a specified amount.

We have employment agreements with certain employees which require the funding of a specific level of payments, if certain events, such as a change in control or termination without cause, occur.

Quantitative and qualitative disclosures about market risk

We are exposed to market risk related to changes in interest rates. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments are in short-term securities. Our available for sale securities are subject to interest rate risk and will fall in value if market interest rates increase.

Recent accounting pronouncements

Effective January 1, 2012, an update to an accounting standard was issued that requires that all nonowner changes in stockholders' equity be presented either in a single continuous statement of comprehensive income (loss) or in two separate but consecutive statements. This update was applied retrospectively. We adopted this pronouncement and elected to present a separate statement of comprehensive income (loss). The updated standard does not change the items that must be reported in comprehensive income, how such items are measure, or when they must be reclassified to net income.

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Business

Overview

We are a biopharmaceutical company focused on the discovery and development of orally administered, proprietary small-molecule drugs that target post-transcriptional control processes. While our discovery programs are directed at targets in multiple therapeutic areas, we are focusing particularly on the development and commercialization of treatments for orphan and ultra-orphan disorders. Our lead product candidate is ataluren for the treatment of patients with genetic disorders that arise from a type of genetic mutation known as a nonsense mutation. We have retained worldwide commercialization rights to ataluren for all indications in all territories. We have initiated a Phase 3 clinical trial of ataluren for the treatment of Duchenne muscular dystrophy caused by nonsense mutations, or nmDMD. We dosed the first patient in this trial in April 2013. In October 2012, we submitted a marketing authorization application, or MAA, to the European Medicines Agency, or EMA, for conditional approval of ataluren for the treatment of nmDMD. We are also planning a Phase 3 clinical trial of ataluren for the treatment of cystic fibrosis caused by nonsense mutations, or nmCF. We plan to begin enrolling trial sites for this trial in the second half of 2013, and we expect to dose the first patient in this trial in the first half of 2014, subject to the conclusion of our ongoing discussions with regulatory authorities regarding our proposed trial design. In addition, we plan to pursue early access programs for ataluren for nmDMD patients in selected territories that support reimbursement for such programs in the second half of 2013. There are currently no marketed therapies approved to treat the underlying cause of nmDMD or nmCF. The EMA has designated ataluren as an orphan medicinal product and the U.S. Food and Drug Administration, or FDA, has granted orphan drug designation to ataluren for the treatment of both nmDMD and nmCF.

The letters "PTC" in our corporate name are an acronym for post-transcriptional control processes, which are the regulatory events that occur in cells after a messenger RNA, or mRNA, molecule is copied, or transcribed, from DNA. The mRNA molecules are key intermediates in protein production. Post-transcriptional control processes regulate the rate and timing of protein production and are essential to proper cellular function. The absence or overproduction of specific proteins can cause disease. The small-molecule compounds that we are developing are designed to alter post-transcriptional control processes to correct or compensate for a genetic defect. We apply proprietary technologies and our extensive knowledge of post-transcriptional control processes in our drug discovery and development activities. We believe that systematically targeting post-transcriptional control processes represents an unexploited approach to drug discovery and development.

We discovered ataluren 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 ataluren interacts with the ribosome, which is the component of the cell that decodes the mRNA molecule and manufactures proteins, to enable the ribosome to read through premature nonsense stop signals on mRNA and allow the cell to produce a full-length, functional protein. As a result, we believe that ataluren has the potential to be an important therapy for muscular dystrophy, cystic fibrosis 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 and cystic fibrosis, to determine if the underlying cause is a nonsense mutation.

Muscular dystrophies involve progressive muscle wasting and weakness and are caused by a mutation in the DNA that results in either the absence or very low levels of the dystrophin protein. Duchenne muscular

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dystrophy is the most common and one of the most severe types of muscular dystrophy. 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.

Cystic fibrosis 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. A nonsense mutation is a type of mutation in the DNA that can cause both Duchenne muscular dystrophy and cystic fibrosis.

We have completed a Phase 2b clinical trial of ataluren for the treatment of nmDMD and a Phase 3 clinical trial of ataluren for the treatment of nmCF. We did not achieve the primary efficacy endpoint in either trial with the pre-specified level of statistical significance. However, we believe that the collective data from these trials, including retrospective and subgroup analyses that we have performed, provide strong support for concluding that ataluren was active and showed clinically meaningful improvements over placebo in these trials. In addition, we believe that our experience in these completed clinical trials has allowed us to enhance the designs of our confirmatory Phase 3 clinical trials and improve our likelihood of success in these trials. Accordingly, we have initiated a confirmatory Phase 3 clinical trial of ataluren for the treatment of nmDMD and are planning a confirmatory Phase 3 clinical trial of ataluren for the treatment of nmCF. Ataluren has been generally well tolerated in all of our clinical trials to date.

In October 2012, we submitted an MAA to the EMA for conditional approval of ataluren for the treatment of nmDMD. In March 2013, the EMA provided an initial response to our MAA submission for conditional approval of ataluren for the treatment of nmDMD. In this response, referred to as the day 120 list of questions, the EMA informed us of major objections that would preclude a recommendation for marketing authorization unless adequately addressed. These major objections relate to, among other things, the EMA's views regarding insufficient evidence of efficacy based on our single Phase 2b clinical trial, resulting in a negative risk-benefit balance for purposes of conditional approval, uncertainties about the effective dose and questions about whether our confirmatory Phase 3 clinical trial for this indication could be continued if the EMA grants conditional approval. We expect to submit responses to the day 120 questions in July 2013.

Although we believe that we have reasonable responses to all of the EMA's major objections, there is substantial risk that the EMA will not grant us this conditional approval. If granted, EMA conditional approval would permit us to market ataluren in the European Union for treatment of nmDMD prior to completion of our confirmatory Phase 3 clinical trial for this indication. We plan to complete our confirmatory Phase 3 clinical trial of ataluren for the treatment of nmDMD before applying for marketing approval from the FDA. In designing our confirmatory Phase 3 clinical trial for the treatment of nmDMD, we have sought to reflect the views expressed by both the EMA and the FDA in our discussions with these regulatory authorities. We expect that these trial results, if favorable, could serve as the basis for full approval by the EMA and the FDA of ataluren for the treatment of nmDMD. If the trial results are favorable, and based on our estimates of patient enrollment and data availability, we expect to be able to submit applications for full marketing approval of ataluren for the treatment of nmDMD in both the European Union and the United States in 2016.

We also have received scientific advice from the EMA regarding the possibility of submitting an MAA for conditional approval of ataluren for the treatment of nmCF and our proposed trial protocol for a

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confirmatory Phase 3 clinical trial of ataluren for this indication. We plan to begin enrolling trial sites for this trial in the second half of 2013, and we expect to dose the first patient in this trial in the first half of 2014, subject to the conclusion of our ongoing discussions with regulatory authorities regarding our proposed trial design. There also is substantial risk that the EMA will not grant us conditional approval of ataluren for the treatment of nmCF.

In addition to ataluren, we have a pipeline of product candidates that are in preclinical development. 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 develop these compounds both on our own and through selective collaboration arrangements with leading pharmaceutical and biotechnology companies. For example, we currently are collaborating 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, for the development and commercialization of compounds for the treatment of spinal muscular atrophy. Through March 31, 2013, we have received total collaboration funding of approximately $268 million and total grant funding and clinical trial support of approximately $89 million.

Our strategy

Our goal is to become a leading biopharmaceutical company focused on discovering, developing and commercializing small-molecule therapeutics that target post-transcriptional control processes and address disorders, particularly in the orphan and ultra-orphan areas, with high unmet medical needs. To achieve our goal, we are pursuing the following strategies:

Complete development of and seek marketing approvals for ataluren in lead indications. We are devoting a significant portion of our resources and business efforts to completing the development of ataluren for the treatment of nmDMD and nmCF. We have initiated a confirmatory Phase 3 clinical trial of ataluren for the treatment of nmDMD and have applied for conditional approval to market ataluren for this indication in the European Union prior to completing this trial. We expect that these trial results, if favorable, could serve as the basis for full approval by the EMA and the FDA of ataluren for the treatment of nmDMD. Subject to the conclusion of our ongoing discussions with regulatory authorities regarding our proposed trial design, we plan to pursue conditional approval and, in the second half of 2013, to begin enrolling trial sites for a confirmatory Phase 3 clinical trial of ataluren for the treatment of nmCF.

Maximize commercial potential of ataluren. We have retained worldwide commercialization rights to ataluren for all indications in all territories. If ataluren receives marketing approval, we plan to commercialize it with our own focused, specialized sales force. We believe that the medical specialists treating Duchenne muscular dystrophy and cystic fibrosis are sufficiently concentrated that we will be able to effectively promote ataluren with targeted sales teams initially in the European Union and the United States and, eventually, in other key territories, such as Asia and Latin America.

Explore additional indications for ataluren. We believe that ataluren has the potential to be an important therapy for other genetic disorders for which a nonsense mutation is the cause of the disease. We estimate that, on average, 11% of patients with any genetic disorder resulting from the absence of a single protein, referred to as monogenic disorders, have a nonsense mutation as the cause of the disease. We plan to select additional indications for further clinical development of ataluren consistent with the criteria that we applied in selecting nmDMD and nmCF, such as high unmet medical need and commercially available genotyping.

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Advance the development of our preclinical product candidates and continue to discover and develop small molecules that alter post-transcriptional control processes. Our preclinical and discovery programs are focused on new treatments for multiple therapeutic areas, including neuromuscular disease, oncology and infectious disease. We are particularly focused on the development and commercialization of treatments for orphan and ultra-orphan disorders. We are applying several proprietary technologies to identify, chemically optimize and develop small molecules designed to alter post-transcriptional control processes to achieve therapeutic effects. Because post-transcriptional control processes offer many targets for therapeutic intervention and because drugs that alter these processes have the potential to both increase and decrease protein production, we believe that our approach may be applicable to a broad range of diseases.

Seek third party grants and support and selectively establish strategic alliances. We have obtained, and we intend to continue to seek, development funding and other assistance from government entities, non-government and philanthropic organizations and patient advocacy groups for our product candidates. We previously have received grant funding and clinical trial support from the National Institutes of Health, the FDA, the Department of Defense, Defense Threat Reduction Agency, the Muscular Dystrophy Association, Parent Project Muscular Dystrophy, The Wellcome Trust Limited, or Wellcome Trust, Cystic Fibrosis Foundation Therapeutics and the SMA Foundation. In addition, for each of our product candidates, and in particular for product candidates that have high anticipated development costs, address markets requiring a large sales and marketing organization to serve effectively or are directed at indications for which a potential collaborator has a particular expertise, we plan to evaluate the merits of entering into collaboration arrangements with leading pharmaceutical or biotechnology companies.

Our product 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	Development and commercial rights
Ataluren for nmDMD	Phase 2b clinical trial completed Confirmatory Phase 3 clinical trial initiated	PTC
Ataluren for nmCF	Phase 3 clinical trial completed Confirmatory Phase 3 clinical trial planned for second half of 2013	PTC
Spinal muscular atrophy	Preclinical Optimization of development compounds ongoing	Roche
Oncology BMI1	Preclinical Lead development compound selected	PTC
Antibacterial	Preclinical Optimization of development compounds ongoing	PTC

We have obtained orphan drug designations from the EMA and from the FDA for ataluren for the treatment of nmDMD and nmCF. We have an effective investigational new drug application, or IND, with the FDA for ataluren for each of nmCF and nmDMD. We plan to submit to the FDA an IND for each of our

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other product candidates prior to initiating clinical trials for any such product candidate in the United States.

Background on genetic disorders and nonsense mutations

A significant number of rare genetic disorders are monogenic disorders that occur as a consequence of the absence of a single protein. The restoration of the production of that single protein has the potential to treat the genetic disorder. We estimate that, on average, 11% of patients with any monogenic disorder have a nonsense mutation as the cause of the disease.

Through the post-transcriptional process of translation, a specialized cellular apparatus, called the ribosome, manufactures functional proteins by translating the genetic code contained in the mRNA. This decoding process reads the building blocks of the mRNA, known as nucleotides, in groups of three. Each group of three nucleotides is called a codon. Three of the 64 possible codons contained in mRNA serve as normal stop signals and indicate the end of the protein-coding region of the mRNA. When functioning properly, the stop codons cause the ribosome to halt translation of the mRNA once the mRNA's genetic code has been completely translated into a full-length, functional protein.

There are four basic types of mutations in DNA that can cause a genetic disorder. These are known as insertion, deletion, missense and nonsense mutations. A nonsense mutation is a single nucleotide alteration in the DNA that, when copied to mRNA, is interpreted by the ribosome as a premature stop signal and terminates translation within the protein-coding region of the mRNA. When a ribosome encounters a premature stop codon, the translation process is terminated before a full-length, functional protein is formed. The resulting truncated protein is usually unstable and unable to serve its necessary function. The absence of a full-length, functional protein may cause disease.

Cells have a mechanism that discriminates a normal stop codon from a premature stop codon, although both types of stop codon result in termination of the translation of the genetic code. A group of proteins, known as the termination surveillance complex, can discriminate the proteins downstream of a normal stop codon to regulate normal translational termination. Because these proteins do not appear to be downstream of a premature stop codon, a normal stop codon can be distinguished from a premature stop codon.

Ataluren

Overview

Ataluren is a novel, orally administered small-molecule compound that targets nonsense mutations. We are developing ataluren for the treatment of genetic disorders in which a nonsense mutation is the cause of the disease. We believe that a drug with a mechanism of action that allows the ribosome to read through premature stop codons without affecting the normal termination of protein synthesis may be able to overcome the effects of nonsense mutations.

Ataluren allows the cellular machinery to read through premature stop codons in mRNA and enable the translation process to produce full-length, functional proteins. As described above, certain factors that are located downstream of a normal stop codon are not present at a premature stop codon. We believe that these factors allow ataluren to be active only at premature stop codons without allowing ataluren to read through normal stop codons. Ataluren is from a distinct structural class that does not have antibiotic properties and we believe acts at a different location on the ribosome than gentamicin. Ataluren has been generally well tolerated in all of our clinical trials to date, which involved approximately 600 individuals dosed with ataluren.

The EMA has designated ataluren as an orphan medicinal product for the treatment of nmDMD and nmCF. The FDA has granted orphan drug designation to ataluren for the treatment of nmDMD and nmCF and fast track designation to ataluren for the treatment of nmDMD. There are currently no marketed therapies approved to treat the underlying cause of nmDMD or nmCF.

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The following table sets forth information regarding our completed, ongoing and planned Phase 2 and Phase 3 clinical trials of ataluren for the treatment of nmDMD and nmCF.

Phase 2 and Phase 3 clinical trials of ataluren for nmDMD and nmCF

Study	Phase, study design, location	Total patients enrolled	Status	Dates
nmDMD				
nmDMD-004	Phase 2a, open label, United States	38	Completed	December 2005 to May 2007
nmDMD-004e	Phase 2a extension, open label, United States	36 (patients previously in nmDMD-004)	Ended	August 2008 to May 2010
nmDMD-008	Phase 2a, open label, United States	6	Ended	January 2010 to March 2010
nmDMD-007	Phase 2b, double-blind, placebo controlled, Australia, Canada, European Union, Israel, United States	174	Completed	February 2008 to December 2009
nmDMD-007e	Phase 2b extension, open label, Australia, Canada, European Union, Israel, United States	173 (patients previously in nmDMD-007)	Ended	January 2009 to May 2010
nmDMD-016	Phase 3 continuation, open label, United States	Up to 122 (patients previously in nmDMD-004 or nmDMD-007)	Ongoing	Initiated in November 2010
nmDMD-019	Phase 3 continuation, open label, Australia, Canada, European Union, Israel	Up to 96 (patients previously in nmDMD-004)	Ongoing	Initiated in May 2012
nmDMD-020	Confirmatory Phase 3, double-blind, placebo controlled, planned as Australia, Canada, European Union, Israel, South America, United States	Approximately 220	Ongoing	Initiated in April 2013

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Study	Phase, study design, location	Total patients enrolled	Status	Dates
nmCF				
nmCF-003	Phase 2, open label, United States	24	Completed	November 2005 to December 2006
nmCF-005	Phase 2, open label, Israel	23	Completed	November 2005 to May 2006
nmCF-005e	Phase 2a extension, open label, Israel	19 (patients previously in nmCF-005)	Completed	January 2007 to June 2007
nmCF-006	Phase 2a, open label, Belgium, France	30	Completed	March 2007 to February 2008
nmCF-009	Phase 3, double-blind, placebo controlled, Canada, European Union, Israel, United States	238	Completed	September 2009 to November 2011
nmCF-009e	Phase 3 extension, open label, Canada, European Union, Israel, United States	191 (patients previously in nmCF-009)	Ongoing	Initiated in August 2010
nmCF-021	Confirmatory Phase 3, double-blind, placebo controlled, global trial sites planned	Approximately 210	Planned	Plan to begin enrolling trial sites in second half of 2013

We have completed a Phase 2b clinical trial of ataluren for the treatment of nmDMD and a Phase 3 clinical trial of ataluren for the treatment of nmCF. We did not achieve the primary efficacy endpoint in either trial with the pre-specified level of statistical significance. However, we believe that the collective data from these trials, including retrospective and subgroup analyses that we have performed, provide strong support for concluding that ataluren was active and showed clinically meaningful improvements over placebo in these trials. Accordingly, we have initiated a confirmatory Phase 3 clinical trial of ataluren for the treatment of nmDMD and are planning a confirmatory Phase 3 clinical trial of ataluren for the treatment of nmCF. We believe that our experience in our completed clinical trials has allowed us to enhance the designs of our confirmatory Phase 3 clinical trials and improve our likelihood of success. We plan to begin enrolling trial sites for our confirmatory Phase 3 clinical trial of ataluren for the treatment of nmCF in the second half of 2013, subject to the conclusion of our ongoing discussions with regulatory authorities regarding our proposed trial design.

Ataluren is administered orally as granules mixed with permitted liquids or semi-solid foods, such as milk, water, applesauce or yogurt. We designed this formulation because children comprise a significant portion of the patient population for ataluren and often have difficulty swallowing pills or capsules. Ataluren is manufactured in reliable and reproducible synthetic processes from readily available starting materials. Ataluren has been generally well tolerated to date in our Phase 2 and Phase 3 clinical trials.

Duchenne muscular dystrophy

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.

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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, or approximately 2,000 patients in the United States and 2,500 patients in the European Union.

Children with Duchenne muscular dystrophy typically begin to show symptoms as early as age three, when they develop a waddling gait, may seem clumsy, frequently fall and have difficulty rising from the floor. Progressive weakness then develops in the voluntary muscles in the arms, legs and trunk. This muscle weakness results in fixations, or contractures, of joints, such as knees, hips, elbows and feet. By the age of eight, most patients have difficulty ascending stairs. By their early teens, patients typically lose walking ability and are confined to wheelchairs. Patients' hearts and respiratory muscles are also affected, typically requiring use of ventilators in their late teens. Further progressive loss of strength and the weakening of heart and lung muscles eventually results in death due to heart and lung failure. The average age of death for Duchenne muscular dystrophy patients is in their mid-twenties.

There is currently no marketed therapy approved for the treatment of the underlying cause of Duchenne muscular dystrophy. Currently available treatments for Duchenne muscular dystrophy are only palliative. These treatments seek to address the symptoms through supportive care measures, such as bracing to give patients some opportunity to remain standing, joint stretching exercises to avoid contractures and tendon release surgery. Corticosteroids are prescribed to mitigate the symptoms of the disease but can cause significant complications because of chronic toxicities. We believe that no other therapy in clinical development for Duchenne muscular dystrophy is designed to treat the underlying cause of nmDMD.

Phase 3 clinical trial of ataluren for nmDMD

We have initiated a multicenter, randomized, double-blind, placebo controlled Phase 3 clinical trial to evaluate the efficacy and safety of ataluren in patients with nmDMD as confirmed by gene sequencing. We dosed the first patient in this trial in April 2013. We plan to conduct this trial in approximately 220 patients at investigational sites worldwide.

The primary objective of this trial is to evaluate the effect of ataluren 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 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

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has become the most common primary endpoint currently used in Duchenne muscular dystrophy clinical trials.

Supportive analyses of ambulation in our trial protocol consist of:

- 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 consist of 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. 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 two secondary endpoints that have not been used previously as outcome measures in published therapeutic clinical trials. The first new endpoint is a functional scale specifically designed for ambulant Duchenne muscular dystrophy patients, referred to as the North Star Ambulatory Assessment, or NSAA. The NSAA is a composite of muscle function tests, such as the ability to rise from the floor, ability to get from lying to sitting, ability to get from sitting to standing and ability to hop, jump and run. The other new endpoint captures patient-reported changes in activities of daily living based on a disease symptom survey that we developed.

The trial protocol specifies the following key inclusion criteria for patients enrolling 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 trial protocol provides for the exclusion of patients from the trial if they have a prior or ongoing clinically significant illness, recently used systemic aminoglycoside antibiotics, recently initiated or changed corticosteroid therapy or previously received ataluren treatment. We will perform study assessments at clinic visits every eight weeks. Patients will undergo 48 weeks of blinded treatment prior to the final analysis.

We plan to stratify patients in this trial based on age, baseline 6-minute walk distance and duration of prior use of corticosteroids. The trial protocol provides that patients will be randomized in a 1:1 ratio to receive either placebo or ataluren at a dosing regimen consisting of 10 mg/kg in the morning, 10 mg/kg at midday and 20 mg/kg in the evening, for a total daily dose of 40 mg/kg. This was the same 10, 10, 20 dose of ataluren that showed beneficial results in our completed Phase 2b clinical trial described below.

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We plan to employ the following methods, among others, to facilitate the recruitment of patients in this trial:

- conducting the trial at sites and with investigators we identify as being well suited for study participation based on access to the targeted patient population, prior clinical trial experience and use of appropriately trained site personnel who are knowledgeable in methods of patient recruitment and retention;

- using technology to increase awareness of the trial in the patient community, including the website at www.clinicaltrials.gov, our corporate website and other online means;

- working with patient groups worldwide to provide trial information to the targeted patient population in local languages;

- collaborating with organizations with strong local expertise to promote region specific recruitment campaigns; and

- providing travel assistance to reduce patient/caregiver burden in traveling to trial sites for study visits.

Based on our estimates regarding patient enrollment, we expect to complete this trial and have initial, top-line data available in mid-2015. At the completion of blinded treatment, an open label continuation trial will be available to patients who successfully complete the trial in countries where ataluren is not commercially available at that time. Patients in the continuation trial will receive ataluren in the same dosing regimen as in the confirmatory Phase 3 clinical trial.

Rationale for design of Phase 3 clinical trial of ataluren for nmDMD

The study population and outcome measures that we are using in our confirmatory Phase 3 clinical trial 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 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 Phase 3 clinical 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.

Natural history data from patients in the placebo group in our Phase 2b clinical trial, based on age and baseline 6-minute walk distance, are illustrated in the figure below, in which each placebo-treated patient from the trial is represented by an arrow. The base of the arrow indicates the patient's 6-minute walk distance at baseline, and the tip of the arrow indicates this measurement at week 48 of the trial.

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Natural history results from placebo-treated patients in Phase 2b clinical trial

In addition, as discussed in more detail below, we performed a post-hoc, retrospective subgroup analysis of patients from our completed Phase 2b clinical trial who would meet the enrollment criteria for our confirmatory Phase 3 clinical trial. This analysis showed a much larger treatment effect in mean change in 6-minute walk distance over 48 weeks between ataluren 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, our confirmatory Phase 3 clinical trial is focusing 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 ataluren'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 our Phase 3 clinical trial than in our Phase 2b clinical trial, the sample size of patients in our Phase 3 clinical trial 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.

Regulatory status and strategy for nmDMD

EMA. On October 30, 2012, we submitted an MAA to the EMA for conditional approval of ataluren for the treatment of nmDMD. The EMA validated the MAA submission on November 21, 2012, which initiated the formal EMA review process of the MAA. In March 2013, the EMA provided an initial response to our MAA submission for conditional approval of ataluren for the treatment of nmDMD. In this response, referred to as the day 120 list of questions, the EMA informed us of major objections that would preclude a recommendation for marketing authorization unless adequately addressed. We expect to submit responses to the day 120 list of questions in July 2013. Based on this response timing, we would then expect to receive a list of outstanding issues from the EMA in September 2013, resulting in a final opinion from the EMA with respect to conditional approval no earlier than November 2013.

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EMA conditional approval would permit us to market ataluren in the European Union for nmDMD prior to the completion of our confirmatory Phase 3 clinical trial. Conditional approval is valid for one year, with annual renewals required thereafter. Upon granting conditional approval, the EMA specifies the obligations and the timeframe to fulfill them for subsequent full approval.

The EMA will consider conditional marketing approval of a product candidate that is being developed to treat a seriously debilitating or life-threatening disease or that is designated as an orphan medicinal product notwithstanding that one or more additional pivotal clinical trials may be required for full approval. Such a product candidate must satisfy each of the four requirements listed below.

The risk-benefit balance of the product candidate must be positive. We believe that the efficacy data from our completed Phase 2b clinical trial of ataluren, although not statistically significant based on the pre-specified methodology for analyzing the data, together with the strong safety data from clinical trials of ataluren conducted to date, indicate that the benefits of ataluren outweigh its risks in this patient population. We believe that in this Phase 2b clinical trial ataluren demonstrated, particularly based on post-hoc refined analyses that were not pre-specified in the clinical trial protocol, clinically meaningful treatment effects on 6-minute walk distance and timed tests of stair-climbing, stair-descending and running/walking 10 meters. These treatment effects are supported by other outcome measures of physical functioning, such as activity and wheelchair use in the community setting, frequency of accidental falling and patient-reported physical functioning.

The applicant must be likely to provide comprehensive data. We dosed the first patient in our confirmatory Phase 3 clinical trial of ataluren for the treatment of nmDMD in April 2013. We expect that patient enrollment in this trial will be complete or nearly complete prior to the completion of regulatory review and frequently lengthy reimbursement processes relating to our conditional approval application, with a substantial proportion of patients having finished the treatment period prior to completion of these processes. Although it is possible that some late-enrolled patients in the European Union may drop out of the trial if ataluren becomes commercially available following conditional approval, we believe that this risk is small, and that the effect on the trial would be minimal because we expect a large number of patients to be enrolled in countries outside the European Union. We also believe that clinical investigators, who may also be the primary physicians for patients in the trial, and patient advocacy groups will encourage patients to remain in the trial.

The product candidate must fulfill an unmet medical need. There are currently no marketed therapies approved to treat the underlying cause of nmDMD. Currently available treatments are only palliative.

The benefits to public health of the immediate availability of the product candidate must outweigh the risks inherent in the fact that additional data are still required. We believe that the benefits of immediate availability of ataluren outweigh the risks of conditional approval for patients with nmDMD. If marketing approval were delayed until comprehensive Phase 3 clinical data are available and patients with nmDMD are not treated, these patients will suffer irreversible loss of function.

The major objections identified by the EMA in the day 120 list of questions relate to the following principal deficiencies:

The EMA considers the evidence for efficacy insufficient in terms of robustness of the data. In our analysis of the results from our Phase 2b clinical trial, we introduced a number of post-hoc modifications to the protocol. According to the EMA, although it acknowledged the motivations for these modifications, the number of post-hoc changes was too large. The EMA recommended additional discussion in our MAA of the post-hoc modifications. We believe that the post-hoc modifications we made were warranted and

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scientifically appropriate. In addition, the 30-meter treatment effect we observed in this trial was present in the pre-specified analysis and is not dependent upon any post-hoc analyses.

The EMA noted that in its view a separation from placebo in 6-minute walk distance was observed only at week 42 and week 48 of the trial, which might indicate either that the trial duration was too short or that the trial results were a chance finding. Accordingly, the EMA recommended further discussion of this point. However, contrary to the EMA's observation, separation from placebo in the 6-minute walk distance test did not occur only at week 42 and week 48, as indicated by the 10% worsening analysis we performed and which is described in greater detail below. A greater effect on 6-minute walk distance was seen over time in the trial, but we believe this is to be expected given ataluren's mechanism of action and the time needed by the body to produce functional levels of dystrophin.

The EMA commented that in its view the outcomes of the primary endpoint were not supported by the results from the secondary endpoints, which were inconsistent and difficult to interpret, and that there was a similar proportion of patients who lost ambulation in all three arms of our trial. The EMA requested that we elaborate further on these topics. We believe that the results in the primary endpoint were supported by trends in secondary endpoints, including timed function tests based on time to climb four stairs, descend four stairs and run/walk 10 meters, patient/caregiver reported frequency of accidental falls, activity and wheelchair use in the community setting, muscle strength and patient reported physical functioning. With respect to loss of ambulation, although we agree that a similar number of patients in all three arms of the trial lost ambulation, this was not a trial endpoint. As a result, we cannot determine the effect of ataluren on the loss of ambulation. We believe a larger and longer trial would be needed to assess loss of ambulation and that it is not appropriate to retrospectively treat loss of ambulation as a relevant endpoint in our trial.

The EMA questioned whether the 30 meter difference we observed in 6-minute walk distance was clinically relevant and requested we discuss this further. We believe 30 meters represents a clinically relevant distance for Duchenne muscular dystrophy patients. In particular, natural history studies have shown that a 10% decrease in walking ability over 48 weeks predicts loss of ambulation over following years. We plan to further justify that a 30 meter difference in the 6-minute walk test represents the minimal clinically important difference in patients with nmDMD. The EMA also commented that efficacy has not been sufficiently supported by pharmacodynamic data. We plan to respond by providing pharmacodynamic data that were generated in our Phase 2a nmDMD trial.

The EMA commented that in light of the perceived weak evidence of efficacy, the risk-benefit balance is negative for purposes of conditional approval. The EMA requested that we elaborate our position on this topic. We believe that any slowing of disease progression is meaningful to patients and families and that the safety profile of ataluren as shown across our trials to date supports a positive finding of risk-benefit.

The EMA considers the choice of the 10, 10, 20 dose of ataluren not to be well substantiated because of the lack of dose-response studies, insufficient data supporting a bell shaped dose response curve theory and uncertainties about the effective dose. The EMA commented that convincing evidence about the bell shaped dose response relationship is essential and requested that we elaborate further on this topic. We believe the bell shaped dose response curve is supported by multiple studies and analyses, including non-clinical data, published studies and our clinical concentration analyses and related modeling efforts demonstrating that plasma concentrations in the effective range are achieved in patients receiving the 10, 10, 20 mg/kg dose. These studies and analyses are described in more detail below.

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The EMA considers the data not to be supportive for the proposed patient population. The EMA expressed concerns that the patient population in our Phase 2b clinical trial was heterogeneous and that disease severity may have influenced the results of the trial. The EMA commented that patients with mild phenotypes may have driven the efficacy results and asked about the proportion of patients in the trial with Becker muscular dystrophy, which is a milder condition than Duchenne muscular dystrophy. In addition, the EMA expressed doubts about extrapolation of the results of our Phase 2b clinical trial to a broader patient population. We believe that our proposed labeling is supportable based on the data from our trials to date. In our analyses, our efficacy results are not driven by subjects with a milder phenotype, and we have safety and exposure data across the entire proposed label population, including in non-ambulatory patients. We believe that it is not possible to provide the number of patients with Becker muscular dystrophy because they were not identified prospectively in our Phase 2b trial. We also believe that given ataluren's mechanism of action there is no reason to expect that it would be effective in ambulatory patients and not effective in non-ambulatory patients.

The EMA advised us that two secondary packaging sites need compliance confirmation by inspection prior to approval. We are in the process of scheduling the required inspections with these sites and expect these inspections to be complete prior to approval.

The day 120 list of questions also included a number of technical questions and comments that do not rise to the level of major objections. We believe we have adequate responses to all of these questions.

The EMA also informed us in scientific advice that it provided in May 2012 that although ataluren falls within the scope of the regulation for conditional approval, it appeared unlikely that a positive risk-benefit assessment for ataluren could be concluded primarily based on the results of our completed Phase 2b clinical trial. In addition, in both the March 2013 day 120 questions and the May 2012 scientific advice, the EMA questioned whether it is practical to believe that a Phase 3 clinical trial for this indication could be completed if the EMA grants conditional approval, which would reduce the likelihood that we could provide comprehensive data following approval.

After receiving the scientific advice from the EMA in May 2012, we held meetings with the rapporteur and the co-rapporteur for regulatory review of ataluren for the treatment of nmDMD. The role of the rapporteur is to perform the scientific evaluation of an application and prepare an assessment report for the EMA. The co-rapporteur prepares an independent assessment report or provides a critique of the rapporteur's report. In our meetings, the rapporteur and the co-rapporteur indicated to us that they support 6-minute walk distance as the primary endpoint and that an endpoint to measure muscle strength would not be required in the proposed confirmatory Phase 3 clinical trial, as had been previously suggested in the scientific advice from the EMA.

Although there is substantial risk that the EMA will not grant us this conditional approval, we are pursuing this approach because we believe the drug is active and should be made commercially available as soon as possible to patients who have no other treatment options. We plan to complete our confirmatory Phase 3 clinical trial of ataluren for the treatment of nmDMD even if the EMA does not grant conditional approval. We expect that these trial results, if favorable, could serve as the basis for full marketing approval in the European Union, the United States and other territories. If the trial results are favorable, and based on our estimates of patient enrollment and data availability, we expect to be able to submit applications for full marketing approval of ataluren for the treatment of nmDMD in both the European Union and the United States in 2016.

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Inspectors acting at the request of the EMA recently conducted good clinical practice, or GCP, inspections of selected clinical sites from our completed Phase 2b clinical trial of ataluren for the treatment of nmDMD and our clinical site relating to our pending MAA for conditional approval of ataluren for the treatment of nmDMD. The reports from these inspections contained a combination of critical and major findings. These findings relate to waivers we granted to admit patients to our completed Phase 2b clinical trial of ataluren for nmDMD in advance of protocol amendments that would have established their eligibility for the trial, as well as our oversight of our trial sites and completeness or sufficiency of trial documentation. We do not believe these findings reflect adversely on the overall integrity of our Phase 2b clinical trial or trial results. In response to these findings, we intend to describe 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 ataluren for the treatment of nmDMD. In addition, we intend to propose corrective action plans to address the inspectors' specific findings. The findings from these inspections, together with our response and inspectors' comments on our response, will be considered by CHMP as it evaluates our MAA and may affect the probability of conditional approval. We believe that we have already addressed many of the critical and major findings in the inspectors' report in the design and ongoing oversight of our confirmatory Phase 3 clinical trial for ataluren for the treatment of nmDMD. We are in the process of implementing other corrective actions to address the remaining findings and that will be part of the corrective action plans we propose to the EMA in our response.

FDA. Following a meeting with the FDA in November 2009 in which we discussed our submission of a new drug application, or NDA, we submitted to the FDA the final component of an NDA in March 2011 for approval of ataluren for the treatment of nmDMD. The FDA refused to file this NDA on the grounds that the single placebo controlled Phase 2b clinical trial contained in the NDA did not achieve statistical significance in the pre-specified analysis. In December 2011, we filed with the FDA a formal dispute resolution request concerning the NDA. We requested review of the issues related to the FDA's refusal to file the NDA and a prospective resubmission of the NDA with updated information and analyses. In January 2012, the FDA reaffirmed the appropriateness of its earlier decision to refuse to file the NDA. In February 2012, we discussed the design of a proposed Phase 3 clinical trial with the FDA. In that meeting, although the FDA indicated that the adequacy of data for filing and approval of an NDA would remain review issues, the FDA had no objections to key elements of our proposed trial design, including the eligibility criteria for patients based on baseline 6-minute walk distance, use of the 6-minute walk test as the primary efficacy endpoint and inclusion of timed tests of muscle function as key secondary endpoints. Consequently, we plan to include the safety and efficacy data from our confirmatory Phase 3 clinical trial of ataluren for the treatment of nmDMD as part of our application for marketing approval from the FDA if we successfully complete this trial.

Phase 2b clinical trial of ataluren for nmDMD

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 ataluren in patients with nmDMD as confirmed by gene sequencing. We conducted this clinical trial in 174 patients at 37 investigational sites in 11 countries. Before this clinical trial, there was no established precedent for an appropriate trial design to evaluate the efficacy of ataluren and little clinical experience in the methodologies used to analyze the resulting data. In addition, at the time we designed and initiated this trial, our knowledge of the natural history of Duchenne muscular dystrophy patients was limited. In particular, there were no data available regarding change in 6-minute walk distance over time for patients with Duchenne muscular dystrophy. As a result of this trial, we improved our understanding of the patient population likely to demonstrate the

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greatest measurable benefit from treatment, the dose of ataluren most likely to demonstrate efficacy and the appropriate statistical plan for analyzing the trial data.

The primary objective of this trial was to evaluate the effect of ataluren on ambulation. The primary efficacy endpoint was the mean change in 6-minute walk distance at week 48 of the trial compared to baseline. 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.

We included many secondary and exploratory endpoints in this trial to gain greater understanding of clinical trial design in Duchenne muscular dystrophy and not with the sole objective of showing a treatment effect. Secondary endpoints in the trial included monitoring changes in:

- tests of muscle function based on time to climb four stairs, descend four stairs, run/walk 10 meters and stand from supine;
- muscle strength;
- patient/caregiver reported frequency of accidental falls;
- patient/caregiver reported health related quality of life;
- patient/caregiver reported treatment satisfaction;
- at-home activity as measured by pedometry;
- verbal memory and attention;
- heart rate function;
- creatine kinase, or CK, values as a measure of whole-body muscle fragility; and
- biceps muscle dystrophin expression.

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 ataluren 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 CK levels and had ongoing difficulty with walking. Patients were excluded from the trial if they had a prior or ongoing clinically significant illness, had a positive hepatitis B or hepatitis C test or had recently used systemic aminoglycosides. Patients receiving corticosteroid therapy were required to have initiated therapy more than six months prior to enrollment and to be on a stable dosing regimen for at least three months prior to entering the trial. The trial protocol specified a clinic visit every six weeks to assess efficacy and safety and an interim laboratory visit every three weeks for the first 24 weeks of the trial. The treatment duration was 48 weeks.

We stratified patients in this trial based on age, baseline 6-minute walk distance and use of corticosteroids. Patients were randomized in a 1:1:1 ratio to receive one of the following:

- placebo;

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ataluren at a dosing regimen consisting of 10 mg/kg in the morning, 10 mg/kg at midday and 20 mg/kg in the evening, for a total daily dose of 40 mg/kg, which we refer to as the 10, 10, 20 dose of ataluren; or

ataluren at a dosing regimen consisting of 20 mg/kg in the morning, 20 mg/kg at midday and 40 mg/kg in the evening, for a total daily dose of 80 mg/kg, which we refer to as the 20, 20, 40 dose of ataluren.

Pre-specified analysis in ITT population. As specified in the trial protocol, we performed the primary analysis of the mean change in 6-minute walk distance from baseline to 48 weeks 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.

In this trial, the patients taking the 10, 10, 20 dose of ataluren had notably less decline in their walking ability than the patients taking placebo. The mean change from baseline to 48 weeks in 6-minute walk distance was -42.6 meters, with a standard deviation from the mean of 90.0 meters, in the placebo group, and -12.9 meters, with a standard deviation from the mean of 72.0 meters, in the ataluren 10, 10, 20 dose group. The difference of 29.7 meters between the 10, 10, 20 dose of ataluren and placebo in mean change in 6-minute walk distance over 48 weeks was consistent with the clinically meaningful treatment effect of 30 meters specified in the trial protocol. However, the resulting nominal p-value of 0.149 was not statistically significant at the pre-specified level of less than 0.05. We had targeted a treatment effect of 30 meters because marketed drugs for other genetic disorders that affect muscle activity were approved on the basis of a difference of approximately 30 meters in 6-minute walk distance.

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.

We believe that the principal reasons for the lack of statistical significance for the primary efficacy endpoint in this trial, notwithstanding having achieved the targeted treatment effect, were the higher than expected mean variability in the results of individual patients over 48 weeks, as measured by the standard deviation from the mean, and the heterogeneous population of nmDMD patients based on age and baseline 6-minute walk distance. We believe that the high standard deviation in the 6-minute walk distance data resulted from the substantial variability of disease progression in Duchenne muscular dystrophy in patients in the wide age range that we enrolled in this trial. In particular, we believe that younger patients and patients with higher baseline 6-minute walk distances are less likely to exhibit measurable declines in 6-minute walk distance over 48 weeks. Based on information available at the time we designed this trial, we selected the sample size of the trial based on an assumed standard deviation of 50 meters and enrolled patients between five and 20 years of age. However, the higher actual standard deviation in the trial of between 72 and 90 meters made it difficult to achieve statistical significance without a larger patient population.

In this trial, there was no difference between placebo and the 20, 20, 40 dose of ataluren in the 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 ataluren in Duchenne muscular dystrophy and other genetic disorders.

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Pre-specified supportive analyses of ambulation. The protocol for our Phase 2b clinical trial included the following two supportive analyses of ambulation:

- an evaluation of the proportion of patients with at least 10% persistent worsening in 6-minute walk distance at week 48 compared to baseline; and
- time to persistent 6-minute walk distance 10% worsening from baseline.

The 10% persistent worsening threshold was defined in advance and reflects the clinical meaningfulness of a 10% change in walking ability in Duchenne muscular dystrophy. Specifically, a change of 10% in walking ability in one year is generally predictive of substantial decline in a patient's clinical status over the following years. The proportion of patients with at least 10% persistent worsening in 6-minute walk distance over the course of the trial is shown in the graph below.

Proportion of patients with persistent 10% worsening in 6-minute walk distance from baseline to week 48 (ITT population)

We believe that this analysis of the 6-minute walk distance indicates a meaningful delay in decline in ambulation for the 10, 10, 20 dose of ataluren compared to placebo and supports the primary analysis of mean change from baseline in 6-minute walk distance in the ITT population.

The analysis of time to 10% persistent worsening indicated that the pre-specified median time to 10% worsening was 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

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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 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 graph and the table below.

Mean change in 6-minute walk distance (6MWD) by visit (corrected ITT analysis)

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

		Treatment arm	
Summary of change from baseline to week 48	**Placebo N=57**	**Ataluren 10, 10, 20 dose N=57**	**Ataluren 20, 20, 40 dose 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 10, 10, 20 dose of ataluren and placebo in mean change in 6-minute walk distance over 48 weeks was 31.3 meters. We observed clear separation between the 10, 10, 20 dose of ataluren and placebo, with the difference between the arms increasingly favoring the 10, 10, 20 dose of ataluren 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 10, 10, 20 dose of ataluren 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 10, 10, 20 dose of ataluren 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.

Subgroup analysis based on enrollment criteria for confirmatory Phase 3 clinical trial. Using the corrected ITT analysis, we also performed a post-hoc, retrospective subgroup analysis of patients in the Phase 2b clinical trial who would meet the enrollment criteria for our confirmatory Phase 3 clinical trial. We expect that these patients would be in the decline phase of the disease, based on age and baseline 6-minute walk distance. Patients in this subgroup were seven through 16 years of age, at baseline, walked no more than 80% of predicted 6-minute walk distance compared to healthy boys matched for age and height, but had the ability to walk at least 150 meters during the 6-minute walk test, and had used systemic corticosteroids for a minimum of six months prior to start of treatment. The results of this subgroup analysis are shown in the graph and the table below.

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Mean change in 6-minute walk distance (6MWD) in Phase 2b subgroup based on enrollment criteria for confirmatory Phase 3 clinical trial (corrected ITT analysis)

Summary of change from baseline to week 48	Placebo N=31	Treatment arm Ataluren 10, 10, 20 dose N=30
Mean (standard deviation), meters	-62.2 (84.9)	-12.3 (69.4)
Mean difference from placebo, meters		49.9
Nominal p-value (vs. placebo)		0.0096

In this subgroup analysis, the difference between the 10, 10, 20 dose of ataluren and placebo in mean change in 6-minute walk distance over 48 weeks was 49.9 meters (nominal p = 0.0096). Because all patients in this subgroup were receiving corticosteroids, the variability was reduced compared to the mixed population in the Phase 2b trial of corticosteroid users and non-users.

Dose-response curve. In our Phase 2b clinical trial, although the 10, 10, 20 dose of ataluren showed clinically meaningful improvements over placebo, the 20, 20, 40 dose of ataluren generally showed little or no difference from placebo. Based on our current understanding of the ribosome's structure, we believe that the 10, 10, 20 dose of ataluren associates with a particular site on the ribosome that allows the ribosome to read through a premature stop signal. We believe that this allows the ribosome to make the full-length, functional dystrophin protein and modulate the defect in muscular dystrophy. At higher doses, such as the 20, 20, 40 dose, we believe that ataluren may also interact with a second site on the ribosome that interferes with the ability of the ribosome to read through the premature stop signal. Therefore, we believe that at higher doses ataluren no longer enables the ribosome to make the full-length, functional dystrophin protein.

The results of our Phase 2b clinical trial are consistent with a bell-shaped dose-response in which the response to treatment initially increases with higher drug concentrations and then subsequently decreases at even higher drug concentrations. We also observed a bell-shaped dose-response to ataluren in non-clinical studies involving mouse and human cellular models of nmDMD and a mouse cellular model of the genetic disorder Hurler's Disease and in two extension trials of ataluren that we conducted.

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Mouse model of nmDMD. In a mouse model of nmDMD, ataluren increased dystrophin production in muscle cells grown in the laboratory, referred to as myotubes, with maximal activity at a concentration of 10 micrograms per milliliter, or µg/ml. In this study, we observed decreased dystrophin production at concentrations of ataluren ranging from 20 µg/ml to 30 µg/ml, indicating a bell-shaped dose-response curve. We assessed dystrophin production based on staining of muscle samples with antibodies as observed under a microscope. The figure below shows the results from this mouse model.

Effect of ataluren on dystrophin staining scores in myotubes isolated from nmDMD mice

Myotubes from nmDMD patients. In non-clinical studies with human myotubes grown from 35 different nmDMD patients, ataluren also exhibited a bell-shaped dose-response curve with maximal dystrophin staining observed at 10 µg/ml of ataluren. At concentrations above 10 µg/ml, there was diminishing response to treatment. The figure below shows the results from these non-clinical studies. In this figure, the values on the vertical axis represent changes in dystrophin expression relative to untreated myotube cultures from patients with nmDMD.

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In vitro **dystrophin expression concentration-response in cultured myotubes from nmDMD patients**

Mean increase relative to control

Mouse model of nonsense mutation Hurler's disease. In addition, ataluren also showed a bell-shaped dose-response in two experiments in a mouse model that we developed for the genetic disorder Hurler's disease in which the mice harbor a nonsense mutation. In cells taken both from the mouse model exposed to increasing concentrations of ataluren, shown in the first figure below, and in spleen samples from mice given increasing doses of ataluren, shown in the second figure below, we observed a bell-shaped dose-response in the reduction in the levels of glycosaminoglycans, or GAGs, elevated levels of which are a hallmark of Hurler's disease.

In vitro **mouse cells**

In vivo **mouse spleen**

Clinical trial data. To gather additional evidence of a bell-shaped dose-response curve, we analyzed the data from our clinical trials based on ataluren plasma concentration. In our Phase 2b clinical trial, we measured ataluren plasma concentrations prior to the morning dose, or C_{0h}, and two hours after the morning dose, or C_{2h}, at each visit. All patients receiving the 10, 10, 20 dose of ataluren had a maximal mean plasma concentration of less than 20 µg/ml. Approximately 40% of patients receiving the 20, 20, 40 dose had mean plasma concentrations in a low concentration range of less than 20 µg/ml, and approximately 60% of these patients had mean plasma concentrations in a high concentration range of 20 µg/ml or greater. The figure below shows mean C_{2h} ataluren data from our Phase 2b clinical trial.

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Mean 2-hour ataluren plasma concentrations

In our Phase 2b clinical trial, we also analyzed 6-minute walk distance and timed function tests by mean C_{0h} and C_{2h} across all visits. Patients who received the 20, 20, 40 dose of ataluren and had mean plasma concentrations in a low concentration range of less than 20 µg/ml had better results in 6-minute walk distance and time function tests than patients who received the 20, 20, 40 dose of ataluren but had mean plasma concentrations in a high concentration range of 20 µg/ml or greater. The figure below shows these results.

Mean change in 6-minute walk distance (6MWD) and timed function tests (TFT(s)) by concentration

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We performed similar concentration-response analyses, based on $C_{0h,}$ in our Phase 2a and Phase 2b open label extension trials in which only the 20, 20, 40 dose of ataluren was evaluated. In both trials, patients with mean plasma concentrations in a low concentration range of less than 20 µg/ml had better results in 6-minute walk distance and timed function tests than patients with mean plasma concentrations in a high concentration range of 20 µg/ml or greater. This indicates that the plasma concentration range associated with the 10, 10, 20 dose is the active concentration range of ataluren.

Secondary endpoints. Our analyses of the data from the secondary efficacy endpoints of this Phase 2b clinical trial are summarized below. There was little or no prior experience with several of these secondary endpoints in Duchenne muscular dystrophy therapeutic trials. In addition, this trial was powered based upon the primary endpoint, 6-minute walk distance, and not to detect statistically significant differences in these secondary endpoints. However, patients in the 10, 10, 20 ataluren dose group trended better than the placebo group in several of these secondary endpoints.

Timed tests of muscle function. Patients treated with ataluren showed less decline in muscle function over 48 weeks, as evidenced by smaller increases in the times to climb four stairs, descend four stairs and run/walk 10 meters, relative to placebo. These trends were more prominent with the 10, 10, 20 dose of ataluren 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 ataluren and placebo.

Muscle strength. We performed myometric evaluations, in which muscle strength is measured in knee flexion, knee extension, elbow flexion, elbow extension and shoulder abduction. Over 48 weeks, patients treated with ataluren generally showed slightly less decline in muscle strength, as evidenced by smaller decreases in most myometry parameters, relative to placebo. These trends were more prominent with the 10, 10, 20 dose of ataluren, although differences were below a threshold considered to be clinically meaningful.

Frequency of accidental falls. The frequency of falls was measured based on a diary kept by patients/caregivers. Trial results showed trends in reductions in accidental falling for ataluren compared to placebo. Accidental falls are a major concern of patients and their families, since they can lead to fractures and, in some cases, loss of ambulation.

Patient-reported health related quality of life and treatment satisfaction. We observed positive trends favoring the 10, 10, 20 dose of ataluren compared to placebo in the patient reported physical functioning aspect of the health related quality of life measurement, although differences were below a threshold considered to be clinically meaningful.

At-home activity as measured by pedometry. In an assessment of time spent at different activity levels in daily life, the largest differences between ataluren and placebo in mean changes at week 48 were observed with the 10, 10, 20 dose of ataluren, which showed trends toward less time spent at no activity and more time spent at medium activity. We performed this assessment on the basis of the number of steps taken per minute as measured by a pedometer worn on the ankle. In conjunction with this step activity monitoring, patients receiving the 10, 10, 20 dose of ataluren showed trends toward less increase in wheelchair use over 48 weeks as compared to placebo.

Biceps muscle dystrophin expression. Because muscular dystrophy is caused by the absence of the dystrophin protein, we sought to collect quantitative data with respect to muscle dystrophin expression as we had observed in our Phase 2a clinical trial described below. However, we were unsuccessful in doing so, in part, because a majority of muscle biopsy samples that we collected were compromised, which precluded meaningful interpretation of the data. In addition, we have since concluded that a

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sensitive and reliable method is not currently available for quantifying dystrophin at the low levels seen in patients with Duschenne muscular dystrophy and that muscle sampling is problematic because of the variation in dystrophin levels within either the same muscle or between different muscles.

Other secondary endpoints. Changes in other secondary efficacy endpoints were generally small, and we did not observe any clear differentiation between ataluren and placebo.

Safety and tolerability. Ataluren 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 ataluren 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 ataluren 10, 10, 20 dose group to the ataluren 20, 20, 40 dose group were nausea (12.3% for placebo, 14.0% for the ataluren 10, 10, 20 dose and 16.7% for the ataluren 20, 20, 40 dose), abdominal pain (7.0% for placebo, 12.3% for the ataluren 10, 10, 20 dose and 16.7% for the ataluren 20, 20, 40 dose), pain in extremity (10.5% for placebo, 12.3% for the ataluren 10, 10, 20 dose and 13.3% for the ataluren 20, 20, 40 dose), flatulence (7.0% for placebo, 8.8% for the ataluren 10, 10, 20 dose and 11.7% for the ataluren 20, 20, 40 dose) and nasal congestion (7.0% for placebo, 8.8% for the ataluren 10, 10, 20 dose and 10.0% for the ataluren 20, 20, 40 dose). An overview of adverse events in this trial is shown in the table below.

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

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

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

Open label continuation trials of ataluren for nmDMD

We are currently conducting two open label continuation trials to evaluate the safety and tolerability of ataluren in patients with nmDMD who previously participated in one of our other clinical trials. We are conducting one of these continuation trials in the United States and the other in countries outside the United States. We plan to enroll up to 122 patients in the U.S. trial and approximately 96 patients in the other trial. We initiated the U.S. trial in November 2010 and the other trial in May 2012. As of March 31, 2013, we had enrolled 107 patients in the U.S. trial and 71 patients in the other trial. Patients in these trials receive the 10, 10, 20 dose of ataluren at morning, midday and evening. Study assessments are performed at clinic visits every 12 weeks. As of March 31, 2013, available data from these continuation trials indicated no change in the safety profile for ataluren in patients with nmDMD.

Phase 2a clinical trial of ataluren for nmDMD

In October 2007, we announced the results of an open label Phase 2a clinical trial evaluating ataluren in 38 patients with nmDMD as confirmed by gene sequencing. We conducted this trial at three academic centers in the United States.

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, or EDB. In this trial, the entire EDB muscle was removed from one foot prior to treatment and the entire EDB muscle was removed from the other foot after treatment. An increase from baseline in study participants' dystrophin levels in the EDB muscle biopsy indicates suppression of the nonsense mutation. We evaluated dystrophin protein levels using immuno-fluorescent staining. Secondary endpoints of the trial included serum CK levels, changes in muscle strength, time taken to perform specified functions such as walking and climbing stairs and compliance with ataluren treatment. The trial also assessed dose-response and the safety and pharmacokinetic profiles of ataluren.

Patients enrolled in this trial were at least five years of age, were diagnosed with nonsense mutation Duchenne muscular dystrophy, had increased levels of serum CK and had absent or diminished dystrophin protein on muscle biopsy.

Participants in the trial were divided into three groups, with all participants in each group receiving ataluren treatment for 28 days. The first group comprised the first six participants in the trial, who received a dosing regimen of ataluren consisting of 4 mg/kg in the morning, 4 mg/kg at midday and 8 mg/kg in the evening. The second group comprised the next 20 participants in the trial, who received the 10, 10, 20 dose of ataluren. The third group comprised the final 12 participants in the trial, who received the 20, 20, 40 dose of ataluren.

We tested the effects of ataluren on trial participants at the end of the 28-day treatment period and conducted a follow-up assessment four weeks after the last dose administration.

In this trial, ataluren 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 ataluren 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 ataluren treatment. Anecdotal reports from

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the parents and teachers of several boys noted evidence of greater activity, increased endurance and less fatigue during ataluren administration. Pharmacokinetic results from this trial indicated that both the 10, 10, 20 dose and the 20, 20, 40 dose regimens achieved plasma concentrations of ataluren that were predicted to have a therapeutic effect, based on preclinical data. The 4, 4, 8 dose regimen did not consistently achieve these levels, and as a result we did not include this dosing regimen in our subsequent Phase 2b trial.

We observed mild treatment emergent adverse events of transient headache and gastrointestinal complaints, which appeared consistent with background symptoms commonly observed in clinical trials. There were no clearly dose dependent increases in frequency or severity of adverse events. No drug related serious adverse events were reported. Patients received approximately 99% of the planned ataluren doses, and no patient discontinued ataluren due to an adverse event.

Cystic fibrosis

Cystic fibrosis is among the most common life-threatening genetic disorders worldwide. 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. The Cystic Fibrosis Foundation estimates that approximately 83% of the active patients in their National Patient Registry have been genotyped. 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.

Cystic fibrosis is caused by defects in a single gene known as the cystic fibrosis transmembrane conductance regulator, or CFTR. The CFTR gene encodes the CFTR protein, which is used by the body to transport chloride across cell membranes. Genetic mutations that result in the loss of function of the CFTR protein cause the body to produce abnormally thick and sticky mucus that clogs multiple organs, including the lungs, pancreas and liver. In particular, the absence or very low levels of CFTR leads to progressive loss of lung function, potentially life-threatening lung infections, permanent pancreatic damage and malnutrition because digestive enzymes from the pancreas do not reach the intestines to help break down and absorb food. Because patients with cystic fibrosis have malabsorption and a high calorie expenditure for breathing, their body weights are often low.

Complications from lung infections are the primary cause of death from cystic fibrosis. From as early as four months of age, patients with cystic fibrosis may begin to develop airway obstruction and inflammation. Over time, most patients develop chronic bacterial infections in the airways, resulting in repeated episodes of pneumonia. Ultimately, progressive lung dysfunction leads to respiratory failure and death. According to the Cystic Fibrosis Foundation's National Patient 2011 Registry, the median predicted age of survival for a cystic fibrosis patient in the United States is approximately 37 years. The median predicted age of survival is the age to which half of the current patients in this registry are expected to survive based on the ages of patients in the registry and the distribution of deaths in 2011. However, the average age of death for cystic fibrosis patients in 2011 was approximately 27 years.

Mutations causing cystic fibrosis are categorized in five different classes, Class I through Class V, as represented in the figure below. 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

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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. Ataluren 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. The FDA recently approved Kalydeco, developed by Vertex Pharmaceuticals, as a treatment for patients with a Class III mutation known as G551D that occurs in approximately 3% to 5% of cystic fibrosis patients. Ataluren and Kalydeco have not been tested in combination in any clinical trials.

Different types of genetic mutations cause cystic fibrosis

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.

Planned Phase 3 clinical trial of ataluren for nmCF

We are planning a multicenter, randomized, double-blind, placebo controlled Phase 3 clinical trial to evaluate the efficacy and safety of ataluren in approximately 210 patients with cystic fibrosis caused by a nonsense mutation as confirmed by gene sequencing. We plan to begin enrolling trial sites for this trial in the second half of 2013, and we expect to dose the first patient in this trial in the first half of 2014, subject to the conclusion of our ongoing discussions with regulatory authorities regarding our proposed trial design. We expect that the primary objective of this trial will be to evaluate the effect of ataluren on pulmonary function relative to placebo based on a primary efficacy endpoint of relative change in percent of predicted FEV_1. Percent of predicted FEV_1, or %-predicted FEV_1, is based on a comparison to healthy

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individuals matched for age, height and gender. We expect that secondary efficacy endpoints in the trial will include the following:

- pulmonary exacerbation rate, based on specified signs and symptoms; and
- other pulmonary function measures as assessed by lung capacity and expiratory flow.

We expect to require that patients in this trial be at least six years of age and have %-predicted FEV_1 within a specified range, sweat chloride in excess of a specified level as evidence of the severity of the disease and documentation of a nonsense mutation in at least one copy of the CFTR gene. We expect to exclude patients from the trial if they are receiving chronic inhaled aminoglycoside antibiotics, have any change in treatment or prophylaxis for cystic fibrosis related conditions within four weeks prior to start of study treatment, have recently been treated with intravenous antibiotics or have major complications of lung disease. We expect to perform study assessments of FEV_1 at clinic visits every eight weeks and that patients will undergo 48 weeks of blinded treatment prior to the final analysis.

We plan to stratify patients based on age, screening %-predicted FEV_1 and chronic use of inhaled antibiotics. We plan to randomize patients in a 1:1 ratio to receive either placebo or ataluren at a dosing regimen of 10 mg/kg in the morning, 10 mg/kg at midday and 20 mg/kg in the evening, for a total daily dose of 40 mg/kg. At the completion of blinded treatment, we plan to make an open label extension trial available to patients who successfully complete the double-blind trial and are not in countries where ataluren is commercially available at that time.

Based on our estimates regarding initiation of the trial and patient enrollment, we expect to complete this trial and have initial, top-line data available in 2016.

Regulatory status and strategy for nmCF

EMA. We have received scientific advice from the EMA regarding the possibility of submitting an MAA for conditional approval of ataluren for the treatment of nmCF and the protocol design of a post-approval confirmatory trial. The EMA recognized that there is an unmet medical need and advised us that it would consider an MAA for conditional approval of ataluren for patients with nmCF. If we submit an MAA for this condition, approval 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. The EMA has informed us that the benefit from ataluren that we observed in our completed Phase 3 clinical trial would have been more demonstrative if we had used absolute change in %-predicted FEV_1 rather than relative change in %-predicted FEV_1 as the primary efficacy endpoint, although the EMA also acknowledged that relative change in %-predicted FEV_1 can nonetheless be considered an acceptable primary endpoint in our planned Phase 3 clinical trial. 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 ataluren for this indication. There is substantial risk that the EMA will not grant us conditional approval of ataluren for the treatment of nmCF.

In particular, the EMA has advised us that we may need to address the following additional matters in our MAA.

- *The clinical relevance of the relative change in %-predicted FEV_1 that we observed in our completed Phase 3 clinical trial after taking into account all possible biases and confounders.* In this trial, the difference between ataluren and placebo in relative change in %-predicted FEV_1 at week 48 in the ITT population was not statistically significant. We believe that use of the inhaled antibiotic tobramycin confounded the results of the trial by interfering with ataluren's mechanism of action. For a subgroup of patients not receiving chronic inhaled aminoglycoside antibiotics, there was a substantial difference in mean relative changes from baseline in %-predicted FEV_1 at the end of the trial favoring ataluren in comparison with placebo. In addition, we believe that even a modest slowing of the decrease in FEV_1 in nmCF patients over time may be clinically meaningful.

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Consideration of alternatives to explain the lack of statistical significance in relative change in %-predicted FEV_1 in our Phase 3 clinical trial other than the plausible explanation that the inhaled antibiotic tobramycin interfered with ataluren's mechanism of action. We believe that other possible explanations of the tobramycin effect can be discounted because the patients in our trial treated with tobramycin are similar clinically based on signs and symptoms of the disease to patients not treated with tobramycin, so that differences between the patient subgroups would not be expected to explain a difference in outcomes.

Lack of clear support of treatment effect from secondary or tertiary endpoints in our completed Phase 3 clinical trial. The results for the secondary endpoint of pulmonary exacerbation were consistent with the primary endpoint in the ITT population and in the subgroups with and without tobramycin. The tertiary endpoints did not clearly support the primary endpoint. However, some of these endpoints were novel, and although tertiary endpoints included pharmacodynamic measurements, there is no established surrogate biomarker in cystic fibrosis.

The imbalance in the baseline %-predicted FEV_1 in favor of ataluren. We believe that the numeric difference between baseline %-predicted FEV_1 for ataluren and placebo (63% for ataluren and 59% for placebo) is small and would not be expected to affect the trial results. Furthermore, our review of scientific literature indicates that a higher baseline FEV_1 is associated with greater decline in FEV_1 than a lower baseline FEV_1, and therefore the imbalance, if it caused any effect, would favor placebo over ataluren.

The evolution of the relative change in %-predicted FEV_1 over 48 weeks in the placebo group being worse than expected. The relative change in %-predicted FEV_1 over 48 weeks in the placebo group in our Phase 3 clinical trial was 5.5%. Although this decrease is larger than expected in 48 weeks in general for patients with cystic fibrosis, we believe that the greater severity of the disease for patients with nmCF as compared to patients with cystic fibrosis caused by other mutations explains the unexpected result.

The lack of analysis of patients based on body weight and height. We plan to provide to the EMA an analysis based on body weight that has been previously performed. We believe that height is not a common outcome measure in clinical trials for cystic fibrosis, although we could perform an analysis if requested by the EMA.

The statistical analysis that we employed. To address concerns about the statistical methodology that we used, we plan to provide to the EMA the results of sensitivity analyses of the primary endpoint.

FDA. We met with the FDA in July 2012 to discuss the results of our completed Phase 3 clinical trial of ataluren for the treatment of nmCF. The FDA indicated that in its view the data from our completed Phase 3 clinical trial and other data from our development program in cystic fibrosis do not by themselves support an NDA submission. Consequently, the FDA informed us that additional clinical data would be required to establish the evidence required to support eventual filing of an NDA for the use of ataluren to treat nmCF. We have begun discussions with the FDA regarding the clinical development design options which would have the potential to support an NDA. Our goal in these continuing discussions is to achieve consensus between the EMA and the FDA that a single placebo controlled Phase 3 clinical trial can serve as the basis for full approval of ataluren to treat nmCF in both the European Union and the United States.

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Completed Phase 3 clinical trial of ataluren for nmCF

In June 2012, we announced the results of a multicenter, international, randomized, double-blind, placebo controlled Phase 3 clinical trial assessing the effects of ataluren in 238 patients with cystic fibrosis caused by a nonsense mutation as confirmed by gene sequencing. The primary objective of this trial was to evaluate the effect of ataluren 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 ataluren at a dosing regimen of 10 mg/kg in the morning, 10 mg/kg at midday and 20 mg/kg in the evening, for a total daily 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 ataluren arm than in the placebo arm. Of the 238 total patients, 120 patients received ataluren and 118 patients received placebo, with 34 patients withdrawing prematurely, including 20 patients on ataluren and 14 patients on placebo. Of these 34 patients, nine withdrew because of adverse events, one was lost to follow-up for unexplained reasons, 18 withdrew consent, one was withdrawn based on an investigator decision, two were withdrawn because of protocol noncompliance and three withdrew for other unspecified reasons. One patient completed 48 weeks of blinded therapy but did not have evaluable FEV_1 data at week 48. This resulted in 203 patients completing the 48-week treatment period with FEV_1 data available at week 48. 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 ataluren 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. The results from this trial are shown in the table below. The table shows information about relative change, which was the primary analysis, and absolute change in %-predicted FEV_1 from baseline to week 48.

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Change in %-predicted FEV_1 from baseline to week 48 (ITT population)

	Placebo N=116		Ataluren 10, 10, 20 dose N=116	
Relative change in %-predicted FEV_1 at week 48				
Mean (standard deviation)	-5.5%	(12.56)	-2.5%	(13.25)
Mean difference from placebo			3.0%	
p-value			0.124	
Relative change in %-predicted FEV_1 averaged over 48 weeks				
Mean	-4.3%		-1.8%	
Mean difference from placebo			2.5%	
p-value			0.0478	
Absolute change in %-predicted FEV_1 at week 48				
Mean (standard deviation)	-3.1%	(7.39)	-1.3%	(8.50)
Mean difference from placebo			1.8%	
p-value			0.136	

The primary analysis of relative change in %-predicted FEV_1 in this trial showed a 3.0% difference (2.5% decrease on ataluren, 5.5% decrease on placebo) at week 48 favoring ataluren (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 ataluren compared to placebo (1.8% decrease on ataluren, 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 ataluren, 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 ataluren'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 ataluren (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 ataluren 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. The results for

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patients not receiving chronic inhaled tobramycin and patients receiving chronic inhaled tobramycin are depicted in the following graphs.

Mean relative change in %-predicted FEV_1 at week 48 by baseline chronic inhaled tobramycin use

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 ataluren (nominal p=0.008), consistent with the targeted treatment effect size. Patients receiving chronic inhaled tobramycin did not show a benefit for ataluren 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.

Both tobramycin and ataluren act through modulation of the ribosomal machinery. We believe that the binding of tobramycin to the ribosome may interfere with ataluren's mechanism of action. We explored this hypothesis in a functional cell-based translation assay. In this experiment, ataluren-induced read-through of premature stop codons was diminished when the cells were exposed to ataluren together with tobramycin or gentamicin, but not when ataluren 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 the 10, 10, 20 dose of ataluren 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 ataluren than placebo (nominal p=0.005). Patients receiving chronic inhaled torbramycin did not show a benefit in pulmonary exacerbation rate on ataluren 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.

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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 ataluren and placebo for each of these endpoints were small and not statistically significant.

Safety and tolerability. Ataluren was generally well tolerated in this clinical trial, and there were generally similar adverse event profiles in patients treated with ataluren 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 ataluren 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 ataluren arm were headache (11.9% for placebo and 16.7% for ataluren), abdominal pain (12.7% for placebo and 15.0% for ataluren), sinusitis (11.9% for placebo and 12.5% for ataluren) and vomiting (8.5% for placebo and 11.7% for ataluren). Eleven patients prematurely discontinued treatment because of adverse events, including eight in the ataluren arm and three in the placebo arm.

There were 19 patients with at least one treatment-emergent renal adverse event, including 15 patients receiving ataluren and 4 patients receiving placebo. In the ataluren arm, five adverse events that involved the renal system led to discontinuation. As compared to the placebo group, the ataluren 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 ataluren 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 ataluren 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 ataluren arm and four patients in the placebo arm.

An overview of adverse events in this trial is shown in the table below.

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

	Treatment arm		
	Placebo	Ataluren	All patients
Parameter	**N=118**	**N=120**	**N=238**
Patients with ≥1 adverse event	115 (97.5%)	118 (98.3%)	233 (97.9%)
Adverse events by severity			
Grade 1 (mild)	20 (16.9%)	18 (15.0%)	38 (16.0%)
Grade 2 (moderate)	65 (55.1%)	81 (67.5%)	146 (61.3%)
Grade 3 (severe)	30 (25.4%)	19 (15.8%)	49 (20.6%)
Grade 4 (life-threatening)			
Adverse events by relatedness			
Unrelated	42 (35.6%)	30 (25.0%)	72 (30.3%)
Unlikely	31 (26.3%)	39 (32.5%)	70 (29.4%)
Possible	35 (29.7%)	34 (28.3%)	69 (29.0%)
Probable	7 (5.9%)	15 (12.5%)	22 (9.2%)
Discontinuations due to adverse events	3 (2.5%)	8 (6.7%)	11 (4.6%)
Serious adverse events	48 (40.7%)	45 (37.5%)	93 (39.1%)
Deaths			

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

Open label extension trial of ataluren for treatment of nmCF

We are currently conducting an open label, extension trial that is providing additional safety information for the long term administration of ataluren in patients with cystic fibrosis who successfully completed 48 weeks of treatment in our completed Phase 3 clinical trial. In addition, this trial is designed to provide supportive long-term efficacy information to better understand the long-term effects of ataluren 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 receive the 10, 10, 20 dose of ataluren for a 96 week treatment period. We are performing study assessments at clinic visits every eight weeks. Currently available data on FEV_1 in patients who have completed a total of 96 weeks of treatment are shown in the figure below. In patients who have received ataluren since the beginning of the Phase 2b clinical trial, FEV_1 has been generally maintained over the course of 96 weeks. In patients who transitioned from placebo to ataluren at the beginning of the open label, extension trial, FEV_1 has remained stable since their transition to ataluren.

The most common adverse events during this trial were cystic fibrosis pulmonary exacerbation (79.1%), cough (27.2%) and viral upper respiratory tract infection (25.7%). 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 ataluren 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 ataluren was made by the trial investigator, based on his or her judgment.

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Change in %-predicted FEV_1 through week 96

Phase 2 clinical trials of ataluren for treatment of nmCF

In 2006, we completed two open label Phase 2 clinical trials of ataluren for the treatment of nmCF in adult patients. In these two trials, we enrolled a combined total of 47 patients age 18 years or older who were diagnosed with cystic fibrosis resulting from a nonsense mutation in the CFTR gene. We conducted the first trial at one site in Israel and the second trial at four sites in the United States. In 2008, we completed a third open label Phase 2 clinical trial of ataluren for the treatment of nmCF in pediatric and adolescent patients. We enrolled 30 patients between 6 and 18 years of age who were diagnosed with cystic fibrosis resulting from a nonsense mutation in the CFTR gene. We conducted this third trial at one site in France and two sites in Belgium. Each of these three trials had a treatment duration of 28 days. We also conducted an open label, extension trial with a treatment duration of three months for the patients who completed the 28-day trial in Israel. The goal of each of these trials was to obtain indications of pharmacological activity and to assess dose-response, safety and pharmacokinetics.

The trial designs for the three Phase 2 clinical trials with 28-day treatment durations were comparable and included two treatment cycles. Each cycle consisted of a two-week period of continuous ataluren treatment, and then a two-week follow-up period without ataluren treatment. During the two weeks of ataluren treatment one of the cycles, participants received ataluren at doses of 4 mg/kg in the morning, 4 mg/kg at midday and 8 mg/kg in the evening, for a total daily dose of 16 mg/kg. During the two weeks of ataluren treatment in the other cycle, the same participants received ataluren at doses of 10 mg/kg in the morning, 10 mg/kg at midday and 20 mg/kg in the evening, for a total daily dose of 40 mg/kg. We evaluated trial participants at the beginning and end of each two-week treatment period and follow-up period in each cycle. In the trial with a treatment duration of three months, patients received either ataluren at doses of 4 mg/kg in the morning, 4 mg/kg at midday and 8 mg/kg in the evening, for a total daily dose of 16 mg/kg, or ataluren at doses of 10 mg/kg in the morning, 10 mg/kg at midday and 20 mg/kg in the evening, for a total daily dose of 40 mg/kg.

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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 the trials conducted in adults in Israel and in children and adolescents in France and Belgium, there were statistically significant improvements at the end of the ataluren 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 in the United States, we did not observe improvements in mean total chloride conductance.

Ataluren was generally well tolerated in these trials. Only one serious adverse event was considered possibly related to ataluren. 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.

Phase 1 clinical trials of ataluren

We have completed two Phase 1 clinical trials of ataluren involving a total of 62 healthy volunteers. The first Phase 1 clinical trial was a single-dose, safety and pharmacokinetic study with a placebo component, conducted in a total of 31 healthy volunteers between 18 and 30 years of age. In the first stage of the trial, subjects were enrolled at escalating dose levels ranging from 3 to 200 mg/kg. In this study, we determined that 100 mg/kg is the maximum tolerated dose based on the observation of increased frequency of headaches, dizziness and mild gastrointestinal events, such as nausea, vomiting and diarrhea, at the 150 mg/kg and 200 mg/kg doses. The drug was palatable, with no obvious odor or taste. In the second stage of this trial, we assessed the effect of food on the safety and pharmacokinetic profiles of ataluren at a dose of 50 mg/kg. This study provided us with pharmacokinetic data that indicated minimal alterations in the pharmacokinetic profile when ataluren was taken after a meal and supported giving ataluren with food to maintain plasma concentrations. The study also provided pharmacokinetic information allowing us to predict ataluren blood exposure levels in future studies.

The second Phase 1 clinical trial was a multiple-dose, open label safety and pharmacokinetic study conducted in a total of 31 healthy volunteers between 18 and 30 years of age. In the first stage of the trial, subjects were enrolled at escalating twice-daily doses ranging from 10 to 50 mg/kg per dose taken with food for seven consecutive days. In the second stage of this trial, subjects were enrolled at a twice-daily dose of 50 mg/kg per dose for 14 days. In this study, there were no clinically significant adverse events reported at any dose tested, although we observed modest elevations of liver enzymes in some subjects. These elevated enzyme levels did not require cessation of ataluren administration, and enzyme levels typically normalized after completion of the treatment phase. As in the single-dose study, we were able to achieve and maintain plasma concentrations of ataluren that were predicted to have a therapeutic effect based on preclinical data. In the multiple-dose trial, as in the single-dose study, we sought to determine whether ataluren promoted improper read-through of normal stop codons. We assessed this by observing whether the trial participants produced improperly large forms of specified proteins. We did not observe any such improper protein formation.

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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 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 post-transcriptional control drug discovery technologies

We have developed and assembled an integrated set of proprietary technologies 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.

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We use proprietary assays to test our library of approximately 240,000 compounds to identify those that are likely to enhance or inhibit expression of the target gene by modulating the post-transcriptional control processes that act through that target's UTRs.

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.

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 ataluren 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 ataluren 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.

Preclinical development programs

SMN2 for spinal muscular atrophy

Using our alternative splicing technology, we have identified and are chemically optimizing several small molecule compounds, with the goal of selecting a lead development compound, for the treatment of spinal muscular atrophy. We have entered into a collaboration agreement with Roche and the SMA Foundation for the development and commercialization of these compounds. Roche is responsible for pursuing clinical development of compounds from the research program under the collaboration and then commercializing any resulting products. We also previously received $13.3 million in sponsored research funding for this program from the Spinal Muscular Atrophy Foundation.

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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. The SMA Foundation estimates that spinal muscular atrophy affects approximately 10,000 to 25,000 children and adults in the United States and that between one in 6,000 and one in 10,000 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, we have identified small molecule splicing modifiers that at very low concentrations in non-clinical studies involving cells 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 of mice with only the SMN2 gene, these compounds are orally bioavailable, penetrate the blood-brain barrier and increase full-length SMN mRNA and protein in various 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. We expect to select a lead development compound in the second half of 2013.

Oncology BMI1 program

We have selected a development candidate, PTC596, for the treatment of chemotherapy resistant cancers through the targeting of cancer stem cells. We are currently conducting IND-enabling preclinical studies with PTC596. We have received grant funding of $5.4 million for our BMI1 program from Wellcome Trust.

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 gene expression that is important for cancer stem cell survival, maintenance, stabilization and differentiation. PRC1 is epigenetic, 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 component of PRC1, the BMI1 protein regulates the self-renewal of adult blood and central nervous system stem cells that regulate cell growth.

PTC596 is an orally active small molecule that targets tumor stem cell populations by reducing the function, activity and amount of BMI1. PTC596 acts by altering and destroying the BMI1 protein through a process called phosphorylation. PTC596 has potently inhibited BMI1 function in multiple tumor cell lines. In *in vitro* tests, PTC596 has preferentially targeted chemotherapy resistant cancer stem cells. Specifically, PTC596 preferentially depleted cancer stem cells in assays with tumor cell lines from 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, weekly oral dosing of PTC596 provided tumor control, including reduction of tumor size. PTC596 and the commonly used chemotherapy paclitaxel were both

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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, after transplanting tumor cells from one animal to another, the resulting tumors treated with PTC596 had lower levels of cancer stem cells than either untreated tumors or tumors treated with paclitaxel. 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.

Antibacterial Program

We have identified and are chemically optimizing several small molecule compounds for the treatment of life-threatening infections caused by multidrug-resistant Gram-negative bacteria. Our goal is to select lead development compounds that can 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 $2.5 million as of March 31, 2013.

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, N. gonorrhoeae, and Staphylococcus aureus.* 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 is 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.

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 an early stage collaboration and discovery agreement with AstraZeneca AB for the discovery and development of potential new therapies for cancer and other diseases.

Roche and the SMA Foundation

In November 2011, we entered into a license and collaboration 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 sponsored research program with the SMA Foundation, as described below, and to research, develop and commercialize other small molecule compounds with potential for therapeutic use in patients with spinal muscular atrophy. Pursuant to the license and collaboration agreement, Roche paid us an upfront non-refundable payment of $30.0 million. Roche has additional financial obligations described below.

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Research and development. The agreement provides for a research and development collaboration under which we and Roche will conduct a program designed to further research and develop specified compounds from our pre-existing collaboration with the SMA Foundation, as described below, and to discover and develop new small molecule compounds that result in increased levels of SMN1 mRNA and protein based on the conversion of SMN2 RNA to SMN1 mRNA. During the research term, Roche has agreed to provide us with funding, based on an agreed-upon full-time equivalent rate, for an agreed-upon number of full-time equivalent employees that we contribute to the research program. The research term is for a minimum of two years from the effective date of the agreement and can be terminated by Roche any time thereafter upon 90 days' notice. Roche is responsible for pursuing worldwide clinical development of compounds from the research program.

Joint steering committee. The 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 that the members of the joint steering committee will act in good faith to cooperate with one another and seek agreement with respect to issues to be decided by the joint steering committee. In addition, we, the SMA Foundation and Roche have agreed to endeavor to make decisions by consensus, but if the joint steering committee cannot reach agreement after following a specified decision resolution procedure, Roche's decision will control. However, Roche may not exercise its final decision-making authority with respect to certain specified matters, including any decision that would increase our or the SMA Foundation's obligations, reduce our or the SMA Foundation's rights, expand Roche's rights, or reduce Roche's obligations under the license and collaboration agreement.

Commercialization. Roche is responsible for commercializing compounds and products from the collaboration. 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.

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. 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.

Exclusivity. Roche has the exclusive right to develop and commercialize compounds from the collaboration. Furthermore, until November 2014, except in specified circumstances involving termination or certain acquisitions, neither we nor Roche is permitted, outside the collaboration, to use alternative splicing to identify any small molecule compound that results in increased levels of SMN1 mRNA and protein based on the conversion of SMN2 RNA to SMN1 mRNA or to engage in any research, development, manufacture or commercialization of any compound that such party knows or believes to be such a small molecule compound identified with alternative splicing.

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.

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Roche's termination rights under the license and collaboration agreement include the following:

- 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

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. 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.

Research collaboration. The agreement established a research collaboration under which we identified and optimized compounds with the potential to treat spinal muscular atrophy by increasing production of the survival motor neuron, or SMN, protein. We expect to designate one of the compounds from the research program as a development candidate in the first half of 2013, and several other compounds from the research program have been designated as potential back-up compounds. As discussed above, we are also collaborating with the SMA Foundation and Roche to further develop these compounds.

Development and commercialization. We have agreed to use commercially reasonable efforts to develop and commercialize at least one product from compounds we advance from the research program, including performing specified activities within agreed timelines. As discussed above, we are also collaborating with the SMA Foundation and Roche to further develop these compounds.

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

Reversion rights. In specified circumstances, including those involving our decision to discontinue development or commercialization of a collaboration product, our uncured failure to meet agreed timelines or those that might arise following our change of control, we may be obligated to grant the SMA Foundation exclusive or non-exclusive sublicensable rights under our intellectual property, in certain collaboration products, among other rights, to assume the development and commercialization of such

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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 (BMI1 for oncology)

In May 2010, we entered into a funding agreement with Wellcome Trust for the research and development of small molecule compounds that selectively decrease the production of BMI1 expression in tumor stem cells. Pursuant to the funding 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.

Research program. We have agreed to use reasonable efforts to achieve each specified research program milestone on or before its corresponding agreed target date. We have designated PTC596 as an experimental drug candidate. The research program term began on the effective date and ends on the earlier of completion of the research program or three years after the effective date.

Development and commercialization. We own all intellectual property that arises from the conduct of the research program, which we refer to as program intellectual property, and are responsible for developing and commercializing the program intellectual property, including PTC596 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.

Continuing financial obligations. 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. Our obligation to pay such royalties would continue on a country-by-country basis until the longer of the expiration of the last patent in the program intellectual property in such country covering the research program product and the expiration of market exclusivity of such product in such country. 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.

Reversion rights. 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

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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.

Termination. Unless terminated earlier, the funding agreement will continue until 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 certain of our other intellectual property.

Wellcome Trust's rights under the funding agreement include the right to terminate the agreement under specified circumstances, including if:

- according to a team of experts from Wellcome Trust, an uncorrected serious failure exists in the progress, management or conduct of the research program, or an uncorrected major external scientific, technical or commercial barrier exists that means the research program is unlikely to succeed in its objectives;
- we cease or threaten to cease to carry on our business or operations necessary for the completion of our obligations under the funding agreement;
- in Wellcome Trust's reasonable opinion, an act or omission by us is incompatible with or has an adverse effect on Wellcome Trust's charitable objectives or reputation or on our ability to comply with our obligations under the funding agreement;
- we enter into any transaction involving the program intellectual property or our background intellectual property without Wellcome Trust's prior written consent;
- specified events take place relating to our principal investigator for the research program; or
- specified situations exist following a change of control of us.

The 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.

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

If the funding agreement terminates prior to the end of the 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.

If Wellcome Trust terminates the funding agreement 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 program intellectual property, grant to Wellcome Trust royalty-free non-exclusive rights under our background intellectual property for the continuation of the research program, if applicable, and the development and commercialization of program intellectual property, and provide Wellcome Trust with other specified transitional assistance.

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If we terminate the funding agreement in specified circumstances, including as a result of Wellcome Trust's uncured material breach or bankruptcy or insolvency, Wellcome Trust's right to receive payments from us with respect to development and commercialization of program intellectual property on a for-profit basis, as well as certain other specified rights, will terminate.

Wellcome Trust (antibacterial)

In December 2011, we entered into an additional funding agreement with Wellcome Trust for the research and development of small molecule compounds that target life-threatening infections caused by multidrug-resistant Gram-negative bacteria. Pursuant to the funding 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. The balance of the grant is payable based on our achievement of three specified milestones. As of March 31, 2013, we have achieved one of these milestones, triggering additional payments to us of $1.6 million.

Research program. We have agreed to use reasonable efforts to achieve each specified research program milestone on or before its corresponding agreed target date. The research program term began on the effective date of the agreement and ends on the earlier of completion of the research program or three years after the effective date.

Development and commercialization. We own all intellectual property that arises from the conduct of the research program, which we refer to as program intellectual property, and have the first right to develop and commercialize the program intellectual property, including compounds, provided that we obtain 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.

Continuing financial obligations. 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. Our obligation to pay such royalties would continue on a country-by-country basis until the longer of the expiration of the last patent in the program intellectual property in such country covering the research program product and the expiration of market exclusivity of such product in such country. 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.

Reversion rights. 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.

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Termination. Unless terminated earlier, the 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.

Wellcome Trust's termination rights under the funding agreement include the right to terminate the funding agreement under specified circumstances, including if:

- according to a team of experts from Wellcome Trust, an uncorrected serious failure exists in the progress, management or conduct of the research program, or an uncorrected major external scientific, technical or commercial barrier exists that means the research program is unlikely to succeed in its objectives;
- we cease or threaten to cease to carry on our business or operations necessary for the completion of our obligations under the funding agreement;
- in Wellcome Trust's reasonable opinion, an act or omission by us is incompatible with or has an adverse effect on Wellcome Trust's charitable objectives or reputation or on our ability to comply with our obligations under the funding agreement;
- we enter into any transaction involving the program intellectual property or our background intellectual property without Wellcome Trust's prior written consent;
- specified events take place relating to our principal investigator for the research program; or
- specified situations exist following a change of control of us.

The 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.

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

If the funding agreement terminates prior to the end of the 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).

If Wellcome Trust terminates the funding agreement 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 program intellectual property, grant to Wellcome Trust royalty-free non-exclusive rights under our background intellectual property for the continuation of the research program (if applicable) and the development and commercialization of program intellectual property, and provide Wellcome Trust with other specified transitional assistance.

If we terminate the funding agreement in specified circumstances, including as a result of Wellcome Trust's uncured material breach or bankruptcy or insolvency, Wellcome Trust's right to receive payments from us with respect to development and commercialization of program intellectual property on a for-profit basis, as well as certain other specified rights, will terminate.

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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 May 31, 2013, we owned or exclusively licensed a total of 60 U.S. patents and 69 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 owned by us consist of thirteen 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. The issued U.S. patents relating to composition of matter are currently scheduled to expire in 2024, and all U.S. patents that issue from U.S. patent applications relating to composition of matter would also be scheduled to expire in 2024. An issued U.S. patent relating to therapeutic method of use is currently scheduled to expire in 2027. All of these patent rights are also the subject of pending counterpart patent applications in a number of other jurisdictions, including Europe and Japan. We own two issued European patents relating to dosing and methods of manufacture of ataluren, and multiple pending European patent applications relating to composition of matter, methods of use, formulation, dosing and methods of manufacture of ataluren. The issued European patents are currently scheduled to expire in 2026 and 2027, and any European patent that issues from the pending European patent application relating to composition of matter would currently be expected to expire in 2024. 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 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 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.

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Similar provisions are available in Europe and certain other foreign jurisdictions to extend the term of a patent that covers an approved drug. In the future, if and when our product candidates receive approval by the FDA or 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 currently own or operate manufacturing facilities for the production of clinical or commercial quantities of ataluren 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 our product candidates and any products 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 ataluren from a single third-party manufacturer. We engage a separate manufacturer to provide fill and finish services for the finished product that we are using in our ongoing clinical trials of ataluren. We are in the process of qualifying an additional manufacturer for the supply of bulk drug substance and for fill and finish services for our future clinical trials of ataluren. We obtain our supplies of the product candidates from these manufacturers pursuant to agreements that include specific supply timelines and volume expectations. If any of these manufacturers should become unavailable to us for any reason, we believe that there are a number of potential replacements, although we might incur some delay in identifying and qualifying such replacements.

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. In particular, ataluren is manufactured in reliable and reproducible synthetic processes from readily available starting materials. The chemistry is amenable to scale up and does not require unusual equipment in the manufacturing process.

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

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.

The competition for ataluren includes the following:

Ataluren for nmDMD. There are currently no marketed therapeutics approved to treat the underlying cause of nmDMD. Current treatments seek to address symptoms through supportive care measures, such as bracing, joint stretching exercises, tendon release surgery, wheelchair use and assisted ventilation. Corticosteroids, such as prednisone and deflazacort are often prescribed to treat some of the symptoms of the disease. We believe that ataluren is the only product candidate in clinical trials that is designed to treat the underlying cause of nmDMD by restoring dystrophin activity. Other biopharmaceutical companies are developing treatments for Duchenne muscular dystrophy based on a different scientific approach known as exon-skipping. Prosensa Therapeutics is developing a product candidate, PRO051, based on exon-skipping that is currently in Phase 3 clinical development in collaboration with GlaxoSmithKline. Sarepta Therapeutics is developing a product candidate, Eteplirsen, based on exon-skipping that is currently in Phase 2b clinical development. We do not believe that either PRO051 or Eteplirsen is applicable for the treatment of patients with nmDMD. 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. In addition, Pfizer has a potentially muscle-enhancing product candidate in Phase 2 clinical development for muscular dystrophy.

Ataluren for nmCF. There are currently no marketed therapeutics approved to treat the underlying cause of nmCF. In 2012, the FDA approved Kalydeco (ivacaftor), a CFTR potentiator developed by Vertex Pharmaceuticals, 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. We do not believe that Kalydeco, which

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is designed for the treatment of patients with a mutation other than a nonsense mutation, is 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 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 ataluren is the only product candidate in clinical trials that is designed to treat the underlying cause of nmCF by restoring CFTR activity. 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 processing block mutation, one of which is in Phase 2 clinical development in combination with Kalydeco.

The key competitive factors affecting the success of ataluren 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

If we receive regulatory approval for our product candidates, we plan to commence commercialization activities by building a focused sales and marketing organization complemented by selective distribution, co-promotion and other arrangements with leading pharmaceutical or biotechnology collaborators.

We generally expect to retain commercial rights for our product candidates for which we receive marketing approvals in situations in which we believe it is possible to access the market through focused, specialized sales force. In particular, we believe that such a sales force could address the community of pulmonologists and neurologists who are the key specialists in treating cystic fibrosis and Duchenne muscular dystrophy, for which we are developing ataluren. Accordingly, if ataluren is approved, we plan to initially build our own internal sales teams to target these specialists.

We also plan to build key capabilities, such as marketing, market access, sales management and medical affairs, to implement marketing and medical strategies for any products that we market through our own sales organization and to oversee and support our sales force. The responsibilities of the marketing organization would include developing educational initiatives with respect to approved products and establishing relationships with thought leaders in relevant fields of medicine.

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, approval, manufacturing, labeling, post-approval monitoring and reporting, 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.

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U.S. government regulation

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 NDA approval 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 or distribution, injunctions, fines, civil penalties or criminal prosecution. Any agency or judicial enforcement action could have a material adverse effect on us.

To market a new drug, 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;
- submission to the FDA of an investigational new drug application, or IND, for clinical testing, which must become effective before clinical trials may begin and which must include independent Institutional Review Board, or IRB, approval before the trials may be initiated;
- performance of adequate and well-controlled clinical trials in accordance with GCP to establish the safety and efficacy of the product for each indication;
- submission to the FDA of an NDA;
- 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, toxicity and formulation, as well as animal studies. An IND applicant must submit the results of the preclinical tests, together with manufacturing information and analytical data, to the FDA as part of the IND. 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.

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Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators. Clinical trials are conducted under 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. In addition, an IRB must approve the protocol and amendments. All research subjects or their legally authorized representatives must provide their informed consent in writing.

Clinical trials typically are conducted in three sequential phases, but the phases may overlap or be combined. Phase 1 clinical trials usually involve the initial introduction of the investigational drug into human subjects. 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.

Phase 1, Phase 2 and Phase 3 testing may not be completed successfully within any specified period, if at all. Furthermore, the FDA or we 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

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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 draft 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 draft guidance refers to the diagnostic tests used with these types of drugs as *in vitro* companion diagnostic devices. According to the draft guidance, *in vitro* companion diagnostic devices ordinarily will be considered to be high risk and, therefore, will require the 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 draft guidance states that the FDA may decline to 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 draft 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 draft guidance is subject to change and is not binding on the FDA or the public.

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. 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 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

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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. 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. 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. Holders of an approved NDA must report certain adverse reactions and production problems to the FDA, provide updated safety and efficacy information, and comply with requirements concerning advertising and promotional labeling for their products. As a condition of approval of an NDA, the FDA may require post marketing testing and surveillance to monitor the product's safety or 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.

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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, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

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.

Newly discovered or developed safety or effectiveness data or other information may 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. Also, 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 ataluren for the treatment of nmCF, nmDMD and spinal muscular atrophy. 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.

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Competitors may receive approval of different drugs or biologics for the indications for which the orphan product has exclusivity.

Fast track designation

We have obtained fast track designation from the FDA for our product candidate ataluren 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.

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Regulation outside the United States

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

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 ataluren for the treatment of nmDMD, Becker muscular dystrophy and nmCF. 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.

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 ataluren 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

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additional written or oral information is to be provided by the applicant in response to questions. More specifically, on day 120 of the procedure, once the CHMP has received the preliminary assessment reports and opinions from the rapporteur and co-rapporteur, it prepares a list of potential outstanding issues, referred to as "other concerns" or "major objections". These are sent to the applicant together with CHMP's recommendation. The CHMP can make one of two recommendations: (1) the marketing authorization could be granted provided that satisfactory answers are given to the "other concerns" and/or "major objections" identified and that all conditions outlined in the list of outstanding issues are implemented and complied with; or (2) the product is not approvable since there are "major objections". Applicants have three months from the date of receiving the potential outstanding issues to respond to the CHMP, and can request a three-month extension if necessary. The granting of a marketing authorization will depend on the recommendations and potential major objections identified by the CHMP as well as the ability of the applicant to adequately respond to these findings. An accelerated assessment can be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest, in particular from the viewpoint of therapeutic innovation. In this circumstance, the EMA ensures that the opinion of the CHMP is given within 150 days. After the adoption of the CHMP opinion, a decision on the MAA must be adopted by the European Commission, after consulting the European Union member states, which in total can take more than 60 days.

In specific circumstances, E.U. legislation enables applicants to obtain a conditional marketing authorization 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 conditional marketing authorization will depend on the applicant's ability to fulfill the conditions imposed within the agreed upon deadline.

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

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

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reference medicinal product. These periods of data exclusivity and market exclusivity do not prevent other companies from obtaining a marketing authorization based on their own independently generated data.

If we obtain authorization for a medicinal product in the European Union, we will be required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products. We will, for example, have to 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. E.U. regulators 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.

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.

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

Early access programs

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

Pharmaceutical pricing and reimbursement

The containment of healthcare costs has become a priority of federal, state and foreign governments, and the prices of pharmaceuticals have been a focus of this effort. 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 rebates for covered outpatient drugs sold to Medicaid programs, extending the Medicaid rebate to Medicaid managed care plans, mandating discounts for certain Medicare Part D beneficiaries, and imposing annual fees based on pharmaceutical companies' share of sales to federal healthcare programs, among other provisions.

In this healthcare regulatory climate, there may be significant delays in and impediments to obtaining coverage and reimbursement for newly approved drugs. 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

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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.

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 negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. In addition, there can be considerably pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. Political, economic and regulatory developments may further complicate pricing 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.

U.S. 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.

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.

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. The government and *qui tam*

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relators have brought False Claims Act actions against pharmaceutical companies on the theory that their practices have caused false claims to be presented to the government. There is also a separate false claims provision imposing criminal penalties.

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.

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.

A number of states also have statutes or regulations similar to the federal Anti-Kickback Statute and False Claims Act that apply to items and services reimbursed under Medicaid and other state programs. Some states have anti-kickback statutes that apply to all payors and not just government payors.

Employees

As of May 31, 2013, we had 127 employees, of whom 123 were employed on a full-time basis, including a total of 52 employees with M.D. or Ph.D. degrees. Of our workforce, 87 employees are engaged in research and development. None of our employees is represented by labor unions or covered by collective bargaining agreements. We consider our relationship with our employees to be good.

Properties

Our principal facilities consist of approximately 82,798 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 have subleased 11,171 square feet of our space in 250 Corporate Court for a two-year term expiring in October 2014.

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. These matters are subject to various uncertainties, and it is possible that some of these matters may be resolved unfavorably to us. However, we believe that the ultimate outcome of the matters that are currently pending will not have a material adverse impact on our business.

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Management

The following table sets forth the name, age and position of each of our executive officers and directors as of the date of this prospectus.

Name	Age	Position
Stuart W. Peltz, Ph.D.	53	Chief Executive Officer and Director
Claudia Hirawat	42	President
Shane Kovacs	39	Chief Financial Officer
Mark E. Boulding	52	Executive Vice President and Chief Legal Officer
Mark A. Rothera	50	Chief Commercial Officer
Neil Almstead, Ph.D.	46	Senior Vice President, Research and CMC
Jay Barth, M.D.	49	Vice President, Clinical Development
Michael Schmertzler(2)(3)	61	Chairman of the Board of Directors
Richard Aldrich(2)	58	Director
Axel Bolte(1)	41	Director
Allan Jacobson, Ph.D.(3)	67	Director
Adam Koppel, M.D., Ph.D.(3)	43	Director
Michael Kranda(1)	59	Director
Geoffrey McDonough, M.D.	42	Director
David P. Southwell(1)(2)	52	Director
Jerome B. Zeldis, M.D., Ph.D.	63	Director

(1) Member of the Audit Committee

(2) Member of the Compensation Committee

(3) Member of the Nominating and Corporate Governance Committee

Stuart W. Peltz, Ph.D. is a co-founder of our company and has served as our Chief Executive Officer and a member of our board of directors since our inception in 1998. Prior to founding our company, Dr. Peltz was a Professor in the Department of Molecular Genetics & Microbiology at the Robert Wood Johnson Medical School, Rutgers University. Dr. Peltz has published over 80 publications in the area of post-transcriptional control processes and has received a number of scientific awards, including being elected as a Fellow of the American Academy for the Advancement of Science. Dr. Peltz received a Ph.D. from the McArdle Laboratory for Cancer Research at the University of Wisconsin. We believe that Dr. Peltz is qualified to serve on our board of directors because of his extensive executive leadership experience, many years of service as one of our directors and our Chief Executive Officer and extensive knowledge of our company and industry.

Claudia Hirawat has served as our President since April 2012, and previously served as our Senior Vice President, Corporate Development from April 2006 to April 2012 and in other positions since joining PTC in September 2000. Prior to joining PTC, Ms. Hirawat served as a Vice President at LedbetterStevens, a management consulting firm focused on the biopharmaceutical industry, from September 1995 to September 2000.

Shane Kovacs has served as our Chief Financial Officer since June 2013. Prior to joining us, Mr. Kovacs served in positions of increasing responsibility at Credit Suisse, an investment banking firm, from March 2004 to May 2013, including most recently as a Managing Director. From July 2002 to March 2004, Mr. Kovacs served as an associate at National Bank Financial, a diversified financial services firm. Mr. Kovacs received a B.Eng. and a B.S. in Chemical Engineering and Life Sciences from Queen's University and an M.B.A. from the University of Western Ontario. Mr. Kovacs is a Chartered Financial Analyst.

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Mark E. Boulding has served as our Executive Vice President and Chief Legal Officer since March 2012, and previously served as our Senior Vice President and General Counsel from April 2002 to February 2012. Prior to joining us, Mr. Boulding served as General Counsel, Executive Vice President and Secretary of MedicaLogic/Medscape, Inc., a provider of digital health records software and healthcare information, from May 2000 to April 2002. From June 1999 to May 2000, Mr. Boulding served as the General Counsel, Vice President and Secretary of Medscape, Inc., a provider of online health information and education. Mr. Boulding previously was a partner in two Washington, D.C.-based law firms. Mr. Boulding received a J.D. from the University of Michigan and a B.A. from Yale College.

Mark A. Rothera has served as our Chief Commercial Officer since April 2013. Prior to joining us, Mr. Rothera served as Global President of Aegerion Pharmaceuticals Inc., a biopharmaceutical company, from April 2012 to January 2013. From January 2006 to March 2012, he served as Vice President and General Manager for the commercial operations of Shire Human Genetic Therapies, Inc. in Europe, the Middle East & Africa. Prior to joining Shire, Mr. Rothera held various global strategic and operational marketing and sales roles with French and UK operations of Glaxo Wellcome. Mr. Rothera received an M.A. in Natural Science from Cambridge University and an M.B.A. from the European Institute for Business Administration.

Neil Almstead, Ph.D. has served as our Senior Vice President, Research and CMC since July 2008, and previously served as our Senior Vice President, Chemistry and CMC from January 2007 to June 2008. Prior to joining PTC, Dr. Almstead served as Project Manager at Procter & Gamble Company, a publicly traded consumer products company. Dr. Almstead has co-authored more than 75 publications and patents pertaining to the design and synthesis of lead candidate compounds for genetic disorders, oncology and inflammatory diseases. Dr. Almstead received a B.S. from Clarkson University and a Ph.D. in Organic Chemistry from the University of Illinois at Urbana-Champaign.

Jay Barth, M.D. has served as our Vice President of Clinical Development since January 2011, and previously served as our Executive Director of Clinical Development from February 2009 to December 2010. Prior to joining us, Dr. Barth served as Executive Director of Clinical Research at Merck, a pharmaceutical company, from July 2007 to October 2008. From June 2005 to June 2007, he served as Vice President, Clinical Research and Medical Affairs at Altana Pharma US, Inc., a pharmaceutical company. Dr. Barth received a B.A. from Columbia University and an M.D. from the University of Pennsylvania School of Medicine.

Michael Schmertzler has served as a member of our board of directors since August 2001 and as the Chairman of our board of directors since November 2004. From 2008 to 2012, Mr. Schmertzler served as Chief Executive Officer and a director of Kolltan Pharmaceuticals, Inc., a biotechnology company. Since 2001, Mr. Schmertzler has served as a Managing Director of Aries Advisors, LLC, the sub-advisor to Credit Suisse First Boston Equity Partners, L.P., a private equity fund, and the Chair of the investment committee. From 1997 to 2001, Mr. Schmertzler was Co-Head of United States and Canadian Private Equity at Credit Suisse First Boston, an investment banking firm. Prior to 1997, Mr. Schmertzler held various management positions with Morgan Stanley and its affiliates, including President of Morgan Stanley Leveraged Capital Funds and head of Morgan Stanley's biotechnology pharmaceuticals group, and was Managing Director and Chief Financial Officer of Lehman Brothers Kuhn Loeb, an investment banking firm. Mr. Schmertzler is currently a director of Lehman Commercial Paper Incorporated, a liquidating post-bankruptcy subsidiary of Lehman Brothers Holdings, Incorporated. Mr. Schmertzler previously served as a director of Cytokinetics, Incorporated. Since 1978, he has been an Adjunct Professor at Yale University. Mr. Schmertzler received a B.A. from Yale College in Molecular Biophysics and Biochemistry, History and City Planning and an M.B.A. from the Harvard Business School. We believe that Mr. Schmertzler is qualified to serve on our board of

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directors due to his extensive experience as an investment banking and financial professional, his extensive personal knowledge of our industry and his many years of service as one of our directors.

Richard Aldrich has served as a member of our board of directors since March 2013. Mr. Aldrich has served as a partner of Longwood Fund, LP, a venture capital investment fund, since 2010. He founded RA Capital Management LLC, a hedge fund, in 2001 and served as a managing member from 2004 to 2008 and as a co-founding member from 2008 until 2011. He co-founded Sirtris Pharmaceuticals, Inc., which was acquired by GlaxoSmithKline plc in 2008, and served on its board of directors from 2004 to 2008; co-founded Concert Pharmaceuticals, Inc. and has served as Chairman of its board of directors since 2006; co-founded Alnara Pharmaceuticals, Inc., which was acquired by Eli Lilly in 2010, and served on its board of directors from 2008 to 2010; and co-founded OvaScience, Inc. and has served on its board of directors since 2011 and as Chairman of the board since 2012. Mr. Aldrich also joined Vertex Pharmaceuticals, Inc. at its founding in 1989 and served as Senior Vice President and Chief Business Officer until 2001. Mr. Aldrich also serves on the board of directors of Verastem, Inc., a publicly traded biopharmaceutical company. Mr. Aldrich received a B.S. from Boston College and an M.B.A from the Amos Tuck School at Dartmouth College. We believe that Mr. Aldrich is qualified to serve on our board of directors because of his experience in the life sciences industry and as an entrepreneur and venture capital investors and his service on the boards of directors of other life sciences companies.

Axel Bolte has served as a member of our board of directors since December 2003. Since March 2003, Mr. Bolte has served as investment advisor to HBM Partners AG, a provider of investment advisory services in the life sciences industry. From March 2001 to February 2003, Mr. Bolte was an investment manager of NMT New Medical Technologies AG, a Swiss venture capital company focused on life sciences. Prior to joining NMT New Medical Technologies AG, Mr. Bolte served as a scientist at Serono SA, a biotechnology company. He currently serves or has served on the board of directors of several biotechnology companies, including Newron Pharmaceuticals SpA, Nabriva Therapeutics AG, Opthotech Corporation, MPex Pharmaceuticals, Inc., Lux Biosciences, Inc. and Kolltan Pharmaceuticals, Inc. Mr. Bolte received an M.B.A from the University of St. Gallen, Switzerland and a degree in biochemistry at the Swiss Federal Institute of Technology, Zurich, Switzerland. We believe that Mr. Bolte is qualified to serve on our board of directors because of his many years of service as one of our directors, his extensive experience as a venture capital investor in the life sciences industry and his service on the boards of directors of other life sciences companies.

Allan Jacobson, Ph.D. is a co-founder of our company and has served as a member of our board of directors since our inception in 1998, and previously served as Chairman of our board of directors from 1998 to 2004. Since 2000, Dr. Jacobson has served as Chairman of our scientific advisory board. Since 1994, Dr. Jacobson has been the Chairman of the Department of Microbiology and Physiological Systems at the University of Massachusetts Medical School. In 1982, Dr. Jacobson co-founded Applied bioTechnology, Inc., a biotechnology company, and served as its chairman until its sale in 1991. From 1987 to 1990, Dr. Jacobson served as special limited partner at Euclid Partners, a venture capital firm. Dr. Jacobson received a Ph.D. from Brandeis University in 1971, has authored over 100 publications in the field of post-transcriptional control processes and is an elected member of the American Academy of Microbiology. We believe that Dr. Jacobson is qualified to serve on our board of directors because of his service as one of our directors since our inception, his knowledge of our company and his extensive experience as a founder and leader of new businesses in the life science industry.

Adam Koppel, M.D., Ph.D. has served as a member of our board of directors since March 2013. Since November 2003, Dr. Koppel has served as a Managing Director of Brookside Capital, the public equity affiliate of Bain Capital. Prior to joining Brookside Capital, he was an Associate Principal with McKinsey &

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Company where he consulted to companies in the pharmaceutical and biotechnology industries. Dr. Koppel received an M.D. and Ph.D. from the University of Pennsylvania School of Medicine, an M.B.A. from the Wharton School of the University of Pennsylvania and a B.A. from Harvard University.

Michael Kranda has served as a member of our board of directors since December 2003. Since September 2006, Mr. Kranda has served as a consultant to Vulcan Capital, the private investment group of Vulcan Inc., and Mr. Kranda served as Managing Director of biotechnology venture investments at Vulcan Capital from September 2003 to September 2006. From July 1996 to July 2002, Mr. Kranda served as Chief Executive Officer at Oxford GlycoSciences, a biotechnology company. Prior to joining Oxford GlycoSciences, Mr. Kranda was President and Chief Operating Officer at Immunex Corporation (now Amgen), a biopharmaceutical company. Mr. Kranda currently serves as Chief Executive Officer and a director of BEAT BioTherapeutics Corporation, a gene therapy company. Mr. Kranda received a B.A. and an M.B.A from the University of Washington School of Business. We believe that Mr. Kranda is qualified to serve on our board of directors because of his many years of service as one of our directors, his extensive experience in the life sciences industry and his service on the boards of directors of other life sciences companies.

Geoffrey McDonough, M.D. has served as a member of our board of directors since November 2012. Since August 2011, Dr. McDonough has served as President and Chief Executive Officer of Swedish Orphan Biovitrum AB (Sobi), a Swedish pharmaceutical company. Prior to joining Sobi, Dr. McDonough held several senior leadership positions at Genzyme Corporation from 2002 to June 2011, including Senior Vice President and General Manager, Personalized Genetic Health, Senior Vice President, Lysosomal Storage Disease (LSD) Therapeutics and most recently, as President of Europe, Middle East and Africa (EMEA). Prior to joining Genzyme, Dr. McDonough co-founded and served as President of Catalyst Medical Solutions, a developer of software for hospital management, and was a practicing internist and pediatrician. Dr. McDonough received a B.A. and a B.Sc. from the University of North Carolina at Chapel Hill and an M.D. from Harvard Medical School. We believe that Dr. McDonough is qualified to serve on our board of directors because of his extensive executive leadership experience and knowledge of our industry.

David P. Southwell has served as a member of our board of directors since December 2005. From March 2010 to September 2012, Mr. Southwell served as the Executive Vice President and Chief Financial Officer, and from 2008 to 2010 served as a member of the board of directors, of Human Genome Sciences, Inc., a biopharmaceutical company. Prior to joining Human Genome Sciences, he served as Executive Vice President and Chief Financial Officer of Sepracor, Inc., a research-based pharmaceutical company, from June 1994 to March 2008, and as Sepracor's Senior Vice President and Chief Financial Officer, from 1994 to 1995. From August 1988 until 1994, Mr. Southwell was associated with Lehman Brothers Inc., a securities firm, in various positions with the investment banking division. Mr. Southwell received a B.A. from Rice University and an M.B.A. from the Tuck School of Business at Dartmouth College. We believe that Mr. Southwell is qualified to serve on our board of directors because of his extensive executive leadership experience and knowledge of our industry.

Jerome B. Zeldis, M.D., Ph.D. has served as a member of our board of directors since September 2012. Dr. Zeldis currently serves as the Chief Executive Officer of Celgene Global Health and the Chief Medical Officer of Celgene Corporation, a public biopharmaceutical company, where he has been employed since 1997. He previously served as Celgene's Senior Vice President of Clinical Research and Medical Affairs. Previously, Dr. Zeldis served as Assistant Professor of Medicine at Harvard Medical School, Associate Professor of Medicine at University of California, Davis, Clinical Associate Professor of Medicine at Cornell Medical School and Professor of Clinical Medicine at the Robert Wood Johnson Medical School. Dr. Zeldis received an A.B. and M.S. from Brown University and an M.Phil., M.D. and Ph.D. in Molecular Biophysics and Biochemistry (immunochemistry) from Yale University. Dr. Zeldis has served on the board of directors

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of Soligenix, Inc., a public biopharmaceutical company, since June 2011, and on the board of directors of Alliqua, Inc., a public biomedical company, since May 2012. We believe that Dr. Zeldis is qualified to serve on our board of directors because of his extensive executive leadership experience and knowledge of our industry.

Board composition and election of directors

Our board of directors is currently authorized to have 11 members. Our board of directors is divided into three classes, class I, class II and class III, with members of each class serving staggered three-year terms. The members of the classes are divided as follows:

- the class I directors are Drs. Peltz and Zeldis and Mr. Bolte, and their term expires at our annual meeting of stockholders to be held in 2014;
- the class II directors are Messrs. Aldrich, Kranda and Schmertzler and Dr. Koppel, and their term expires at our annual meeting of stockholders to be held in 2015; and
- the class III directors are Drs. Jacobson and McDonough and Mr. Southwell, and their term expires at our annual meeting of stockholders to be held in 2016.

Upon the expiration of the term of a class of directors, directors in that class are eligible to be elected for a new three-year term at the annual meeting of stockholders in the year in which their term expires. In accordance with the terms of our certificate of incorporation and bylaws that will become effective upon the closing of this offering, our directors may be removed only for cause by the affirmative vote of the holders of 75% or more of our voting stock.

Under applicable NASDAQ rules, a director will only qualify as an "independent director" if, in the opinion of our board of directors, that person does not have a relationship that would interfere with the exercise of independent judgment in carrying out the responsibilities of a director. Our board of directors has determined that all of our directors, other than Dr. Peltz, are independent directors, as defined by the applicable NASDAQ Rules. In making such determination, the board of directors considered the relationships that each such non-employee director has with our company and all other facts and circumstances that the board of directors deemed relevant in determining their independence, including the beneficial ownership of our capital stock by each non-employee director.

There are no family relationships among any of our directors or executive officers.

Board committees

Our board of directors has established an audit committee, a compensation committee and a nominating and corporate governance committee, each of which will operate, upon the closing of this offering, under a charter that has been approved by our board. The composition of each committee will be effective upon the closing of this offering.

Our board of directors has determined that all of the members of the audit committee, the compensation committee and the nominating and corporate governance committee are independent as defined under the NASDAQ Rules, including, in the case of all the members of our audit committee, the independence requirements contemplated by Rule 10A-3 under the Exchange Act. In making such determination, our board of directors considered the relationships that each such director has with our company and all other facts and circumstances that our board of directors deemed relevant in determining independence, including the beneficial ownership of our capital stock by each non-employee director.

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Audit committee

The members of our audit committee are Messrs. Bolte, Kranda and Southwell. Mr. Kranda chairs the audit committee. Upon the closing of this offering, our audit committee's responsibilities will include:

- appointing, approving the compensation of, and assessing the independence of our registered public accounting firm;
- overseeing the work of our independent registered public accounting firm, including through the receipt and consideration of reports from such firm;
- reviewing and discussing with management and our independent registered public accounting firm our annual and quarterly financial statements and related disclosures;
- monitoring our internal control over financial reporting, disclosure controls and procedures and code of business conduct and ethics;
- overseeing our internal audit function;
- overseeing our risk assessment and risk management policies;
- establishing policies regarding hiring employees from our independent registered public accounting firm and procedures for the receipt and retention of accounting related complaints and concerns;
- meeting independently with our internal auditing staff, our independent registered public accounting firm and management;
- reviewing and approving or ratifying any related person transactions; and
- preparing the audit committee report required by Securities and Exchange Commission, or SEC, rules.

All audit and non-audit services, other than *de minimis* non-audit services, to be provided to us by our independent registered public accounting firm must be approved in advance by our audit committee.

Our board of directors has determined that Mr. Southwell is an "audit committee financial expert" as defined in applicable SEC rules.

Compensation committee

The members of our compensation committee are Messrs. Aldrich, Schmertzler and Southwell. Mr. Southwell chairs the compensation committee. Upon the closing of this offering, our compensation committee's responsibilities will include:

- reviewing and approving, or making recommendations to our board with respect to, the compensation of our chief executive officer and our other executive officers;
- overseeing an evaluation of our senior executives;

overseeing and administering our cash and equity incentive plans;

reviewing and making recommendations to our board with respect to director compensation;

reviewing and discussing annually with management our compensation disclosure required by SEC rules; and

preparing the compensation committee report required by SEC rules.

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Nominating and corporate governance committee

The members of our nominating and corporate governance committee are Drs. Jacobson and Koppel and Mr. Schmertzler. Mr. Schmertzler chairs the nominating and corporate governance committee. Upon the closing of this offering, our nominating and corporate governance committee's responsibilities will include:

identifying individuals qualified to become members of our board;

recommending to our board the persons to be nominated for election as directors and to each of our board's committees;

reviewing and making recommendations to our board with respect to our board leadership structure;

reviewing and making recommendations to our board with respect to management succession planning;

developing and recommending to our board corporate governance principles; and

overseeing a periodic evaluation of our board.

Compensation committee interlocks and insider participation

None of our executive officers serves as a member of the board of directors or compensation committee, or other committee serving an equivalent function, of any other entity that has one or more of its executive officers serving as a member of our board of directors or our compensation committee. None of the members of our compensation committee is, or has ever been, an officer or employee of our company.

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Executive compensation

This section describes the material elements of compensation awarded to, earned by or paid to each of our named executive officers in 2012. Our "named executive officers" for 2012 are Stuart W. Peltz, our Chief Executive Officer, Claudia Hirawat, our President, and Jay Barth, our Vice President, Clinical Development. This section also provides qualitative information regarding the manner and context in which compensation is awarded to and earned by our executive officers and is intended to place in perspective the data presented in the tables and narrative that follow.

Summary compensation table

The following table sets forth information regarding compensation awarded to, earned by or paid to our named executive officers during 2012.

Name and principal position	Year	Salary ($)	Bonus ($)	Option awards ($)(1)	Non-equity incentive plan compensation ($)(2)	All other compensation ($)(3)	Total ($)
Stuart W. Peltz, Ph.D.(4) *Chief Executive Officer*	2012	446,250		67,175	204,829	4,362	722,616
Claudia Hirawat *President*	2012	281,039		30,900	83,609	56,668	452,216
Jay Barth, M.D. *Vice President, Clinical Development*	2012	325,000	40,000(5)	21,496	78,540	3,112	468,148

(1) The amounts reported in the "Option awards" column reflect the aggregate fair value of share-based compensation awarded during the year computed in accordance with the provisions of Financial Accounting Standards Board Accounting Standard Codification, or ASC, Topic 718. See Note 2 to our financial statements appearing at the end of this prospectus regarding assumptions underlying the valuation of equity awards.

(2) The amounts reported in the "Non-equity incentive plan compensation" column represents awards to our named executive officers under our annual cash bonus program.

(3) The amounts reported in the "All other compensation" column reflect, for each named executive officer, the sum of the incremental cost to us of all perquisites and other personal benefits and are comprised of (i) the amount we contributed to our 401(k) plan in respect of such executive officer; (ii) the dollar value of medical and life insurance premiums paid by us on behalf of each of the named executive officers; and (iii) with respect to Ms. Hirawat, an income tax gross-up amount of $53,593.

(4) Dr. Peltz also serves a member of our board of directors but does not receive any additional compensation for his service as a director.

(5) We granted Dr. Barth a retention bonus of $40,000 in March 2012.

In 2012, we paid base salaries of $446,250 to Dr. Peltz, $281,039 to Ms. Hirawat and $325,000 to Dr. Barth. Base salaries are used to recognize the experience, skills, knowledge and responsibilities required of all our employees, including our named executive officers. None of our named executive officers is currently party to an employment agreement or other agreement or arrangement that provides for automatic or scheduled increases in base salary. In addition, for 2012, we paid annual cash bonuses pursuant to a non-equity incentive plan of $204,829 to Dr. Peltz, $83,609 to Ms. Hirawat and $78,540 to Dr. Barth.

Although we do not have a formal policy with respect to the grant of equity incentive awards to our executive officers, or any formal equity ownership guidelines applicable to them, we believe that equity grants provide our executives with a strong link to our long-term performance, create an ownership culture and help to align the interests of our executives and our stockholders. In addition, we believe that equity grants with a time-based vesting feature promote executive retention because this feature incents our

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executive officers to remain in our employment during the vesting period. Accordingly, our board of directors periodically reviews the equity incentive compensation of our named executive officers and from time to time may grant equity incentive awards to them in the form of stock options. In 2012, based upon our overall performance, we granted to Dr. Peltz an option to purchase 416 shares of our common stock, to Ms. Hirawat an option to purchase 191 shares of our common stock and to Dr. Barth an option to purchase 133 shares of our common stock.

Outstanding option awards at December 31, 2012

The following table sets forth information regarding outstanding stock options held by our named executive officers as of December 31, 2012:

Name	Number of securities underlying unexercised options exercisable (#)	Number of securities underlying unexercised options unexercisable (#)	Option exercise price ($/share)	Option expiration date
Stuart W. Peltz, Ph.D.	5,649		226.80	11/5/2014
Chief Executive Officer	144		226.80	5/25/2015
	136		392.40	3/1/2016
	323		626.40	4/18/2017
	708		735.60	1/25/2018
	294		735.60	4/1/2018
	546	36(1)	451.20	5/15/2019
	401	182(2)	1,149.60	2/2/2020
	237	304(3)	490.80	4/27/2021
		416(4)	218.40	1/10/2022
Claudia Hirawat	890		226.80	11/5/2014
President	106		226.80	5/24/2015
	136		392.40	3/1/2016
	250		626.40	4/18/2017
	166		735.60	1/25/2018
	195		735.60	4/1/2018
	218	14(1)	451.20	5/15/2019
	137	62(2)	1,149.60	2/2/2020
	102	131(3)	490.80	4/27/2021
		191(4)	218.40	1/10/2022
Jay Barth, M.D.	125	41(1)	451.20	5/15/2019
Vice President, Clinical Development	43	19(2)	1,149.60	2/2/2020
	80	103(3)	490.80	4/27/2021
		133(4)	218.40	1/10/2022

(1) This option vests over four years, with 25% of the shares underlying the option vested on January 1, 2010 and 6.25% of the shares underlying the option vesting quarterly thereafter.

(2) This option vests over four years, with 25% of the shares underlying the option vested on January 1, 2011 and 6.25% of the shares underlying the option vesting quarterly thereafter.

(3) This option vests over four years, with 25% of the shares underlying the option vested on January 1, 2012, the first anniversary of the date of grant, and 6.25% of the shares underlying the option vesting quarterly thereafter.

(4) This option vests over four years, with 25% of the shares underlying the option vested on January 1, 2013, the first anniversary of the date of grant, and 6.25% of the shares underlying the option vesting quarterly thereafter.

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In March 2013, our board of directors granted restricted stock awards to our executive officers, including our named executive officers, pursuant to our 2013 stock incentive plan, or the 2013 plan, as follows:

Name	Stock award (#)	Grant date fair value ($)(1)
Stuart W. Peltz, Ph.D.	188,803	1,999,424
Claudia Hirawat	50,057	530,104
Jay Barth, M.D.	7,387	78,228
Mark E. Boulding	42,284	447,788
Neil Almstead, Ph.D.	40,740	431,437

(1) See Note 2 to the financial statements included at the end of this prospectus regarding assumptions underlying the valuation of equity awards.

In May 2013, our board of directors granted stock options to our executive officers, including our named executive officers, pursuant to our 2009 equity and long term incentive plan, as amended, or the 2009 plan, as follows:

Name	Option award (#)(1)	Exercise price per share ($)	Grant date fair value ($)
Stuart W. Peltz, Ph.D.	571,000	10.85	(2)
Claudia Hirawat	135,000	10.85	(2)
Mark A. Rothera	165,000	10.85	(2)
Jay Barth, M.D.	55,000	10.85	(2)
Mark E. Boulding	120,000	10.85	(2)
Neil Almstead, Ph.D.	110,000	10.85	(2)
Shane Kovacs	126,000	10.85	(2)

(1) Includes performance based option awards to our executive officers as follows: Dr. Peltz: 171,000 shares; Ms. Hirawat: 20,000 shares; Mr. Rothera: 15,000 shares; Dr. Barth 15,000 shares; Mr. Boulding: 20,000 shares; and Mr. Almstead: 15,000 shares. The performance options vest over four years and are conditioned upon achievement of specified performance objectives. The remaining option awards to our executive officers vest as to 25% of the original number of shares underlying such options on the first anniversary of the date of grant and as to an additional 2.083% of the original number of shares at the end of each subsequent month thereafter.

(2) The amounts reported in this column represent the aggregate grant date fair value of the options granted to our executive officers, computed in accordance with ASC 718. The fair value per share of the option awards granted in May 2013 will be calculated in connection with the preparation of our unaudited financial statements for the three months ended June 30, 2013.

In connection with retaining Shane Kovacs to work with us, in May 2013, our board of directors granted Mr. Kovacs a restricted stock award of 14,000 shares of our common stock pursuant to our 2009 plan. The fair value per share of Mr. Kovacs' stock award will be calculated in connection with the preparation of our unaudited financial statements for the three months ended June 30, 2013.

Employment agreements with executive officers

In May 2013, we entered into employment agreements with our executive officers. These agreements amend and restate the existing employment agreements that we previously entered into with Dr. Peltz, Ms. Hirawat and Messrs. Boulding and Almstead. Each of these agreements provides that employment will continue until either we or the executive officer provides written notice of termination in accordance with the terms of the agreement. In addition, each of these agreements prohibits our executive officers from disclosing confidential information and competing with us during the term of their employment and for a specified time thereafter.

Pursuant to their respective employment agreements, each of our executive officers is entitled to receive an annual base salary as follows: Dr. Peltz: $460,000; Ms. Hirawat: $289,470; Dr. Barth: $339,900; Mr. Boulding: $312,998; Mr. Rothera: $400,000; Mr. Almstead: $273,156; and Mr. Kovacs: $335,000.

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Following the consummation of this offering, each of our executive officers will be entitled to receive an annual base salary as follows: Dr. Peltz: $460,000; Ms. Hirawat: $340,000; Dr. Barth: $339,900; Mr. Boulding: $330,000; Mr. Rothera: $400,000; Mr. Almstead: $295,000; and Mr. Kovacs: $335,000.

In addition, each of our executive officers is eligible to receive an annual cash bonus, which is based on the percentage achievement of all individual and functional performance objectives in aggregate and calculated as a percentage of the executive's annual base salary, and which will be determined by our board of directors, in its sole discretion. For 2013, Dr. Peltz's target annual bonus is 50% of his annual base salary, and the target annual bonus for each of our other executive officers is 40% of his or her annual base salary.

Upon execution and effectiveness of a release of claims, each of our executive officers will be entitled to severance payments if his or her employment is terminated under specified circumstances.

Potential payments upon termination or change in control

Dr. Peltz. If we terminate Dr. Peltz's employment without cause or if Dr. Peltz terminates his employment with us for good reason, each as defined in his employment agreement, absent a change in control, or "corporate change", as defined in his employment agreement, we are obligated to: pay Dr. Peltz a lump sum amount equal to his base salary for 18 months; accelerate 25% of Dr. Peltz's outstanding unvested equity awards granted on or prior to May 15, 2013 other than the restricted stock awards granted in March 2013, which unvested restricted stock awards will accelerate in full; extend the exercise period of certain of Dr. Peltz's option awards, subject to specified limitations; and, to the extent allowed by applicable law and the applicable plan documents, continue to provide Dr. Peltz and certain of his dependents with group health insurance for a period of 18 months.

If we terminate Dr. Peltz's employment without cause or if Dr. Peltz terminates his employment with us for good reason, in each case within six months prior to or 18 months following a corporate change, we are obligated to: pay Dr. Peltz a lump sum amount equal to his base salary for 24 months; accelerate in full the vesting of all of Dr. Peltz's outstanding equity awards; extend the exercise period of certain of Dr. Peltz's option awards, subject to specified limitations; pay Dr. Peltz his target annual bonus for the year in which he is terminated; and, to the extent allowed by applicable law and the applicable plan documents, continue to provide Dr. Peltz and certain of his dependents with group health insurance for a period of 24 months.

If under any circumstances we terminate Dr. Peltz's employment without cause or if Dr. Peltz terminates his employment with us for good reason, we are obligated to: engage Dr. Peltz as a consultant for up to 24 months, at his per-diem base salary rate immediately before termination of his employment plus reimbursement of reasonable out-of-pocket expenses, in order to transition Dr. Peltz's responsibilities as our chief executive officer to his successor; and, subject to specified limitations, permit Dr. Peltz to continue to purchase coverage under our group health insurance plan following the expiration of any benefits continuation provided by us as described above until such time as he is eligible for Medicare.

If under any circumstances Dr. Peltz terminates his employment with us for good reason, we are obligated to accelerate in full the outstanding unvested restricted stock awards that we granted to Dr. Peltz in March 2013. In the event of a change in control, regardless of whether Dr. Peltz's employment with us is terminated, we are obligated to accelerate 50% of Dr. Peltz's outstanding unvested option awards granted in May 2013 and 100% of Dr. Peltz's unvested restricted stock awards granted in March 2013.

In addition, we have agreed to indemnify Dr. Peltz in any action or proceeding arising out of his service to us, unless he initiates such action or proceeding. These indemnification obligations may require us, among other things, to indemnify Dr. Peltz for certain expenses, including attorneys' fees, that are incurred by him, and to advance to Dr. Peltz such expenses upon request.

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Other executive officers. For our executive officers other than Dr. Peltz, if we terminate an executive officer's employment without cause or if an executive officer terminates his or her employment with us for good reason, each as defined in such executive officer's employment agreement, in each case absent a change in control, or "corporate change", as defined the employment agreement, we are obligated to: pay such executive officer's base salary for a period of 12 months; to the extent allowed by applicable law and the applicable plan documents, continue to provide to such executive officer and certain of his or her dependents with group health insurance for a period of 12 months; and, upon a termination without cause only, accelerate in full the vesting of each executive officer's outstanding unvested restricted stock awards granted in March 2013.

If we terminate any such executive officer's employment without cause or if such executive officer terminates his or her employment with us for good reason, in each case within three months prior to or 12 months following a corporate change, we are obligated to: pay such executive officer a lump sum amount equal to his or her base salary for 12 months; to the extent allowed by applicable law and the applicable plan documents, continue to provide to such executive officer and certain of his or her dependents with group health insurance for a period of 12 months; accelerate in full the vesting of all outstanding equity awards held by such executive officer; and pay each such executive officer his or her target annual bonus for the year in which he or she is terminated.

In the event of a change in control, regardless of whether any executive officer's employment with us is terminated, we are obligated to accelerate 50% of each such executive officer's outstanding unvested option awards granted in May 2013 and 100% of each executive officer's outstanding unvested restricted stock awards granted in March 2013.

Taxation. To the extent that any severance or other compensation payment to any of our executive officers pursuant to an employment agreement or any other agreement constitutes an "excess parachute payment" within the meaning of Sections 280G and 4999 of the Internal Revenue Code of 1986, as amended, then such executive officer will receive the full amount of such severance and other payments, or a reduced amount intended to avoid the application of Sections 280G and 4999, whichever provides the executive with the highest amount on an after-tax basis.

Stock option and other compensation plans

The four equity incentive plans described in this section are the 1998 employee, director and consultant stock option plan, as amended and restated, or the 1998 plan, the 2009 plan, the 2013 plan and the 2013 long term incentive plan, or the 2013 public company plan. Prior to this offering, we granted awards to eligible participants under the 1998 plan, the 2009 plan and the 2013 plan. Following the closing of this offering, we expect to grant awards to eligible participants under the 2013 public company plan.

1998 employee, director and consultant stock option plan

The 1998 plan was adopted by our board of directors and approved by our stockholders. The 1998 plan provides for the grant of incentive stock options and non-statutory stock options. A maximum of 33,133 shares of our common stock are authorized for issuance under the 1998 plan.

In accordance with the terms of the 1998 plan, our board of directors has authorized our compensation committee to administer the plan.

The terms of awards under the 1998 plan are set forth in the applicable option certificates.

Under the 1998 plan, in the event of a stock dividend or stock split, the number of shares of common stock deliverable upon the exercise of options may be proportionately increased or decreased, with appropriate adjustments to the applicable exercise price.

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If a merger of our company or similar corporate event occurs, the administrator of the plan or the board of directors of the successor corporation, in its discretion, shall:

provide that the outstanding options under the 1998 plan be assumed or substituted by the successor corporation;

upon written notice to optionees, provide that all unexercised options will terminate, unless exercised, immediately prior to the consummation of such transaction; or

provide that all or any of the outstanding options will terminate in exchange for a cash payment equal to their value.

In the event of a recapitalization or other reorganization where securities of the company or another corporation are issued with respect to the outstanding shares of common stock, options are exercisable for securities that would have been received if such options had been exercised prior to such recapitalization or reorganization.

As of May 31, 2013, there were options to purchase 23,800 shares of our common stock outstanding under the 1998 plan, at a weighted-average exercise price of $400.88 per share, and options to purchase 1,057 shares of our common stock had been exercised. In August 2008, the 1998 plan expired and since then no further grants of stock options have been made under this plan. All shares available to grant under the 1998 plan automatically transferred to the 2009 plan at that time.

2009 equity and long term incentive plan

The 2009 plan was adopted by our board of directors in February 2009 and approved by our stockholders in March 2009. The 2009 plan provides for the grant of incentive stock options, nonstatutory stock options, restricted stock awards, restricted stock unit awards, stock appreciation rights and other stock-based and cash-based awards. Our employees, officers, directors, consultants and advisors are eligible to receive awards under our 2009 plan; however, incentive stock options may only be granted to our employees. Our board of directors administers the 2009 plan.

The maximum number of shares of our common stock with respect to which awards may be granted to any participant under the 2009 plan is 3,333 per year. No award may be granted under the 2009 stock plan after May 8, 2019, but the vesting and effectiveness of awards granted before that date may extend beyond that date. Our board of directors may amend, suspend or terminate the 2009 stock plan at any time, subject to applicable law or stock market requirements.

The 2009 plan provides that the number of shares of our common stock reserved for issuance under the plan is 2,506,666 shares (the initial number of shares provided to the plan), *plus* an annual evergreen equal to the lowest of 2,506,666 shares of our common stock, 4% of our shares of common stock outstanding on January 1 of each year (including all shares of common stock issuable upon conversion of shares of our preferred stock) and an amount determined by our board of directors, *plus* the sum (up to a maximum of 32,083 shares) of any shares of our common stock reserved for issuance under the 1998 plan and any shares of our common stock that have expired or terminated, or are otherwise surrendered, canceled, forfeited or repurchased by the company, pursuant to the 1998 plan.

Upon the occurrence of a fundamental event, as defined in the 2009 plan, our board of directors shall provide that all outstanding stock options be assumed, or substantially equivalent awards be substituted, by the acquiring or successor corporation (or an affiliate thereof). Restricted stock awards generally remain unchanged. Upon a change in control event, as defined in the 2009 plan, then, with respect to any unvested stock option, or restricted stock award, as applicable, one-half of the number of unvested shares subject to such option or restricted stock award, as applicable, shall vest and become immediately exercisable upon the occurrence of such change in control event and all remaining unvested shares subject

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to such option or restricted stock award, as applicable, shall continue to vest accordance with the original vesting schedule, provided that all such unvested shares shall become immediately vested and/or exercisable in full if, on or prior to the first anniversary of the date of the consummation of the change in control event, the participant's employment with us or the acquiring or succeeding corporation is terminated for good reason by the participant or without good cause by the company or acquiring or succeeding corporation (in each case as defined in the 2009 plan).

In the event the acquiring or successor corporation does not agree to assume, or substitute for, options granted under the 2009 plan, or in the event of a liquidation or dissolution of the company, our board of directors will provide that all unexercised options will become exercisable in full as of a specified time prior to the fundamental event and will terminate upon the consummation of such fundamental event unless exercised by the participant. In the event of a fundamental event where holders of our common stock will receive a cash payment for surrendering such shares, then our board of directors may instead provide that all outstanding options will terminate upon the consummation of such fundamental event and that each participant will receive a cash payment equal to the value of the participant's options.

In the event of a stock dividend, stock split or similar event, our board of directors will equitably adjust the terms of awards granted under the 2009 plan.

Our board of directors may at any time provide that any award will become immediately exercisable in full or in part, free of some or all restrictions or conditions, or otherwise realizable in full or in part, as the case may be.

As of May 31, 2013, there were options to purchase an aggregate of 2,021,323 shares of common stock, at a weighted average exercise price of $15.80 per share and 396,200 shares of restricted common stock outstanding under the 2009 plan, as well as an aggregate of 13 shares of common stock issued upon the exercise of options granted under the 2009 plan. If the 2013 public company plan is approved by our stockholders, we will grant no further stock options or other awards under the 2009 plan. However, any shares of common stock reserved for issuance under the 2009 plan that remain available for issuance and any shares of common stock subject to awards under the 2009 plan that expire, terminate, or are otherwise surrendered, canceled, forfeited or repurchased without having been fully exercised or resulting in any common stock being issued shall be available for grant under the 2013 public company plan up to a specified number of shares.

2013 stock incentive plan

The 2013 plan was adopted by our board of directors and approved by our stockholders on March 5, 2013. The 2013 plan provides for the grant of incentive stock options, nonstatutory stock options, restricted stock awards and other stock-based awards. A maximum of 739,937 shares of our common stock are authorized for issuance under the 2013 plan. Our employees, officers, directors, consultants and advisors are eligible to receive awards under the 2013 plan.

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Pursuant to the terms of the 2013 plan, our board of directors administers the plan and, subject to any limitations in the plan, selects the recipients of awards and determines:

- the number of shares of our common stock covered by options and the dates upon which the options become exercisable;
- the type of options to be granted;
- the duration of options, which may not be in excess of ten years;
- the exercise price of options, which must be at least equal to the fair market value of our common stock on the date of grant; and
- the number of shares of our common stock subject to and the terms of any stock appreciation rights, restricted stock awards, restricted stock units or other stock-based awards and the terms and conditions of such awards, including conditions for repurchase, issue price and repurchase price.

Upon a merger or other reorganization event, our board of directors may, in its sole discretion, take any one or more of the following actions pursuant to the 2013 plan as to some or all outstanding awards other than restricted stock:

- provide that all outstanding awards shall be assumed, or substantially equivalent awards shall be substituted, by the acquiring or successor corporation (or an affiliate thereof);
- upon written notice to a participant, provide that all of the participant's unexercised awards will terminate immediately prior to the consummation of such reorganization event unless exercised by the participant;
- provide that outstanding awards shall become exercisable, realizable or deliverable, or restrictions applicable to an award shall lapse, in whole or in part, prior to or upon such reorganization event;
- in the event of a reorganization event pursuant to which holders of shares of our common stock will receive a cash payment for each share surrendered in the reorganization event, make or provide for a cash payment to the participants with respect to each award held by a participant equal to (1) the number of shares of our common stock subject to the vested portion of the award (after giving effect to any acceleration of vesting that occurs upon or immediately prior to such reorganization event) multiplied by (2) the excess, if any, of the cash payment for each share surrendered in the reorganization event over the exercise, measurement or purchase price of such award and any applicable tax withholdings, in exchange for the termination of such award; and/or
- provide that, in connection with a liquidation or dissolution, awards shall convert into the right to receive liquidation proceeds.

Our board of directors does not need to take the same action with respect to all awards and may take different actions with respect to portions of the same award.

In the case of certain restricted stock units that are subject to Section 409A of the Internal Revenue Code, additional provisions of the 2013 plan apply in connection with reorganization events.

Upon the occurrence of a reorganization event other than a liquidation or dissolution, the repurchase and other rights with respect to outstanding awards of restricted stock will continue for the benefit of the successor company and will, unless the board of directors may otherwise determine, apply to the cash, securities or other property into which shares of our common stock are converted or exchanged pursuant to the reorganization event. Upon the occurrence of a reorganization event involving a liquidation or dissolution, all restrictions and conditions on each outstanding award of restricted stock will automatically

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be deemed terminated or satisfied, unless otherwise provided in the agreement evidencing the award of restricted stock.

At any time, our board of directors may, in its sole discretion, provide that any award under the 2013 plan will become immediately exercisable in full or in part, free of some or all restrictions or conditions, or otherwise realizable in full or in part.

No award may be granted under the 2013 plan on or after March 5, 2023. Our board of directors may amend, suspend or terminate the 2013 plan at any time, except that stockholder approval may be required to comply with applicable law or stock market requirements.

As of May 31, 2013, options to purchase 4,613 shares of our common stock, at a weighted average exercise price of $10.59, and 734,508 shares of restricted common stock were outstanding under the 2013 plan. If the 2013 public company plan is approved by our stockholders, we will grant no further stock options or other awards under the 2013 plan. However, any shares of common stock subject to awards under the 2013 plan that expire, terminate or are otherwise surrendered, canceled, forfeited or repurchased without having been fully exercised or resulting in any common stock being issued shall be available for grant under the 2013 public company plan up to a specified number of shares.

2013 long term incentive plan

In May 2013, our board of directors adopted, and our stockholders then approved, the 2013 public company plan, which will become effective immediately prior to the closing of this offering. The 2013 public company plan provides for the grant of incentive stock options, nonstatutory stock options, restricted stock awards and other stock-based awards. Upon effectiveness of the 2013 public company plan, the number of shares of our common stock that will be reserved for issuance under the 2013 public company plan will be the sum of (1) 122,296 shares of our common stock available for issuance under the 2009 plan and the 2013 plan plus (2) the number of shares (up to 3,040,444 shares) equal to the sum of the number of shares of our common stock subject to outstanding awards under the 1998 plan, the 2009 plan and the 2013 plan that expire, terminate or are otherwise surrendered, cancelled, forfeited or repurchased by us at their original issuance price pursuant to a contractual repurchase right plus (3) an annual increase, to be added on the first day of each fiscal year until the expiration of the 2013 public company plan, equal to the lowest of 2,500,000 shares of our common stock, 4% of the number of shares of our common stock outstanding on the first day of the fiscal year and an amount determined by our board of directors.

Our employees, officers, directors, consultants and advisors are eligible to receive awards under the 2013 public company plan. However, incentive stock options may only be granted to our employees.

Pursuant to the terms of the 2013 public company plan, our board of directors administers the plan and, subject to any limitations in the plan, selects the recipients of awards and determines:

- the number of shares of our common stock covered by options and the dates upon which the options become exercisable;
- the type of options to be granted;
- the duration of options, which may not be in excess of ten years;

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the exercise price of options, which must be at least equal to the fair market value of our common stock on the date of grant; and

the number of shares of our common stock subject to and the terms of any stock appreciation rights, restricted stock awards, restricted stock units or other stock-based awards and the terms and conditions of such awards, including conditions for repurchase, issue price and repurchase price.

If our board of directors delegates authority to an executive officer to grant awards under the 2013 public company plan, the executive officer has the power to make awards to all of our employees, except executive officers. Our board of directors will fix the terms of the awards to be granted by such executive officer, including the exercise price of such awards, and the maximum number of shares subject to awards that such executive officer may make.

Upon a merger or other reorganization event, our board of directors may, in its sole discretion, take any one or more of the following actions pursuant to the 2013 public company plan as to some or all outstanding awards other than restricted stock:

provide that all outstanding awards shall be assumed, or substantially equivalent awards shall be substituted, by the acquiring or successor corporation (or an affiliate thereof);

upon written notice to a participant, provide that all of the participant's unexercised awards will terminate immediately prior to the consummation of such reorganization event unless exercised by the participant;

provide that outstanding awards shall become exercisable, realizable or deliverable, or restrictions applicable to an award shall lapse, in whole or in part, prior to or upon such reorganization event;

in the event of a reorganization event pursuant to which holders of shares of our common stock will receive a cash payment for each share surrendered in the reorganization event, make or provide for a cash payment to the participants with respect to each award held by a participant equal to (1) the number of shares of our common stock subject to the vested portion of the award (after giving effect to any acceleration of vesting that occurs upon or immediately prior to such reorganization event) multiplied by (2) the excess, if any, of the cash payment for each share surrendered in the reorganization event over the exercise, measurement or purchase price of such award and any applicable tax withholdings, in exchange for the termination of such award; and/or

provide that, in connection with a liquidation or dissolution, awards shall convert into the right to receive liquidation proceeds.

Our board of directors does not need to take the same action with respect to all awards and may take different actions with respect to portions of the same award.

In the case of certain restricted stock units, no assumption or substitution is permitted, and the restricted stock units will instead be settled in accordance with the terms of the applicable restricted stock unit agreement.

Upon the occurrence of a reorganization event other than a liquidation or dissolution, the repurchase and other rights with respect to outstanding restricted stock awards will continue for the benefit of the successor company and will, unless the board of directors may otherwise determine, apply to the cash, securities or other property into which shares of our common stock are converted or exchanged pursuant to the reorganization event. Upon the occurrence of a reorganization event involving a liquidation or dissolution, all restrictions and conditions on each outstanding restricted stock award will automatically be

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deemed terminated or satisfied, unless otherwise provided in the agreement evidencing the restricted stock award.

At any time, our board of directors may, in its sole discretion, provide that any award under the 2013 public company plan will become immediately exercisable in full or in part, free of some or all restrictions or conditions, or otherwise realizable in full or in part.

No award may be granted under the 2013 public company plan on or after June 3, 2023. Our board of directors may amend, suspend or terminate the 2013 public company plan at any time, except that stockholder approval may be required to comply with applicable law or stock market requirements.

401(k) retirement plan

We maintain a 401(k) retirement plan that is intended to be a tax-qualified defined contribution plan under Section 401(k) of the Internal Revenue Code. In general, all of our employees are eligible to participate, beginning on the first day of the month following commencement of their employment. The 401(k) plan includes a salary deferral arrangement pursuant to which participants may elect to reduce their current compensation by up to the statutorily prescribed limit, equal to $17,500 in 2013, and have the amount of the reduction contributed to the 401(k) plan.

Limitations on liability and indemnification

Our certificate of incorporation, which will become effective upon the closing of this offering, limits the personal liability of directors for breach of fiduciary duty to the maximum extent permitted by the Delaware General Corporation Law and provides that no director will have personal liability to us or to our stockholders for monetary damages for breach of fiduciary duty or other duty as a director. However, these provisions do not eliminate or limit the liability of any of our directors:

- for any breach of the director's duty of loyalty to us or our stockholders;
- for acts or omissions not in good faith or that involve intentional misconduct or a knowing violation of law;
- for voting for or assenting to unlawful payments of dividends, stock repurchases or other distributions; or
- for any transaction from which the director derived an improper personal benefit.

Any amendment to or repeal of these provisions will not eliminate or reduce the effect of these provisions in respect of any act, omission or claim that occurred or arose prior to such amendment or repeal. If the Delaware General Corporation Law is amended to provide for further limitations on the personal liability of directors of corporations, then the personal liability of our directors will be further limited to the greatest extent permitted by the Delaware General Corporation Law.

In addition, our certificate of incorporation, which will become effective upon the closing of this offering, provides that we must indemnify our directors and officers and we must advance expenses, including attorneys' fees, to our directors and officers in connection with legal proceedings, subject to very limited exceptions.

We maintain a general liability insurance policy that covers certain liabilities of our directors and officers arising out of claims based on acts or omissions in their capacities as directors or officers. In addition, we have entered into indemnification agreements with our directors. These indemnification agreements may require us, among other things, to indemnify each such director for some expenses, including attorneys'

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fees, judgments, fines and settlement amounts incurred by him in any action or proceeding arising out of his service as one of our directors.

Certain of our non-employee directors may, through their relationships with their employers, be insured and/or indemnified against certain liabilities incurred in their capacity as members of our board of directors.

Rule 10b5-1 sales plans

Our directors and executive officers may adopt written plans, known as Rule 10b5-1 plans, in which they will contract with a broker to buy or sell shares of our common stock on a periodic basis. Under a Rule 10b5-1 plan, a broker executes trades pursuant to parameters established by the director or officer when entering into the plan, without further direction from the director or officer. The director or officer may amend or terminate the plan in some circumstances. Our directors and executive officers may also buy or sell additional shares outside of a Rule 10b5-1 plan when they are not in possession of material, nonpublic information.

Director compensation

Dr. Peltz, one of our directors who also serves as our Chief Executive Officer, does not receive any additional compensation for his service as a director.

Our non-employee directors are compensated for their services on our board of directors as follows:

- each non-employee director receives an annual retainer of an option to purchase 83 shares of our common stock; and
- each non-employee directors who serves as chairman of the board of directors, chairman of a committee of the board or a member of a committee of the board, receives additional equity compensation as follows:
  - chairman of the board an additional annual stock option to purchase shares of our common stock having a value on the date of grant of $25,000;
  - chairman of the audit committee, compensation committee or the nominating and corporate governance committee with respect to each such position, an additional annual stock option to purchase shares of our common stock having a value on the date of grant of $5,000; and
  - member of the audit committee, compensation committee or the nominating and corporate governance committee with respect to each such membership, an additional annual stock option to purchase shares of our common stock having a value on the date of grant of $2,500.

The stock options granted to our non-employee directors have an exercise price equal to the fair market value of our common stock on the date of grant, expire ten years after the date of grant, subject to the director's continued service on our board, and are exercisable quarterly over a three year period from the date of grant.

Each member of our board of directors is also entitled to be reimbursed for reasonable travel and other expenses incurred in connection with attending meetings of the board of directors and any committee on which he or she serves.

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For the year ended December 31, 2012, the only compensation we awarded or paid to our directors, other than Dr. Peltz, were stock option awards, as set forth in the following table.

Name	Option award ($)(1)
Michael Schmertzler	43,688
Axel Bolte	16,054
Soren Carlsen, Ph.D.(2)	
Allan Jacobson, Ph.D.	13,159
Michael Kranda	14,606
Geoffrey McDonough, M.D.	
Deepa Pakianathan, Ph.D.(2)	13,159
David Southwell	17,501
Peter Svennilson(2)	21,186
Jerome Zeldis, M.D., Ph.D.	
Carl Goldfischer, M.D.	17,501

(1) The amounts reported in this column represent the aggregate grant date fair value of the options granted to our non-employee directors during 2012 computed in accordance with ASC 718. See Note 2 to the financial statements included at the end of this prospectus regarding assumptions underlying the valuation of equity awards.

(2) Drs. Carlsen and Pakianathan and Mr. Svennilson resigned from our board of directors on March 7, 2013.

In March 2013, our board of directors granted restricted stock awards and stock options to certain of our directors, pursuant to our 2013 stock incentive plan as follows:

Name	Stock award (#)(1)	Option award (#)(2)	Grant date fair value ($)(3)
Deepa Pakianathan, Ph.D.(4)		3,637	26,256
Allan Jacobson, Ph.D.	38,080		403,267
Michael Kranda	5,928		62,778
Geoffrey McDonough, M.D.	909		9,626
Michael Schmertzler	26,766		283,452
David Southwell	13,238		140,190
Peter Svennilson(4)		976	7,045

(1) The restricted stock reported in this column vests as to 50% of the award on each of the first and second anniversary of the date of grant.

(2) The options reported in this column were fully vested on the date of grant.

(3) See Note 2 to the financial statements included at the end of this prospectus regarding assumptions underlying the valuation of equity awards.

(4) Dr. Pakianathan and Mr. Svennilson resigned from our board of directors on March 7, 2013.

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In May 2013, our board of directors granted stock options to our directors pursuant to our 2009 plan as follows:

Name	Option award (#)(1)	Exercise price per share ($)	Grant date fair value ($)
Richard Aldrich	20,000	10.85	(2)
Allan Jacobson, Ph.D.	63,000	10.85	(2)
Adam Koppel, M.D., Ph.D.	20,000	10.85	(2)
Michael Kranda	20,000	10.85	(2)
Geoffrey McDonough, M.D.	30,000	10.85	(2)
Michael Schmertzler	60,000	10.85	(2)
David Southwell	30,000	10.85	(2)

(1) The option awards reported in this column vest as to 8.33% of the original number of shares underlying such options at the end of each successive three-month period following the date of grant.

(2) The amounts reported in this column represent the aggregate grant date fair value of the options granted to our directors, computed in accordance with ASC 718. The fair value per share of the option awards granted on May 15, 2013 will be calculated in connection with the preparation of our unaudited financial statements for the three months ended June 30, 2013.

Effective upon the closing of this offering, our non-employee directors will be compensated for their service on our board of directors as follows:

- an annual retainer for board service of $35,000;
- for any newly elected non-employee director, an option grant to purchase 20,000 shares of our common stock, which will vest annually over three years;
- an annual option grant to purchase 10,000 shares of our common stock, which will vest in full on the first anniversary of the date of grant;
- for the chairman of our board of directors, an additional annual option grant to purchase 10,000 shares of our common stock, which will vest in full on the first anniversary of the date of grant;
- for members of the audit committee, an additional annual retainer of $8,000 ($16,000 for the chair);
- for members of the compensation committee, an additional annual retainer of $5,000 ($10,000 for the chair); and
- for members of the nominating and corporate governance committee, an additional annual retainer of $3,000 ($6,000 for the chair).

The stock options granted to our non-employee directors will have an exercise price equal to the fair market value of our common stock on the date of grant and will expire ten years after the date of grant, subject to the director's continued service on our board.

Each member of our board of directors will also be entitled to reimbursement for reasonable travel and other expenses incurred in connection with attending meetings of the board of directors and any committee on which he or she serves.

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Transactions with related persons

Since January 1, 2010, we have engaged in the following transactions with our directors, executive officers and holders of more than 5% of our voting securities, and affiliates of our directors, executive officers and holders of more than 5% of our voting securities. We believe that all of these transactions were on terms as favorable as could have been obtained from unrelated third parties.

Series four senior preferred stock financing and reclassification of outstanding preferred stock

In March 2013, we issued and sold an aggregate of 4,497,035 shares of our series four senior preferred stock, at a price per share of $12.00, for an aggregate purchase price of $53,964,420. In addition, we issued an aggregate of 502,919 shares of our series four senior preferred stock upon conversion of the convertible promissory notes described below that we originally issued in January and February 2013. The following table sets forth the number of shares of our series four senior preferred stock purchased by our directors, executive officers and 5% stockholders and their affiliates and the number of shares of our series four senior preferred stock that we issued to our directors, executive officers and 5% stockholders and their affiliates upon conversion of the convertible promissory notes described below.

Name	Shares of series four senior preferred stock purchased	Shares of series four senior preferred stock issued upon conversion of convertible promissory notes
Credit Suisse First Boston Equity Partners, L.P. and affiliates(1)	165,464	111,389
HBM Healthcare Investments (Cayman) Ltd.(2)	187,220	92,958
Vulcan Ventures Incorporated and affiliates(3)	114,608	68,725
Brookside Capital Partners Fund, L.P.(4)	1,083,333	
Celgene European Investment Company LLC and affiliate(5)	76,915	51,778
Delphi Ventures and affiliates(6)		50,058
Section Six Partners, L.P.(7)	103,819	51,547

(1) Consists of (i) 129,220 shares purchased and 86,989 shares issued upon conversion of convertible promissory notes held by Credit Suisse First Boston Equity Partners, L.P.; (ii) 36,120 shares purchased and 24,316 shares issued upon conversion of convertible promissory notes held by Credit Suisse First Boston Equity Partners (Bermuda), L.P.; and (iii) 124 shares purchased and 84 shares issued upon conversion of convertible promissory notes held by Credit Suisse First Boston U.S. Executive Advisors, L.P. Mr. Schmertzler, a member of our board of directors, is a Managing Director of Aries Advisors, LLC, the sub-advisor to Credit Suisse First Boston Equity Partners, L.P. and affiliates. Mr. Schmertzler disclaims beneficial ownership of the shares held by entities affiliated with Credit Suisse First Boston Equity Partners, L.P. and affiliates except to the extent of any pecuniary interest therein.

(2) The board of directors of HBM Healthcare Investments (Cayman) Ltd. has sole voting and investment power with respect to the shares by held by such entity. The board of directors of HBM Healthcare Investments (Cayman) Ltd. is comprised of John Arnold, Richard Coles, Sophia Harris, Dr. Andreas Wicki and John Urquhart, none of whom has individual voting or investment power with respect to such shares, and each disclaims beneficial ownership of such shares except to the extent of any pecuniary interest therein. Mr. Bolte, a member of our board of directors, is an advisor to HBM Partners (Cayman) Ltd. HBM Partners (Cayman) Ltd. provides investment management services to HBM Healthcare Investments (Cayman) Ltd. Mr. Bolte has no voting or investment power over the shares held by HBM Healthcare Investments (Cayman) Ltd., and disclaims beneficial ownership of such shares except to the extent of any pecuniary interest therein.

(3) Consists of shares held by VCVC III LLC. Mr. Kranda, a member of our board of directors, is a consultant to Vulcan Capital Venture Capital I LLC. VCVC III LLC and Vulcan Capital Venture Capital I LLC are each controlled by entities owned by Paul Allen. Mr. Kranda does not have voting or investment power over the shares held by Vulcan Ventures Incorporated and its affiliates, and disclaims beneficial ownership of such shares except to the extent

of any pecuniary interest therein.

(4) Dr. Koppel, a member of our board of directors, is a Managing Director of Brookside Capital, LLC, the investment advisor to Brookside Capital Partners Fund, L.P., Dr. Koppel disclaims beneficial ownership of the shares held by Brookside Capital Partners Fund, L.P. except to the extent of any pecuniary interest therein.

(5) Consists of (i) 76,915 shares purchased by Celgene European Investment Company LLC and (ii) 51,778 shares issued upon conversion of convertible promissory notes held by Celgene Corporation. Dr. Zeldis, a member of our board of directors, is an employee of Celgene

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Corporation. Celgene European Investment Company LLC is a wholly owned subsidiary of Celgene Corporation. Dr. Zeldis disclaims beneficial ownership of the shares held by Celgene European Investment Company LLC and Celgene Corporation except to the extent of any pecuniary interest therein.

(6) Consists of (i) 31,306 shares issued to Delphi Ventures V, L.P.; (ii) 339 shares issued to Delphi BioInvestments V, L.P.; (iii) 9,115 shares issued to Delphi Ventures VII, L.P.; (iv) 91 shares issued to Delphi BioInvestments VII, L.P.; (v) 9,118 shares issued to Delphi Ventures VIII, L.P.; and (vi) 89 shares issued to Delphi BioInvestments VIII, L.P.

(7) Mr. Schmertzler is a general and limited partner of, and trustee of certain family trusts holding interests in, Section Six Partners, L.P., and disclaims beneficial ownership of the shares held by Section Six Partners, L.P. except to the extent of any pecuniary interest therein.

In connection with the series four senior preferred stock financing, we effected a one-for-120 reverse stock split of our common stock and a reclassification of our previously outstanding preferred stock into an aggregate of 6,700,487 shares of series five junior preferred stock. In addition, we issued an aggregate of 2,095,515 shares of our series five junior preferred stock upon the automatic exercise of the preferred stock warrants described below that we originally issued in January 2013. The following table sets forth the number of shares of our series five junior preferred stock that we issued to our directors, executive officers and 5% stockholders and their affiliates upon the reclassification of our previously outstanding preferred stock and the number of shares of our series five junior preferred stock that we issued to our directors, executive officers and 5% stockholders and their affiliates upon the automatic exercise of the preferred stock warrants described below.

Name	Shares of series five junior preferred stock issued upon reclassification of outstanding preferred stock	Shares of series five junior preferred stock issued upon automatic exercise of preferred stock warrants
Credit Suisse First Boston Equity Partners, L.P. and affiliates(1)	1,515,800	464,229
HBM Healthcare Investments (Cayman) Ltd.(2)	1,173,898	387,419
Vulcan Ventures Incorporated and affiliates(3)	898,664	286,401
Celgene European Investment Company LLC and affiliate(4)	726,725	215,794
Delphi Ventures and affiliates(5)	697,108	208,600
Section Six Partners, L.P.(6)	394,166	214,504

(1) Consists of (i) 1,180,858 shares issued upon reclassification and 362,542 shares issued upon automatic exercise held by Credit Suisse First Boston Equity Partners, L.P.; (ii) 330,081 shares issued upon reclassification and 101,338 shares issued upon automatic exercise held by Credit Suisse First Boston Equity Partners (Bermuda), L.P.; (iii) 1,140 shares issued upon reclassification and 349 shares issued upon automatic exercise held by Credit Suisse First Boston U.S. Executive Advisors, L.P.; (iv) 234 shares issued upon automatic exercise held by Credit Suisse First Boston Finders & Screeners LP; and (v) 3,487 shares issued upon reclassification held by EMA Private Equity Fund 1999, LP. Mr. Schmertzler, a member of our board of directors, is a Managing Director of Aries Advisors, LLC, the sub-advisor to Credit Suisse First Boston Equity Partners, L.P. and affiliates. Mr. Schmertzler disclaims beneficial ownership of the shares held by entities affiliated with Credit Suisse First Boston Equity Partners, L.P. and affiliates except to the extent of any pecuniary interest therein.

(2) The board of directors of HBM Healthcare Investments (Cayman) Ltd. has sole voting and investment power with respect to the shares by held by such entity. The board of directors of HBM Healthcare Investment (Cayman) Ltd. is comprised of John Arnold, Richard Coles, Sophia Harris, Dr. Andreas Wicki and John Urquhart, none of whom has individual voting or investment power with respect to such shares, and each disclaims beneficial ownership of such shares except to the extent of any pecuniary interest therein. Mr. Bolte, a member of our board of

directors, is an advisor to HBM Partners (Cayman) Ltd. HBM Partners (Cayman) Ltd. provides investment management services to HBM Healthcare Investments (Cayman) Ltd. Neither HBM Partners AG nor Mr. Bolte has no voting or investment power over the shares held by HBM Healthcare Investments (Cayman) Ltd., and disclaims beneficial ownership of such shares except to the extent of any pecuniary interest therein.

(3) Consists of 101,562 shares issued upon reclassification held by Vulcan Ventures Incorporated; (ii) 797,102 shares issued upon reclassification held by Vulcan Capital Venture Capital I LLC; and (iii) 286,401 shares issued upon automatic exercise held by VCVC III LLC. Mr. Kranda, a member of our board of directors, is a consultant to Vulcan Capital Venture Capital I LLC. Vulcan Capital Venture Capital I LLC, VCVC III LLC, and Vulcan Ventures Incorporated are each controlled by entities owned by Paul Allen. Mr. Kranda does not have voting or investment power over the shares held by Vulcan Ventures Incorporated and its affiliates, and disclaims beneficial ownership of such shares except to the extent of any pecuniary interest therein.

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(4) Consists of (i) 726,725 shares issued upon reclassification held by Celgene European Investment Company LLC and (ii) 215,794 shares issued upon automatic exercise held by Celgene Corporation. Dr. Zeldis, a member of our board of directors, is an employee of Celgene Corporation. Celgene European Investment Company LLC is a wholly owned subsidiary of Celgene Corporation. Dr. Zeldis disclaims beneficial ownership of the shares held by Celgene European Investment Company LLC and Celgene Corporation except to the extent of any pecuniary interest therein.

(5) Consists of (i) 412,965 shares issued upon reclassification and 130,465 shares issued upon automatic exercise held by Delphi Ventures V, L.P.; (ii) 4,475 shares issued upon reclassification and 1,411 shares issued upon automatic exercise held by Delphi BioInvestments V, L.P.; (iii) 138,448 shares issued upon reclassification and 37,982 shares issued upon automatic exercise held by Delphi Ventures VII, L.P.; (iv) 1,384 shares issued upon reclassification and 378 shares issued upon automatic exercise held by Delphi BioInvestments VII, L.P.; (v) 138,483 shares issued upon reclassification and 37,994 shares issued upon automatic exercise held by Delphi Ventures VIII, L.P.; and (vi) 1,353 shares issued upon reclassification and 370 shares issued upon automatic exercise held by Delphi BioInvestments VIII, L.P.

(6) Mr. Schmertzler is a general and limited partner of, and trustee of certain family trusts holding interests in, Section Six Partners, L.P., and disclaims beneficial ownership of the shares held by Section Six Partners, L.P. except to the extent of any pecuniary interest therein.

Bridge financing

In January and February 2013, we issued convertible promissory notes in an aggregate principal amount of $6,000,000. In connection with this bridge financing, we also issued to the holders of the promissory notes warrants to purchase an aggregate of 515,186 shares of our series one preferred stock, at an exercise price of $0.01 per share, and warrants to purchase an aggregate of 2,012,489 shares of our series two preferred stock, an exercise price of $0.01 per share. The following table sets forth the principal amount of the promissory notes and the number of series two warrants and series three warrants that we issued to our directors, executive officers and 5% stockholders and their affiliates.

Name	Aggregate principal amount of promissory notes	Warrants to purchase shares of series one preferred stock(1)	Warrants to purchase shares of series two preferred stock(1)
Credit Suisse First Boston Equity Partners, L.P. and affiliates(2)	$ 1,329,182	114,131	445,828
HBM Healthcare Investments (Cayman) Ltd.(3)	1,109,250	95,247	372,061
Vulcan Ventures Incorporated and affiliates(4)	820,021	70,412	275,048
Celgene Corporation(5)	617,860	53,053	207,240
Delphi Ventures and affiliates(6)	597,299	51,285	200,342
Section Six Partners, L.P.(7)	614,172	52,736	206,003

(1) In connection with the recapitalization and reverse stock split described above, the warrants described in the table above were automatically adjusted to be exercisable into shares of our series five preferred stock at the applicable conversion ratio.

(2) Consists of (i) $1,038,024 principal amount of notes, 89,131 series one warrants, and 348,170 series two warrants held by Credit Suisse First Boston Equity Partners, L.P.; (ii) $290,154 principal amount of notes, 24,914 series one warrants, and 97,322 series two warrants held by Credit Suisse First Boston Equity Partners (Bermuda), L.P.; and (iii) $1,004 principal amount of notes, 86 series one warrants, and 336 series two warrants held by Credit Suisse First Boston U.S. Executive Advisors, L.P. Mr. Schmertzler, a member of our board of directors, is a

Managing Director of Aries Advisors, LLC, the sub-advisor to Credit Suisse First Boston Equity Partners, L.P. and affiliates, who disclaims beneficial ownership of the shares held by entities affiliated with Credit Suisse First Boston Equity Partners, L.P. and affiliates except to the extent of any pecuniary interest therein.

(3) The board of directors of HBM Healthcare Investments (Cayman) Ltd. has sole voting and investment power with respect to the shares by held by such entity. The board of directors of HBM Healthcare Investments (Cayman) Ltd. is comprised of John Arnold, Richard Coles, Sophia Harris, Dr. Andreas Wicki and John Urquhart, none of whom has individual voting or investment power with respect to such shares, and each disclaims beneficial ownership of such shares except to the extent of any pecuniary interest therein. Mr. Bolte, a member of our board of directors, is an advisor to HBM Partners (Cayman) Ltd. HBM Partners (Cayman) Ltd. provides investment management services to HBM Healthcare Investments (Cayman) Ltd. Mr. Bolte has no voting or investment power over the shares held by HBM Healthcare Investments (Cayman) Ltd., and disclaims beneficial ownership of such shares except to the extent of any pecuniary interest therein.

(4) Consists of notes and warrants held by VCVC III LLC. Mr. Kranda, a member of our board of directors, is a consultant to Vulcan Capital Venture Capital I LLC. VCVC III LLC and Vulcan Capital Venture Capital I LLC controlled by entities owned by Paul Allen. Mr. Kranda does not have voting or investment power over the shares held by Vulcan Ventures Incorporated and its affiliates, and disclaims beneficial ownership of such shares except to the extent of any pecuniary interest therein.

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(5) Dr. Zeldis, a member of our board of directors, is an employee of Celgene Corporation. Celgene European Investment Company LLC is a wholly owned subsidiary of Celgene Corporation. Dr. Zeldis disclaims beneficial ownership of the shares held by Celgene Corporation except to the extent of any pecuniary interest therein.

(6) Consists of (i) $373,548 principal amount of notes, 32,075 series one warrants, and 125,294 series two warrants held by Delphi Ventures V, L.P.; (ii) $4,050 principal amount of notes, 347 series one warrants, and 1,358 series two warrants held by Delphi BioInvestments V, L.P.; (iii) $108,761 principal amount of notes, 9,338 series one warrants, and 36,480 series two warrants held by Delphi Ventures VII, L.P.; (iv) $1,088 principal amount of notes, 93 series one warrants, and 364 series two warrants held by Delphi BioInvestments VII, L.P.; (v) $108,790 principal amount of notes, 9,341 series one warrants, and 36,490 series two warrants held by Delphi Ventures VIII, L.P.; and (vi) $1,062 principal amount of notes, 91 series one warrants, and 356 series two warrants held by Delphi BioInvestments VIII, L.P.

(7) Mr. Schmertzler is a general and limited partner of, and trustee of certain family trusts holding interests in, Section Six Partners, L.P., and disclaims beneficial ownership of the shares held by Section Six Partners, L.P. except to the extent of any pecuniary interest therein.

In connection with the series four senior preferred stock financing, the outstanding convertible promissory notes converted into an aggregate of 502,919 shares of series four senior preferred stock and the outstanding warrants for series one preferred stock and series two preferred stock were automatically exercised for an aggregate of 2,095,515 shares of series five junior preferred stock.

Series one preferred stock financing and reclassification of outstanding preferred stock

In May and July 2012, we issued and sold an aggregate of 1,483,337 shares of our series one preferred stock, at a price per share of $20.00, for an aggregate purchase price of $29,666,740. In connection with the series one preferred stock financing, we also effected a reclassification of our previously outstanding preferred stock into an aggregate of 10,701,405 shares of series two preferred stock and 2,853,517 shares of series three preferred stock. Stockholders who participated in the series one preferred stock financing received series two preferred stock following the reclassification of our outstanding preferred stock. The following table sets forth the number of shares of our series one preferred stock purchased by our directors, executive officers and 5% stockholders and their affiliates and the number of shares of our series two preferred stock that we issued to our directors, executive officers and 5% stockholders and their affiliates upon the reclassification of our previously outstanding preferred stock.

Name	Shares of series one preferred stock purchased	Shares of series two preferred stock issued upon reclassification of outstanding preferred stock
Credit Suisse First Boston Equity Partners, L.P.(1)	328,604	2,706,450
HBM Healthcare Investments (Cayman) Ltd.(2)	274,232	1,529,875
Vulcan Ventures Incorporated and affiliates(3)	202,728	1,377,780
Celgene European Investment Company LLC(4)	152,749	1,435,000
Delphi Ventures and affiliates(5)	147,666	1,343,826
Section Six Partners, L.P.(6)	110,000	

(1) Consists of (i) 256,623 shares purchased and 2,090,351 shares issued upon reclassification held by Credit Suisse First Boston Equity Partners, L.P.; (ii) 71,733 shares purchased and 584,305 shares issued upon reclassification held by Credit Suisse First Boston Equity Partners (Bermuda), L.P.; (iii) 248 shares purchased and 2,019 shares issued upon reclassification held by Credit Suisse First Boston U.S. Executive Advisors, L.P. (iv) 1,875 shares issued upon reclassification held by Credit Suisse First Boston Finders & Screeners LP; and (v) 27,900 shares issued upon reclassification held by EMA Private Equity Fund 1999, LP. Mr. Schmertzler, a member of our board of directors, is a

Managing Director of Aries Advisors, LLC, the sub-advisor to Credit Suisse First Boston Equity Partners, L.P. and affiliates. Mr. Schmertzler disclaims beneficial ownership of the shares held by entities affiliated with Credit Suisse First Boston Equity Partners, L.P. and affiliates except to the extent of any pecuniary interest therein.

(2) The board of directors of HBM Healthcare Investments (Cayman) Ltd. has sole voting and investment power with respect to the shares by held by such entity. The board of directors of HBM Healthcare Investments (Cayman) Ltd. is comprised of John Arnold, Richard Coles, Sophia Harris, Dr. Andreas Wicki and John Urquhart, none of whom has individual voting or investment power with respect to such shares, and each

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disclaims beneficial ownership of such shares except to the extent of any pecuniary interest therein. Mr. Bolte, a member of our board of directors, is an advisor to HBM Partners (Cayman) Ltd. HBM Partners (Cayman) Ltd. provides investment management services to HBM Healthcare Investments (Cayman) Ltd. Mr. Bolte has no voting or investment power over the shares held by HBM Healthcare Investments (Cayman) Ltd., and disclaims beneficial ownership of such shares except to the extent of any pecuniary interest therein.

(3) Consists of (i) 812,500 shares issued upon reclassification held by Vulcan Ventures Incorporated and (ii) 202,728 shares purchased and 565,280 shares issued upon reclassification held by Vulcan Capital Venture Capital I LLC. Mr. Kranda, a member of our board of directors, is a consultant to Vulcan Incorporated Capital Venture Capital I LLC. Vulcan Ventures Incorporated and Vulcan Capital Venture Capital I LLC are each controlled by entities owned by Paul Allen. Mr. Kranda does not have voting or investment power over the shares held by Vulcan Ventures and its affiliates, and disclaims beneficial ownership of such shares except to the extent of any pecuniary interest therein.

(4) Dr. Zeldis, a member of our board of directors, is an employee of Celgene Corporation. Celgene European Investment Company LLC is a wholly owned subsidiary of Celgene Corporation. Dr. Zeldis disclaims beneficial ownership of the shares held by Celgene European Investment Company LLC except to the extent of any pecuniary interest therein.

(5) Consists of (i) 92,350 shares purchased and 656,367 shares issued upon reclassification held by Delphi Ventures V, L.P.; (ii) 1,001 shares purchased and 7,115 shares issued upon reclassification held by Delphi BioInvestments V, L.P.; (iii) 26,888 shares purchased and 336,804 shares issued upon reclassification held by Delphi Ventures VII, L.P.; (iv) 269 shares purchased and 3,368 shares issued upon reclassification held by Delphi BioInvestments VII, L.P.; (v) 26,895 shares purchased and 336,882 shares issued upon reclassification held by Delphi Ventures VIII, L.P.; and (vi) 263 shares purchased and 3,290 shares issued upon reclassification held by Delphi BioInvestments VIII, L.P.

(6) Mr. Schmertzler is a general and limited partner of, and trustee of certain family trusts holding interests in, Section Six Partners, L.P. Mr. Schmertzler disclaims beneficial ownership of the shares held by Section Six Partners, L.P. except to the extent of any pecuniary interest therein.

Placement agent fees

In connection with our series four preferred stock financing, including our issuance of an additional 375,000 shares of our series four senior preferred stock in May 2013, we paid Credit Suisse Securities (USA) LLC an aggregate fee of $2,598,977 for its service as a placement agent for the transaction. Credit Suisse Securities (USA) LLC is an affiliate of Credit Suisse First Boston Equity Partners, L.P. and affiliated funds, which together hold more than 5% of our voting securities.

Asset purchase agreement with VivoMetrics

In March 2010, we entered into an asset purchase agreement with VivoMetrics, Inc., pursuant to which we purchased certain of VivoMetrics's inventory for the conduct of our then-ongoing clinical trials for an aggregate purchase price of $275,000. Credit Suisse First Boston Equity Partners, L.P., a 5% stockholder of ours, and certain of its affiliates owned stock in, and were affiliates of, VivoMetrics.

Familial relationship

Ellen Welch, Ph.D., the domestic partner of Stuart W. Peltz, our Chief Executive Officer, is employed by us as a Director, Biology. In 2012, Dr. Welch received an annual base salary of $161,630 and a performance bonus of $22,850, and we granted her an option to purchase 38 shares of our common stock at an exercise price of $218.40 per share. In 2011, Dr. Welch received an annual base salary of $155,780 and a performance bonus of $24,850, and we granted her an option to purchase 58 shares of our common stock at an exercise price of $490.80 per share. In 2010, Dr. Welch received an annual base salary of $144,010 and a performance bonus of $21,420, and we granted her an option to

purchase 37 shares of our common stock at an exercise price of $1,149.60 per share. In March 2013, we granted Dr. Welch a restricted stock award of 9,753 shares of our common stock. In May 2013, we granted Dr. Welch a restricted stock award of 7,800 shares of our common stock and an option to purchase 3,900 shares of our common stock at an exercise price of $10.85 per share. Dr. Peltz does not participate in the supervision of or compensation decisions regarding Dr. Welch, and we believe her compensation is fair and commensurate with what her compensation would be if she had no relationship to Dr. Peltz.

Participation in this offering

Brookside Capital Partners Fund, L.P., HBM Healthcare Investments (Cayman) Ltd., Section Six Partners, L.P., Longwood Fund, L.P. and Vulcan Ventures Incorporated, which are existing principal

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stockholders of ours or their affiliates and entities affiliated with certain of our directors, have agreed to purchase an aggregate of 3,250,000 shares of our common stock in this offering at the initial public offering price in the following amounts: Brookside Capital Partners Fund, L.P.: 1,250,000 shares; HBM Healthcare Investments (Cayman) Ltd.: 666,667 shares; Section Six Partners, L.P.: 533,333 shares; Longwood Fund, L.P.: 466,667 shares; and Vulcan Ventures Incorporated: 333,333 shares.

Registration rights

We are a party to an investors' rights agreement with the holders of our preferred stock, including some of our directors and 5% stockholders and their affiliates and entities affiliated with our directors. The investors' rights agreement provides these holders the right, following the completion of this offering, to demand that we file a registration statement or request that their shares be covered by a registration statement that we are otherwise filing. See "Description of capital stock registration rights" for additional information regarding these registration rights.

Indemnification agreements

Our certificate of incorporation in effect upon the closing of this offering provides that we will indemnify our directors and officers to the fullest extent permitted by Delaware law. In addition, we have entered into indemnification agreements with our directors. See "Executive compensation limitation of liability and indemnification" for additional information regarding these agreements.

Policies and procedures for related person transactions

Our board of directors has adopted written policies and procedures for the review of any transaction, arrangement or relationship in which PTC is a participant, the amount involved exceeds $120,000 and one of our executive officers, directors, director nominees or 5% stockholders, or their immediate family members, each of whom we refer to as a "related person," has a direct or indirect material interest.

If a related person proposes to enter into such a transaction, arrangement or relationship, which we refer to as a "related person transaction," the related person must report the proposed related person transaction to our Chief Legal Officer. The policy calls for the proposed related person transaction to be reviewed and, if deemed appropriate, approved by our audit committee. Whenever practicable, the reporting, review and approval will occur prior to entry into the transaction. If advance review and approval is not practicable, the committee will review, and, in its discretion, may ratify the related person transaction. The policy also permits the chairman of the audit committee to review and, if deemed appropriate, approve proposed related person transactions that arise between committee meetings, subject to ratification by the committee at its next meeting. Any related person transactions that are ongoing in nature will be reviewed annually.

A related person transaction reviewed under the policy will be considered approved or ratified if it is authorized by the audit committee after full disclosure of the related person's interest in the transaction. As appropriate for the circumstances, the committee will review and consider:

- the related person's interest in the related person transaction;
- the approximate dollar value of the amount involved in the related person transaction;
- the approximate dollar value of the amount of the related person's interest in the transaction without regard to the amount of any profit or loss;
- whether the transaction was undertaken in the ordinary course of our business;

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whether the terms of the transaction are no less favorable to us than terms that could have been reached with an unrelated third party;

the purpose of, and the potential benefits to us of, the transaction; and

any other information regarding the related person transaction or the related person in the context of the proposed transaction that would be material to investors in light of the circumstances of the particular transaction.

The audit committee may approve or ratify the transaction only if the committee determines that, under all of the circumstances, the transaction is in our best interests. The committee may impose any conditions on the related person transaction that it deems appropriate.

In addition to the transactions that are excluded by the instructions to the SEC's related person transaction disclosure rule, our board of directors has determined that the following transactions do not create a material direct or indirect interest on behalf of related persons and, therefore, are not related person transactions for purposes of this policy:

interests arising solely from the related person's position as an executive officer of another entity (whether or not the person is also a director of such entity) that is a participant in the transaction, where (a) the related person and all other related persons own in the aggregate less than a 10% equity interest in such entity, (b) the related person and his or her immediate family members are not involved in the negotiation of the terms of the transaction and do not receive any special benefits as a result of the transaction and (c) the amount involved in the transaction is less than the greater of $200,000 or 5% of the annual gross revenues of the company receiving payment under the transaction; and

a transaction that is specifically contemplated by provisions of our charter or bylaws.

The policy provides that transactions involving compensation of executive officers shall be reviewed and approved by the compensation committee in the manner specified in its charter.

We did not have a written policy regarding the review and approval of related person transactions prior to this offering. Nevertheless, with respect to such transactions, it was our policy for our board of directors to consider the nature of and business reason for such transactions, how the terms of such transactions compared to those which might be obtained from unaffiliated third parties and whether such transactions were otherwise fair to and in the best interests of, or not contrary to, our best interests. In addition, all related person transactions required prior approval, or later ratification, by our board of directors.

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Principal stockholders

The following table sets forth information with respect to the beneficial ownership of our common stock as of May 31, 2013 by:

- each of our directors;
- each of our named executive officers;
- all of our directors and executive officers as a group; and
- each person, or group of affiliated persons, who is known by us to beneficially own more than 5% of our common stock.

The column entitled "Percentage of shares beneficially owned before offering" is based on a total of 15,306,190 shares of our common stock outstanding as of May 31, 2013, including 14,170,956 shares of our common stock issuable upon the automatic conversion of all outstanding shares of our preferred stock upon the closing of this offering. The column entitled "Percentage of shares beneficially owned after offering" is based on shares of our common stock to be outstanding after this offering, including the 8,372,000 shares of our common stock that we are selling in this offering, but not including any additional shares issuable upon exercise of outstanding options or warrants.

Beneficial ownership is determined in accordance with the rules and regulations of the SEC and includes voting or investment power with respect to our common stock. Shares of our common stock subject to options or warrants that are currently exercisable or exercisable within 60 days of May 31, 2013 are considered outstanding and beneficially owned by the person holding the options or warrants for the purpose of calculating the percentage ownership of that person but not for the purpose of calculating the percentage ownership of any other person. Except as otherwise noted, the persons and entities in this table have sole voting and investing power with respect to all of the shares of our common stock beneficially owned by them, subject to community property laws, where applicable. The table below does not reflect any shares of our common stock that our directors and executive officers may purchase in this offering, including through the directed share program, as described in the "Underwriting" section of this prospectus. Except as otherwise set forth below, the address of the beneficial owner is c/o PTC Therapeutics Inc., 100 Corporate Court, South Plainfield, New Jersey 07080.

Certain of our existing principal stockholders or their affiliates and entities affiliated with certain of our directors have agreed to purchase an aggregate of 3,250,000 shares of our common stock in this offering at the initial public offering price. The following table does not reflect any such purchases by these stockholders or entities in this offering. See the footnotes to the following table for more information about the beneficial ownership of our common stock after this offering by these stockholders after giving effect to the purchase of the shares that they have agreed to purchase in this offering.

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Name of beneficial owner	Shares beneficially owned	Percentage of shares beneficially owned Before offering (%)	After offering (%)
Named executive officers and directors			
Stuart W. Peltz, Ph.D.(1)	197,641	1.3	*
Claudia Hirawat(2)	52,423	*	*
Jay Barth, M.D.(3)	7,772	*	*
Richard Aldrich(4)	583,333	3.8	2.5
Axel Bolte(5)		*	*
Allan Jacobson, Ph.D.(6)	39,878	*	*
Adam Koppel, M.D., Ph.D.(7)	1,083,333	7.1	4.6
Michael Kranda(8)	6,228	*	*
Geoffrey McDonough, M.D.(9)	909	*	*
Michael Schmertzler(10)	3,048,998	19.9	12.9
David P. Southwell(11)	13,878	*	*
Jerome B. Zeldis, M.D., Ph.D.(12)	1,071,212	7.0	4.5
All executive officers and directors as a group (17 persons)(13)	6,211,444	40.5	26.2
5% stockholders			
Credit Suisse First Boston Equity Partners, L.P. and affiliates(14)	2,256,882	14.7	9.5
HBM Healthcare Investments (Cayman) Ltd.(15)	1,841,495	12.0	7.8
Vulcan Ventures Incorporated and affiliates(16)	1,368,398	8.9	5.8
Brookside Capital Partners Fund, L.P.(17)	1,083,333	7.1	4.6
Celgene European Investment Company LLC and affiliate(18)	1,071,212	7.0	4.5
Delphi Ventures and affiliates(19)	955,766	6.2	4.0
Section Six Partners, L.P.(20)	764,036	5.0	3.2

* Less than one percent.

(1) Consists of (a) 8,838 shares of common stock underlying options that are exercisable as of May 31, 2013 or will become exercisable within 60 days after such date and (b) 188,803 shares of common stock.

(2) Consists of (a) 2,366 shares of common stock underlying options that are exercisable as of May 31, 2013 or will become exercisable within 60 days after such date and (b) 50,057 shares of common stock.

(3) Consists of (a) 385 shares of common stock underlying options that are exercisable as of May 31, 2013 or will become exercisable within 60 days after such date and (b) 7,387 shares of common stock.

(4) Consists of 583,333 shares held by Longwood Fund LP. The managing members of Longwood Fund LP share voting and investment power with respect to the shares held by such entity. The managing members are Richard Aldrich, Michelle Dip and Christoph Westphal, each of whom disclaims beneficial ownership of the shares held by Longwood Fund LP except to the extent of any pecuniary interest therein. The percentage of shares beneficially owned after this offering will be 4.4%, assuming the purchase of all of the 466,667 shares of our common stock that Longwood Fund LP has agreed to purchase in this offering.

(5) Mr. Bolte is an advisor to HBM Partners AG. HBM Partners AG acts as an investment advisor to HBM Partners (Cayman) Ltd. HBM Partners (Cayman) Ltd. provides investment management services to HBM Healthcare Investments (Cayman) Ltd. Neither HBM Partners AG nor Mr. Bolte has voting or investment power over the shares held by HBM Healthcare Investments (Cayman) Ltd. and each disclaims beneficial ownership of such shares except to the extent of any pecuniary interest therein. See also footnote 15.

(6) Consists of (a) 1,798 shares of common stock underlying options that are exercisable as of May 31, 2013 or will become exercisable within 60 days after such date and (b) 38,080 shares of common stock.

(7) Consists of 1,083,333 shares held by Brookside Capital Partners Fund, L.P. Dr. Koppel disclaims beneficial ownership of such shares except to the extent of any pecuniary interest therein. See also footnote 17. The percentage of shares beneficially owned after this offering will be 9.9%, assuming the purchase of all of the 1,250,000 shares of our common stock that Brookside Capital Partners Fund, L.P. has agreed to purchase in this offering.

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(8) Consists of (a) 300 shares of common stock underlying options that are exercisable as of May 31, 2013 or will become exercisable within 60 days of such date and (b) 5,928 shares of common stock. See also footnote 16.

(9) Consists of 909 shares of common stock.

(10) Consists of (a) 2,256,882 shares held by Credit Suisse First Boston Equity Partners, L.P. and affiliates; (b) 764,036 shares held by Section Six Partners, L.P.; (c) 1,314 shares of common stock underlying options that are exercisable as of May 31, 2013 or will become exercisable within 60 days after such date; and (d) 26,766 shares of common stock held by Mr. Schmertzler. Mr. Schmertzler disclaims beneficial ownership of the shares held by Credit Suisse First Boston Equity Partners, L.P. and its affiliates and by Section Six Partners, L.P., except in each case to the extent of his pecuniary interest therein. See also footnotes 14 and 20. The percentage of shares beneficially owned after this offering will be 15.1%, assuming the purchase of all of the 533,333 shares of our common stock that Section Six Partners, L.P. has agreed to purchase in this offering.

(11) Consists of (a) 640 shares of common stock underlying options that are exercisable as of May 31, 2013 or will become exercisable within 60 days after such date and (b) 13,238 shares of common stock.

(12) Consists of 1,071,212 shares held by Celgene European Investment Company LLC and affiliate. Dr. Zeldis disclaims beneficial ownership of such shares except to the extent of any pecuniary interest therein. See also footnote 18.

(13) Consists of (a) 19,816 shares of common stock underlying options that are exercisable as of May 31, 2013 or will become exercisable with 60 days after such date and (b) 6,191,628 shares of common stock. Certain of our existing principal stockholders or their affiliates and entities affiliated with certain of our directors have agreed to purchase an aggregate of 3,250,000 shares of our common stock in this offering at the initial public offering price. If such stockholders purchase all of the shares they have agreed to purchase, the number of shares of our common stock beneficially owned after the closing of this offering by our executive officers and directors as a group will, in the aggregate, increase to 37.1% of our capital stock.

(14) The address for Credit Suisse First Boston Equity Partners, L.P. and affiliates is Eleven Madison Avenue, 16th Floor, New York, NY 10010. Consists of (a) 1,759,609 shares held by Credit Suisse First Boston Equity Partners, L.P.; (b) 491,855 shares held by Credit Suisse First Boston Equity Partners (Bermuda), L.P.; (c) 3,487 shares held by EMA Private Equity Fund 1999, L.P.; (d) 1,697 shares held by Credit Suisse First Boston U.S. Executive Advisors, L.P.; and (e) 234 shares held by Credit Suisse First Boston Finders & Screeners, L.P. Mr. Schmertzler, a member of our board of directors, is a Managing Director of Aries Advisors, LLC, the sub-advisor to Credit Suisse First Boston Equity Partners, L.P., who disclaims beneficial ownership of the shares held by entities affiliated with Credit Suisse First Boston Equity Partners, L.P. except to the extent of any pecuniary interest therein.

(15) The address for HBM Healthcare Investments (Cayman) Ltd. is Centennial Towers, Suite 305, 2454 West Bay Road, Grand Cayman, Cayman Islands, B.V.I. The board of directors of HBM Healthcare Investments (Cayman) Ltd. has sole voting and investment power with respect to the shares by held by such entity. The board of directors of HBM Healthcare Investments (Cayman) Ltd. is comprised of John Arnold, Richard Coles, Sophia Harris, Dr. Andreas Wicki and John Urquhart, none of whom has individual voting or investment power with respect to such shares and each disclaims beneficial ownership of the shares held by HBM Healthcare Investments (Cayman) Ltd. except to the extent of any pecuniary interest therein. Mr. Bolte, a member of our board of directors, is an advisor to HBM Partners (Cayman) Ltd. HBM Partners (Cayman) Ltd. provides investment management services to HBM Healthcare Investments (Cayman) Ltd. Mr. Bolte has no voting or investment power over the shares held by HBM Healthcare

Investments (Cayman) Ltd. and disclaims beneficial ownership of such shares except to the extent of any pecuniary interest therein. The percentage of shares beneficially owned after this offering will be 10.6%, assuming the purchase of all of the 666,667 shares of our common stock that HBM Healthcare Investments (Cayman) Ltd. has agreed to purchase in this offering.

(16) The address for Vulcan Ventures Incorporated and affiliates is 505 Fifth Avenue, Suite 900, Seattle, WA 98104. Consists of (a) 797,102 shares held by Vulcan Capital Venture Capital I LLC; (b) 469,734 shares held by VCVC III LLC; and (c) 101,562 shares held by Vulcan Ventures Incorporated. Mr. Kranda, a member of our board of directors, is a consultant to Vulcan Capital Venture Capital I LLC. Vulcan Capital Venture Capital I LLC, VCVC III LLC, and Vulcan Ventures Incorporated are each controlled by entities owned by Paul Allen. Mr. Kranda does not have voting or investment power over the shares held by Vulcan Ventures Incorporated and its affiliates and disclaims beneficial ownership of such shares except to the extent of any beneficial ownership therein. The percentage of shares beneficially owned after this offering will be 7.2%, assuming the purchase of all of the 333,333 shares of our common stock that entities affiliated with Vulcan Ventures Incorporated and its affiliates have agreed to purchase in this offering.

(17) The address for Brookside Capital Partners Fund, L.P. is John Hancock Tower, 200 Clarendon Street, Boston, MA 02116. Dr. Koppel, a member of our board of directors, is a Managing Director of Brookside Capital, LLC, the investment advisor to Brookside Capital Partners Fund, L.P. Dr. Koppel disclaims beneficial ownership of the shares held by Brookside Capital Partners Fund, L.P. except to the extent of any pecuniary interest therein. The percentage of shares beneficially owned after this offering will be 9.9%, assuming the purchase of all of the 1,250,000 shares of our common stock that Brookside Capital Partners Fund, L.P. has agreed to purchase in this offering.

(18) The address for Celgene European Investment Company LLC and affiliate is 86 Morris Avenue, Summit, NJ 07901. Consists of (a) 803,640 shares held by Celgene European Investment Company LLC and (b) 267,572 shares held by Celgene Corporation. Dr. Zeldis, a member of our board of directors, is an employee of Celgene Corporation. Celgene European Investment Company LLC is a wholly owned subsidiary of Celgene Corporation. Dr. Zeldis disclaims beneficial ownership of the shares held by Celgene European Investment Company LLC and Celgene Corporation except to the extent of any pecuniary interest therein.

(19) The address for Delphi Ventures and affiliates is 3000 Sand Hill Road, 1-135, Menlo Park, CA 94025. Consists of (a) 574,736 shares held by Delphi Ventures V, L.P.; (b) 6,225 shares held by Delphi BioInvestments V, L.P.; (c) 185,545 shares held by Delphi Ventures VII, L.P.; (d) 1,853 shares held by Delphi BioInvestments VII, L.P.; (e) 185,595 shares held by Delphi Ventures VII, L.P.; and (f) 1,812 shares held by Delphi BioInvestments VII, L.P.

(20) The address for Section Six Partners, L.P. is 1300 Valley Road, New Canaan, CT 06840. Mr. Schmertzler, a member of our board of directors, is a general and limited partner of, and trustee of certain family trusts holding interests in, Section Six Partners, L.P., who disclaims beneficial ownership of the shares held by Section Six Partners, L.P. except to the extent of any pecuniary interest therein. The percentage of shares beneficially owned after this offering will be 5.5%, assuming the purchase of all of the 533,333 shares of our common stock that Section Six Partners, L.P. has agreed to purchase in this offering.

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Description of capital stock

General

The following description of our capital stock and provisions of our certificate of incorporation and bylaws are summaries and are qualified by reference to the certificate of incorporation and the bylaws that will be in effect upon the closing of this offering. We have filed copies of these documents with the SEC as exhibits to our registration statement of which this prospectus forms a part. The description of the capital stock reflects changes to our capital structure that will occur upon the closing of this offering.

Upon the closing of this offering, our authorized capital stock will consist of 125,000,000 shares of our common stock, par value $0.001 per share, and 5,000,000 shares of our preferred stock, par value $0.001 per share, all of which preferred stock will be undesignated.

As of May 31, 2013, we had issued and outstanding:

- 1,135,234 shares of our common stock held by 169 stockholders of record;
- 5,374,954 shares of our series four senior preferred stock that are convertible into 5,374,954 shares of our common stock; and
- 8,796,002 shares of our series five junior preferred stock that are convertible into 8,796,002 shares of our common stock;

As of May 31, 2013, we also had outstanding:

- options to purchase 2,049,737 shares of our common stock, at a weighted average exercise price of $20.26 per share;
- warrants to purchase 645 shares of our common stock, at a weighted average exercise price of $2,520 per share; and
- warrants to purchase 16,368 shares of our series five junior preferred stock, at a weighted average exercise price of $128 per share.

Upon the closing of this offering:

- all of the outstanding shares of our preferred stock will automatically convert into an aggregate of 14,170,956 shares of our common stock;
- the warrants to purchase an aggregate of 645 shares of our common stock will remain outstanding and exercisable to purchase shares of our common stock, at a weighted average exercise price of $2,520 per share;
- the warrants to purchase 16,368 shares of our series five junior preferred stock at an exercise price of $128 per share will automatically become warrants to purchase 16,368 shares of our common stock, at an exercise price of $128 per share.

Common stock

Holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders and do not have cumulative voting rights. Each election of directors by our stockholders will be determined by a plurality of the votes cast by the stockholders entitled to vote on the

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election. Holders of common stock are entitled to receive proportionately any dividends as may be declared by our board of directors, subject to any preferential dividend rights of outstanding preferred stock.

In the event of our liquidation or dissolution, the holders of our common stock are entitled to receive proportionately all assets available for distribution to stockholders after the payment of all debts and other liabilities and subject to the prior rights of any of our outstanding preferred stock. Holders of our common stock have no preemptive, subscription, redemption or conversion rights. The rights, preferences and privileges of holders of our common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of our preferred stock that we may designate and issue in the future.

Preferred stock

Under the terms of our certificate of incorporation that will become effective upon the closing of this offering, our board of directors is authorized to issue shares of preferred stock in one or more series without stockholder approval. Our board of directors has the discretion to determine the rights, preferences, privileges and restrictions, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences, of each series of preferred stock.

The purpose of authorizing our board of directors to issue preferred stock and determine its rights and preferences is to eliminate delays associated with a stockholder vote on specific issuances. The issuance of preferred stock, while providing flexibility in connection with possible acquisitions, future financings and other corporate purposes, could have the effect of making it more difficult for a third party to acquire, or could discourage a third party from seeking to acquire, a majority of our outstanding voting stock. Upon the closing of this offering, there will be no shares of preferred stock outstanding, and we have no present plans to issue any shares of preferred stock.

Warrants

As of May 31, 2013, we had outstanding:

- warrants to purchase 645 shares of our common stock, at a weighted average exercise price of $2,520 per share; and
- warrants to purchase an aggregate of 16,368 shares of our series five junior preferred stock, at a weighted average exercise price of $128 per share.

Upon the closing of this offering, and after giving effect to the automatic conversion of our preferred stock into common stock, the warrants to purchase shares of our series five junior preferred stock will be exercisable, at the election of the holders, for an aggregate of 16,368 shares of our common stock, at an exercise price of $128 per share. These warrants provide for adjustments in the event of specified mergers, reorganizations, reclassifications, stock dividends, stock splits or other changes in our corporate structure. These warrants expire on January 28, 2020.

Options

As of May 31, 2013, options to purchase 2,049,737 shares of our common stock, at a weighted average exercise price of $20.26 per share, were outstanding.

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Delaware anti-takeover law and certain charter and by-law provisions

Delaware law

We are subject to Section 203 of the Delaware General Corporation Law. Subject to certain exceptions, Section 203 prevents a publicly held Delaware corporation from engaging in a "business combination" with any "interested stockholder" for three years following the date that the person became an interested stockholder, unless either the interested stockholder attained such status with the approval of our board of directors, the business combination is approved by our board of directors and stockholders in a prescribed manner or the interested stockholder acquired at least 85% of our outstanding voting stock in the transaction in which it became an interested stockholder. A "business combination" includes, among other things, a merger or consolidation involving us and the "interested stockholder" and the sale of more than 10% of our assets. In general, an "interested stockholder" is any entity or person beneficially owning 15% or more of our outstanding voting stock and any entity or person affiliated with or controlling or controlled by such entity or person. The restrictions contained in Section 203 are not applicable to any of our existing stockholders that will own 15% or more of our outstanding voting stock upon the closing of this offering.

Staggered board; removal of directors

Our certificate of incorporation and our bylaws divide our board of directors into three classes with staggered three-year terms. In addition, our certificate of incorporation and our bylaws provide that directors may be removed only for cause and only by the affirmative vote of the holders of 75% of our shares of capital stock present in person or by proxy and entitled to vote. Under our certificate of incorporation and bylaws, any vacancy on our board of directors, including a vacancy resulting from an enlargement of our board of directors, may be filled only by vote of a majority of our directors then in office. Furthermore, our certificate of incorporation provides that the authorized number of directors may be changed only by the resolution of our board of directors. The classification of our board of directors and the limitations on the ability of our stockholders to remove directors, change the authorized number of directors and fill vacancies could make it more difficult for a third party to acquire, or discourage a third party from seeking to acquire, control of our company.

Stockholder action; special meeting of stockholders; advance notice requirements for stockholder proposals and director nominations

Our certificate of incorporation and our bylaws provide that any action required or permitted to be taken by our stockholders at an annual meeting or special meeting of stockholders may only be taken if it is properly brought before such meeting and may not be taken by written action in lieu of a meeting. Our certificate of incorporation and our bylaws also provide that, except as otherwise required by law, special meetings of the stockholders can only be called by our chairman of the board, our president or chief executive officer or our board of directors. In addition, our bylaws establish an advance notice procedure for stockholder proposals to be brought before an annual meeting of stockholders, including proposed nominations of candidates for election to our board of directors. Stockholders at an annual meeting may only consider proposals or nominations specified in the notice of meeting or brought before the meeting by or at the direction of our board of directors, or by a stockholder of record on the record date for the meeting, who is entitled to vote at the meeting and who has delivered timely written notice in proper form to our secretary of the stockholder's intention to bring such business before the meeting. These provisions could have the effect of delaying until the next stockholder meeting stockholder actions that are favored by the holders of a majority of our outstanding voting securities. These provisions also could discourage a third party from making a tender offer for our common stock, because even if it acquired a majority of our

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outstanding voting stock, it would be able to take action as a stockholder, such as electing new directors or approving a merger, only at a duly called stockholders meeting and not by written consent.

Super-majority voting

The Delaware General Corporation Law provides generally that the affirmative vote of a majority of the shares entitled to vote on any matter is required to amend a corporation's certificate of incorporation or bylaws, unless a corporation's certificate of incorporation or bylaws, as the case may be, requires a greater percentage. Our bylaws may be amended or repealed by a majority vote of our board of directors or the affirmative vote of the holders of at least 75% of the votes that all our stockholders would be entitled to cast in any annual election of directors. In addition, the affirmative vote of the holders of at least 75% of the votes that all our stockholders would be entitled to cast in any election of directors is required to amend or repeal or to adopt any provisions inconsistent with any of the provisions of our certificate of incorporation described above.

Registration rights

We have entered into a second amended and restated investors' rights agreement, dated March 7, 2013, which we refer to as the investors' rights agreement, with the holders of our preferred stock. Upon the completion of this offering, holders of a total of 14,183,589 shares of our common stock as of May 31, 2013, including shares issuable upon conversion of our preferred stock, will have the right to require us to register these shares under the Securities Act of 1933, as amended, or Securities Act, and to participate in future registrations of securities by us, under the circumstances described below. After registration pursuant to these rights, these shares will become freely tradable without restriction under the Securities Act. If not otherwise exercised, the rights described below will expire three years after the closing of this offering.

Demand registration rights

Beginning 180 days after the effective date of the registration statement of which this prospectus forms a part, subject to specified limitations set forth in the investors' rights agreement, at any time, the holders of 20% of the then-outstanding shares having rights under the investors' rights agreement, which we refer to as registrable shares, may at any time demand in writing that we register all or a portion of the registrable shares under the Securities Act if the total amount of registrable shares registered have an aggregate offering price of at least $10 million (net of selling expenses). We are not obligated to file a registration statement pursuant to this provision on more than two occasions, and we are not obligated to file a registration statement pursuant to this provision within 60 days before or 180 days after the effective date of any other registration statement that we may file or if we determine in good faith that it would be seriously detrimental to us or our stockholders.

Form S-3 registration rights

In addition, at any time after we become eligible to file a registration statement on Form S-3, subject to specified limitations set forth in the investors' rights agreement, the holders of registrable shares may demand in writing that we register on Form S-3 all or a portion of the registrable shares so long as the total amount of registrable shares being registered have an aggregate offering price of at least $5 million (net of selling expenses). We are not obligated to file a Form S-3 pursuant to this provision on more than four occasions, and we are not obligated to file a registration statement pursuant to this provision within 30 days before or 90 days after the effective date of any other registration statement that we may file or if we determine in good faith that it would be seriously detrimental to us or our stockholders.

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Incidental registration rights

If, at any time after the closing of this offering, we propose to file a registration statement under the Securities Act, other than pursuant to the demand registration rights described above, the holders of registrable shares will be entitled to notice of the registration and, subject to specified exceptions, including market conditions, have the right to require us to register all or a portion of the registrable shares then held by them.

In the event that any registration in which the holders of registrable shares elect to participate pursuant to our investors' rights agreement is intended to be an underwritten public offering, we have agreed to enter into an underwriting agreement containing customary representation and warranties and covenants, including without limitation customary provisions with respect to indemnification of the underwriters of such offering. Holders of registrable securities must agree to any such underwriting agreement as a condition to participation in the offering.

Expenses

Pursuant to the investors' rights agreement, we are required to pay all registration expenses, including registration and filing fees, exchange listing fees, printing expenses and accounting fees and the fees and expenses of one counsel to represent the selling stockholders, in addition to any underwriting discounts and commissions, that are related to any demand or incidental registration described above. The registration rights agreement contains customary cross-indemnification provisions, pursuant to which we are obligated to indemnify the selling stockholders in the event of material misstatements or omissions in the registration statement attributable to us, and they are obligated to indemnify us for material misstatements or omissions in the registration statement attributable to them.

Transfer agent and registrar

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company, LLC.

NASDAQ Global Select Market

Our common stock has been approved for listing on The NASDAQ Global Select Market under the symbol "PTCT".

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Shares eligible for future sale

Prior to this offering, there has been no public market for our common stock, and a liquid trading market for our common stock may not develop or be sustained after this offering. Future sales of substantial amounts of our common stock in the public market, including shares issued upon exercise of outstanding options, or the anticipation of these sales, could adversely affect market prices prevailing from time to time and could impair our ability to raise capital through sales of equity securities.

Upon the closing of this offering, we will have outstanding 23,678,190 shares of our common stock, after giving effect to the issuance of 8,372,000 shares of our common stock in this offering, assuming no exercise by the underwriters of their over-allotment option and no exercise of options or warrants outstanding as of May 31, 2013.

Of the shares to be outstanding immediately after the closing of this offering, we expect that the 8,372,000 shares to be sold in this offering will be freely tradable without restriction under the Securities Act unless purchased by our "affiliates," as that term is defined in Rule 144 under the Securities Act. The remaining 15,306,190 shares of our common stock outstanding after this offering will be "restricted securities" under Rule 144, and we expect that substantially all of these restricted securities will be subject to the 180-day lock-up period under the lock-up agreements as described below. These restricted securities may be sold in the public market only if registered or pursuant to an exemption from registration, such as Rule 144 or Rule 701 under the Securities Act.

Rule 144

In general, under Rule 144, beginning 90 days after the date of this prospectus, any person who is not our affiliate and has held their shares for at least six months, including the holding period of any prior owner other than one of our affiliates, may sell shares without restriction, subject to the availability of current public information about us. In addition, under Rule 144, any person who is not our affiliate and has not been our affiliate at any time during the preceding three months and has held their shares for at least one year, including the holding period of any prior owner other than one of our affiliates, would be entitled to sell an unlimited number of shares immediately upon the closing of this offering without regard to whether current public information about us is available.

Beginning 90 days after the date of this prospectus, a person who is our affiliate or who was our affiliate at any time during the preceding three months and who has beneficially owned restricted securities for at least six months, including the holding period of any prior owner other than one of our affiliates, is entitled to sell a number of shares within any three-month period that does not exceed the greater of:

- 1% of the number of shares of our common stock then outstanding, which will equal approximately 236,782 shares immediately after this offering; and
- the average weekly trading volume of our common stock on The NASDAQ Global Select Market during the four calendar weeks preceding the filing of a Notice of Proposed Sale of Securities Pursuant to Rule 144 with respect to the sale.

Sales under Rule 144 by our affiliates are also subject to manner of sale provisions and notice requirements and to the availability of current public information about us.

Upon expiration of the 180-day lock-up period described below, approximately 15,306,190 shares of our common stock will be eligible for sale under Rule 144, including shares eligible for resale immediately

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upon the closing of this offering as described above. We cannot estimate the number of shares of our common stock that our existing stockholders will elect to sell under Rule 144.

Rule 701

In general, under Rule 701 of the Securities Act, any of our employees, consultants or advisors, other than our affiliates, who purchased or otherwise received shares from us in connection with a qualified compensatory stock plan or other written agreement is eligible to resell these shares 90 days after the date of this prospectus in reliance on Rule 144, but without compliance with the holding period requirements of Rule 144 and without regard to the volume of such sales or the availability of public information about us. Subject to the 180-day lock-up period described below and vesting terms of restricted stock, approximately 1,131,778 shares of our common stock will be eligible for sale in accordance with Rule 701.

Lock-up agreements

We and each of our directors and executive officers and certain holders of our outstanding common stock, who collectively own 15,124,642 shares of our common stock, based on shares outstanding as of May 31, 2013, have agreed that, without the prior written consent of J.P. Morgan Securities LLC and Credit Suisse Securities (USA) LLC, on behalf of the underwriters, we and they will not, subject to limited exceptions, during the period ending 180 days after the date of this prospectus, either directly or indirectly:

- offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, or otherwise transfer or dispose of any shares of our common stock or any securities convertible into or exercisable or exchangeable for common stock, whether such transaction is to be settled by delivery of shares of our common stock or such other securities, in cash or otherwise, or publicly disclose an intention to do the same;

- enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of our common stock, whether such transaction is to be settled by delivery of shares of our common stock or such other securities, in cash or otherwise; or

- make any demand for or exercise any right with respect to the registration of any shares of our common stock or any security convertible into or exercisable or exchangeable for shares of our common stock, or with respect to the filing of any registration statement in connection therewith under the Securities Act.

The lock-up restrictions and specified exceptions are described in more detail under "Underwriting."

Registration rights

Upon the closing of this offering, the holders of 14,183,589 shares of our common stock or their permitted transferees will be entitled to various rights with respect to the registration of these shares under the Securities Act. Registration of these shares under the Securities Act would result in these shares becoming fully tradable without restriction under the Securities Act immediately upon the effectiveness of the registration, except for shares purchased by affiliates. See "Description of capital stock registration rights" for additional information. Shares covered by a registration statement will be eligible for sale in the public market upon the expiration or release from the terms of lock-up agreements applicable to such shares.

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Stock options

As of May 31, 2013, we had outstanding options to purchase 2,049,737 shares of our common stock, of which options to purchase 40,995 shares were vested. Following this offering, we intend to file one or more registration statements on Form S-8 under the Securities Act to register all of the shares of our common stock subject to outstanding options and options and other awards issuable pursuant to the 2013 public company plan and our pre-IPO stock incentive plans. See "Executive compensation stock option and other compensation plans" for additional information regarding these plans. Accordingly, shares of our common stock registered under the registration statements will be available for sale in the open market, subject to Rule 144 volume limitations applicable to affiliates, and subject to any vesting restrictions and lock-up agreements applicable to these shares.

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Material federal U.S. tax considerations for non-U.S. holders of common stock

The following is a general discussion of material U.S. federal income and estate tax considerations relating to ownership and disposition of our common stock by a non-U.S. holder. For purposes of this discussion, the term "non-U.S. holder" means a beneficial owner of our common stock that is not, for U.S. federal income tax purposes:

- an individual who is a citizen or resident of the United States;
- a corporation, or other entity treated as a corporation for U.S. federal income tax purposes, created or organized in or under the laws of the United States or of any political subdivision of the United States;
- an estate the income of which is subject to U.S. federal income taxation regardless of its source; or
- a trust, if a U.S. court is able to exercise primary supervision over the administration of the trust and one or more U.S. persons have authority to control all substantial decisions of the trust or if the trust has a valid election to be treated as a U.S. person under applicable U.S. Treasury Regulations.

This discussion is based on current provisions of the U.S. Internal Revenue Code of 1986, as amended, which we refer to as the Code, existing and proposed U.S. Treasury Regulations promulgated thereunder, current administrative rulings and judicial decisions, all as in effect as of the date of this prospectus and all of which are subject to change or to differing interpretation, possibly with retroactive effect. Any change could alter the tax consequences to non-U.S. holders described in this prospectus. In addition, the Internal Revenue Service, or the IRS, could challenge one or more of the tax consequences described in this prospectus.

We assume in this discussion that each non-U.S. holder holds shares of our common stock as a capital asset (generally, property held for investment). This discussion does not address all aspects of U.S. federal income and estate taxation that may be relevant to a particular non-U.S. holder in light of that non-U.S. holder's individual circumstances nor does it address any aspects of U.S. state, local or non-U.S. taxes. This discussion also does not consider any specific facts or circumstances that may apply to a non-U.S. holder and does not address the special tax rules applicable to particular non-U.S. holders, such as:

- financial institutions;
- brokers or dealers in securities;
- tax-exempt organizations;
- pension plans;
- owners that hold our common stock as part of a straddle, hedge, conversion transaction, synthetic security or other integrated investment;
- insurance companies;
- controlled foreign corporations;

passive foreign investment companies; and

certain U.S. expatriates.

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In addition, this discussion does not address the tax treatment of partnerships or persons who hold their common stock through partnerships or other entities which are pass-through entities for U.S. federal income tax purposes. A partner in a partnership or other pass-through entity that will hold our common stock should consult his, her or its own tax advisor regarding the tax consequences of the ownership and disposition of our common stock through a partnership or other pass-through entity, as applicable.

Prospective investors should consult their own tax advisors regarding the U.S. federal, state, local and non-U.S. income and other tax considerations of acquiring, holding and disposing of our common stock.

Dividends

If we pay distributions on our common stock, those distributions generally will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. If a distribution exceeds our current and accumulated earnings and profits, the excess will be treated as a tax-free return of the non-U.S. holder's investment, up to such holder's tax basis in the common stock. Any remaining excess will be treated as capital gain, subject to the tax treatment described below under the heading "Gain on disposition of common stock." Any such distribution would also be subject to the discussion below under the section titled "Withholding and information reporting requirements FATCA."

As discussed under "Dividend policy," we do not expect to pay cash dividends to holders of our common stock in the foreseeable future. In the event we do pay dividends, dividends paid to a non-U.S. holder generally will be subject to withholding of U.S. federal income tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and such holder's country of residence.

Dividends that are treated as effectively connected with a trade or business conducted by a non-U.S. holder within the United States, and if an applicable income tax treaty so provides, that are attributable to a permanent establishment or a fixed base maintained by the non-U.S. holder within the United States, are generally exempt from the 30% withholding tax if the non-U.S. holder satisfies applicable certification and disclosure requirements. However, such U.S. effectively connected income, net of specified deductions and credits, is taxed at the same graduated U.S. federal income tax rates applicable to U.S. persons (as defined in the Code). Any U.S. effectively connected income received by a non-U.S. holder that is a corporation may also, under certain circumstances, be subject to an additional "branch profits tax" at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and such holder's country of residence.

A non-U.S. holder of our common stock who claims the benefit of an applicable income tax treaty between the United States and such holder's country of residence generally will be required to provide a properly executed IRS Form W-8BEN (or successor form) and satisfy applicable certification and other requirements. Non-U.S holders are urged to consult their own tax advisors regarding their entitlement to benefits under a relevant income tax treaty.

A non-U.S. holder that is eligible for a reduced rate of U.S. withholding tax under an income tax treaty may obtain a refund or credit of any excess amounts withheld by timely filing an appropriate claim with the IRS.

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Gain on disposition of common stock

A non-U.S. holder generally will not be subject to U.S. federal income tax on gain recognized on a disposition of our common stock unless:

- the gain is effectively connected with the non-U.S. holder's conduct of a trade or business in the United States, and if an applicable income tax treaty so provides, the gain is attributable to a permanent establishment or fixed base maintained by the non-U.S. holder in the United States; in these cases, the non-U.S. holder will be taxed on a net income basis at the regular graduated rates and in the manner applicable to U.S. persons, and if the non-U.S. holder is a corporation, an additional branch profits tax at a rate of 30%, or a lower rate as may be specified by an applicable income tax treaty, may also apply;

- the non-U.S. holder is a nonresident alien present in the United States for 183 days or more in the taxable year of the disposition and certain other requirements are met, in which case the non-U.S. holder will be subject to a 30% tax (or such lower rate as may be specified by an applicable income tax treaty) on the net gain derived from the disposition, which may be offset by U.S.-source capital losses of the non-U.S. holder, if any; or

- we are, or have been at any time during the five-year period preceding such disposition (or the non-U.S. holder's holding period, if shorter), a "U.S. real property holding corporation," unless our common stock is regularly traded on an established securities market and the non-U.S. holder held no more than 5% of our outstanding common stock, directly or indirectly, during the shorter of the five-year period ending on the date of the disposition or the period that the non-U.S. holder held our common stock. Generally, a corporation is a "U.S. real property holding corporation" if the fair market value of its "U.S. real property interests" (as defined in the Code and applicable regulations) equals or exceeds 50% of the sum of the fair market value of its worldwide real property interests plus its other assets used or held for use in a trade or business.

Although there can be no assurance, we believe that we are not currently, and we do not anticipate becoming, a "U.S. real property holding corporation" for U.S. federal income tax purposes.

No assurance can be provided that our common stock will be regularly traded on an established securities market for purposes of the rule described above.

Information reporting and backup withholding

We must report annually to the IRS and to each non-U.S. holder the gross amount of the distributions on our common stock paid to such holder and the tax withheld, if any, with respect to such distributions. Non-U.S. holders may have to comply with specific certification procedures to establish that the holder is not a U.S. person (as defined in the Code) in order to avoid backup withholding at the applicable rate, currently 28%, with respect to dividends on our common stock. Generally, a holder will comply with such procedures if it provides a properly executed IRS Form W-8BEN (or other applicable Form W-8) or otherwise meets documentary evidence requirements for establishing that it is a non-U.S. holder, or otherwise establishes an exemption. Dividends paid to non-U.S. holders subject to withholding of U.S. federal income tax, as described above under the heading "Dividends," will generally be exempt from U.S. backup withholding.

Information reporting and backup withholding generally will apply to the proceeds of a disposition of our common stock by a non-U.S. holder effected by or through the U.S. office of any broker, U.S. or foreign, unless the holder certifies its status as a non-U.S. holder and satisfies certain other requirements, or

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otherwise establishes an exemption. Generally, information reporting and backup withholding will not apply to a payment of disposition proceeds to a non-U.S. holder where the transaction is effected outside the United States through a non-U.S. office of a broker. However, for information reporting purposes, dispositions effected through a non-U.S. office of a broker with substantial U.S. ownership or operations generally will be treated in a manner similar to dispositions effected through a U.S. office of a broker. Non-U.S. holders should consult their own tax advisors regarding the application of the information reporting and backup withholding rules to them.

Copies of information returns may be made available to the tax authorities of the country in which the non-U.S. holder resides or is incorporated under the provisions of a specific treaty or agreement.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules from a payment to a non-U.S. holder can be refunded or credited against the non-U.S. holder's U.S. federal income tax liability, if any, provided that an appropriate claim is timely filed with the IRS.

Federal estate tax

Common stock owned or treated as owned by an individual who is a non-U.S. holder (as specially defined for U.S. federal estate tax purposes) at the time of death will be included in the individual's gross estate for U.S. federal estate tax purposes and, therefore, may be subject to U.S. federal estate tax, unless an applicable estate tax or other treaty provides otherwise.

Withholding and information reporting requirements FATCA

Recently enacted legislation, which is commonly referred to as "FATCA," will impose U.S. federal withholding tax of 30% on payments of dividends of, and gross proceeds from the sale or disposition of, our common stock if paid to a foreign entity unless (i) if the foreign entity is a "foreign financial institution," the foreign entity undertakes certain due diligence, reporting, withholding, and certification obligations, (ii) if the foreign entity is not a "foreign financial institution," the foreign entity identifies certain of its U.S. investors, if any, or (iii) the foreign entity is otherwise exempt under FATCA. Although this legislation is effective with regards to amounts paid after December 31, 2012, under final regulations issued by the U.S. Department of Treasury on January 17, 2013, withholding under FATCA will only apply (1) to payments of dividends on our common stock made after December 31, 2013 and (2) to payments of gross proceeds from a sale or other disposition of our common stock made after December 31, 2016. Under certain circumstances, a non-U.S. holder may be eligible for refunds or credits for such taxes.

Prospective investors should consult their own tax advisors regarding the possible impact of the FATCA rules on their investment in our common stock, and the entities through which they hold our common stock, including, without limitation, the process and deadlines for meeting the applicable requirements to prevent the imposition of this 30% withholding tax under FATCA.

The preceding discussion of material U.S. federal tax considerations is for general information only. It is not tax advice. Prospective investors should consult their own tax advisors regarding the particular U.S. federal, state, local and non-U.S. tax consequences of purchasing, holding and disposing of our common stock, including the consequences of any proposed changes in applicable laws.

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Underwriting

We are offering the shares of our common stock described in this prospectus through a number of underwriters. J.P. Morgan Securities LLC and Credit Suisse Securities (USA) LLC are acting as joint book running managers of the offering and as representatives of the underwriters. We have entered into an underwriting agreement with the representatives. Subject to the terms and conditions of the underwriting agreement, we have agreed to sell to the underwriters, and each underwriter has severally agreed to purchase, at the public offering price less the underwriting discounts and commissions set forth on the cover page of this prospectus, the number of shares of our common stock listed next to its name in the following table:

Name	Number of shares
J.P. Morgan Securities LLC	3,516,240
Credit Suisse Securities (USA) LLC	2,762,760
Cowen and Company, LLC	1,465,100
Wedbush Securities Inc.	627,900
Total	8,372,000

The underwriters are committed to purchase all the common shares offered by us if they purchase any shares. The underwriting agreement also provides that if an underwriter defaults, the purchase commitments of non-defaulting underwriters may also be increased or the offering may be terminated.

Certain of our existing principal stockholders or their affiliates and entities affiliated with certain of our directors have agreed to purchase an aggregate of 3,250,000 in shares of our common stock in this offering at the initial public offering price.

At our request, the underwriters have reserved up to 345,000 shares of our common stock offered by this prospectus for sale, at the initial public offering price, to our directors and officers, and certain employees and other parties related to us, in addition to shares that certain of our existing principal stockholders or their affiliates and entities affiliated with certain of our directors have indicated an interest in purchasing as described above. Shares purchased by our directors and officers will be subject to the 180-day lock-up restriction described below. The number of shares of common stock available for sale to the general public will be reduced to the extent these individuals purchase such reserved shares. Any reserved shares that are not so purchased will be offered by the underwriters to the general public on the same basis as the other shares offered by this prospectus.

The underwriters propose to offer the common shares directly to the public at the initial public offering price set forth on the cover page of this prospectus and to certain dealers at that price less a concession not in excess of $0.63 per share. After the initial public offering of the shares, the offering price and the selling concession may be changed by the underwriters. Sales of shares made outside of the United States may be made by affiliates of the underwriters.

The underwriters have an option to buy up to 1,255,800 additional shares of our common stock from us to cover sales of shares by the underwriters which exceed the number of shares specified in the table above. The underwriters have 30 days from the date of this prospectus to exercise this over-allotment option. If any shares are purchased with this over-allotment option, the underwriters will purchase shares in approximately the same proportion as shown in the table above. If any additional shares of our common

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stock are purchased, the underwriters will offer the additional shares on the same terms as those on which the shares are being offered.

The underwriting fee is equal to the public offering price per share of common stock less the amount paid by the underwriters to us per share of common stock. The underwriting fee is $1.05 per share. The following table shows the per share and total underwriting discounts and commissions to be paid to the underwriters assuming both no exercise and full exercise of the underwriters' over-allotment option.

		Without over-allotment exercise		**With full over-allotment exercise**
Per Share	$	1.05	$	1.05
Total	$	8,790,600	$	10,094,700

We estimate that the total expenses of this offering, including registration, filing and listing fees, printing fees and legal and accounting expenses, but excluding the underwriting discounts and commissions, will be approximately $2,625,000. We have agreed to reimburse the underwriters for all expenses relating to the clearance of this offering with the Financial Industry Regulatory Authority, Inc., or FINRA, in the amount of $60,000.

Shane Kovacs, our Chief Financial Officer, received consulting fees in the amount of $5,250 from us, while he was employed by Credit Suisse Securities (USA) LLC, as consideration for providing financial analysis and other services. In May 2013, our board of directors granted Mr. Kovacs 126,000 stock options at an exercise price of $10.85 per share and a restricted stock award of 14,000 shares of our common stock. FINRA deems such securities and consulting fees to be underwriting compensation.

A prospectus in electronic format may be made available on the web sites maintained by one or more underwriters, or selling group members, if any, participating in the offering. The underwriters may agree to allocate a number of shares to underwriters and selling group members for sale to their online brokerage account holders. Internet distributions will be allocated by the representatives to underwriters and selling group members that may make Internet distributions on the same basis as other allocations.

We have agreed that we will not (1) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase or otherwise transfer or dispose of, directly or indirectly, or file with the Securities and Exchange Commission a registration statement under the Securities Act relating to, any shares of our common stock or securities convertible into or exchangeable or exercisable for any shares of our common stock, or publicly disclose the intention to make any offer, sale, pledge, disposition or filing, or (2) enter into any swap or other arrangement that transfers all or a portion of the economic consequences associated with the ownership of any shares of our common stock or any such other securities (regardless of whether any of these transactions are to be settled by the delivery of shares of our common stock or such other securities, in cash or otherwise), in each case without the prior written consent of J.P. Morgan Securities LLC and Credit Suisse Securities (USA) LLC for a period of 180 days after the date of this prospectus, other than (A) the shares of our common stock to be sold hereunder, (B) any shares of our common stock issued upon the exercise of options granted under our existing management incentive plans or warrants described as outstanding in this prospectus, (C) any options and other awards granted under our existing management incentive plans, (D) our filing of a registration statement on Form S-8 or a successor form thereto and (E) shares of our common stock or other securities issued in connection with a transaction that includes a commercial relationship (including joint ventures, marketing or distribution arrangements, collaboration agreements or intellectual property license agreements) or any acquisition of assets or not less than a majority or controlling portion of the equity of another entity; provided that the aggregate number of

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shares of stock issued pursuant to clause (E) shall not exceed 5.0% of the total number of outstanding shares of our common stock immediately following the issuance and sale of the underwritten shares pursuant to the underwriting agreement; provided, further, the recipient of any such shares of our common stock and securities issued pursuant to clauses (C) or (E) during the 180-day restricted period described above shall enter into an agreement substantially in the form described below.

Our directors and executive officers, and certain of our significant stockholders, have entered into lock up agreements with the underwriters prior to the commencement of this offering pursuant to which each of these persons or entities, for a period of 180 days after the date of this prospectus, may not, without the prior written consent of J.P. Morgan Securities LLC and Credit Suisse Securities (USA) LLC, (1) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, or otherwise transfer or dispose of, directly or indirectly, any shares of our common stock or any securities convertible into or exercisable or exchangeable for our common stock (including, without limitation, common stock or such other securities which may be deemed to be beneficially owned by such directors, executive officers, managers and members in accordance with the rules and regulations of the SEC and securities which may be issued upon exercise of a stock option or warrant) or publicly disclose the intention to make any offer, sale, pledge or disposition or (2) enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of our common stock or such other securities, whether any such transaction described in clause (1) or (2) above is to be settled by delivery of common stock or such other securities, in cash or otherwise, or (3) make any demand for or exercise any right with respect to the registration of any shares of our common stock or any security convertible into or exercisable or exchangeable for our common stock, in each case subject to certain exceptions, including (A) shares of common stock to be sold pursuant to the underwriting agreement, (B) transfers of shares of common stock or other securities as bona fide gifts, (C) transfers or dispositions of shares of common stock or other securities to any trust for the direct or indirect benefit of the director, officer or stockholder or the immediate family of such person in a transaction not involving a disposition for value, (D) transfers or dispositions of shares of common stock or other securities to any affiliate of the director, officer or stockholder or to any investment fund or other entity controlled or managed by such director, officer or stockholder; (E) transfers or dispositions of shares of common stock or other securities by will, other testamentary document or intestate succession to the legal representative, heir, beneficiary or a member of the immediate family of the director, officer or stockholder, and (F) distributions of shares of common stock or other securities to any of the stockholder's partners, members or stockholders. In the case of any transfer, disposition or distribution pursuant to clause (B), (C), (D), (E) or (F), each transferee, donee or distributee must execute and deliver to J.P. Morgan Securities LLC and Credit Suisse Securities (USA) LLC a lock-up agreement. In addition, in the case of any transfer, disposition or distribution pursuant to clause (B), (C), (D) or (F), no filing by any party under the Exchange Act, or other public announcement reporting a reduction in the beneficial ownership of common stock held by the director, officer or stockholder, may be required or voluntarily made in connection with such transfer, disposition or distribution, other than a filing on a Form 5 made after the expiration of the 180-day period referred to above. In addition, notwithstanding the foregoing restrictions, the director, officer or stockholder may (i) exercise an option to purchase shares of common stock granted under any stock incentive plan or stock purchase plan, provided that the underlying shares of common stock continue to be subject to the restrictions on transfer set forth in the lock-up agreement, (ii) transfer such stockholder's common stock or any security convertible into or exercisable or exchangeable for common stock to us pursuant to any contractual arrangement in effect on the date of the lock-up agreement that provides for the repurchase of such stockholder's common stock or such other securities by us or in connection with the termination of such stockholder's employment with us, (iii) establish a trading plan pursuant to Rule 10b5-1 under the Exchange Act for the transfer of common stock, provided

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that such plan does not provide for any transfers of common stock, and no filing with the SEC or other public announcement shall be required or voluntarily made by the director, officer or stockholder or any other person in connection therewith, in each case during the 180-day restricted period pursuant to the lock-up agreement, and (iv) transfer or dispose of shares of common stock acquired in the offering, subject to certain restrictions with respect to company directed shares, or on the open market following the offering, provided that certain limitations on filings under the Exchange Act or other public announcements reporting a reduction in the beneficial ownership of common stock held by the director, officer or stockholder apply in connection with such transfer or disposition.

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act of 1933.

Our common stock has been approved for listing on The NASDAQ Global Select Market under the symbol "PTCT".

In connection with this offering, the underwriters may engage in stabilizing transactions, which involves making bids for, purchasing and selling shares of our common stock in the open market for the purpose of preventing or retarding a decline in the market price of the common stock while this offering is in progress. These stabilizing transactions may include making short sales of the common stock, which involves the sale by the underwriters of a greater number of shares of our common stock than they are required to purchase in this offering, and purchasing shares of our common stock on the open market to cover positions created by short sales. Short sales may be "covered" shorts, which are short positions in an amount not greater than the underwriters' over-allotment option referred to above, or may be "naked" shorts, which are short positions in excess of that amount. The underwriters may close out any covered short position either by exercising their over-allotment option, in whole or in part, or by purchasing shares in the open market. In making this determination, the underwriters will consider, among other things, the price of shares available for purchase in the open market compared to the price at which the underwriters may purchase shares through the over-allotment option. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market that could adversely affect investors who purchase in this offering. To the extent that the underwriters create a naked short position, they will purchase shares in the open market to cover the position.

The underwriters have advised us that, pursuant to Regulation M of the Securities Act of 1933, they may also engage in other activities that stabilize, maintain or otherwise affect the price of the common stock, including the imposition of penalty bids. This means that if the representatives of the underwriters purchase common stock in the open market in stabilizing transactions or to cover short sales, the representatives can require the underwriters that sold those shares as part of this offering to repay the underwriting discount received by them.

These activities may have the effect of raising or maintaining the market price of the common stock or preventing or retarding a decline in the market price of the common stock, and, as a result, the price of the common stock may be higher than the price that otherwise might exist in the open market. If the underwriters commence these activities, they may discontinue them at any time. The underwriters may carry out these transactions on The NASDAQ Global Select Market, in the over the counter market or otherwise.

Prior to this offering, there was no public market for our common stock. The initial public offering price was determined by negotiations between us and the representatives of the underwriters. In determining

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the initial public offering price, we and the representatives of the underwriters considered a number of factors including:

- the information set forth in this prospectus and otherwise available to the representatives;
- our prospects and the history and prospects for the industry in which we compete;
- an assessment of our management;
- our prospects for future earnings;
- the general condition of the securities markets at the time of this offering;
- the recent market prices of, and demand for, publicly traded common stock of generally comparable companies; and
- other factors deemed relevant by the underwriters and us.

Neither we nor the underwriters can assure investors that an active trading market will develop for our common shares, or that the shares will trade in the public market at or above the initial public offering price.

Other than in the United States, no action has been taken by us or the underwriters that would permit a public offering of the securities offered by this prospectus in any jurisdiction where action for that purpose is required. The securities offered by this prospectus may not be offered or sold, directly or indirectly, nor may this prospectus or any other offering material or advertisements in connection with the offer and sale of any such securities be distributed or published in any jurisdiction, except under circumstances that will result in compliance with the applicable rules and regulations of that jurisdiction. Persons into whose possession this prospectus comes are advised to inform themselves about and to observe any restrictions relating to the offering and the distribution of this prospectus. This prospectus does not constitute an offer to sell or a solicitation of an offer to buy any securities offered by this prospectus in any jurisdiction in which such an offer or a solicitation is unlawful.

Certain of the underwriters and their affiliates have provided in the past to us and our affiliates and may provide from time to time in the future certain commercial banking, financial advisory, investment banking and other services for us and such affiliates in the ordinary course of their business, for which they have received and may continue to receive customary fees and commissions. In addition, from time to time, certain of the underwriters and their affiliates may effect transactions for their own account or the account of customers, and hold on behalf of themselves or their customers, long or short positions in our debt or equity securities or loans, and may do so in the future.

Credit Suisse Securities (USA) LLC is an affiliate of Credit Suisse First Boston Equity Partners, L.P. and affiliated funds, which together hold more than 5% of our voting securities.

Selling restrictions

European Economic Area

In relation to each Member State of the European Economic Area which has implemented the Prospectus Directive (each, a "Relevant Member State"), from and including the date on which the European Union Prospectus Directive (the "E.U. Prospectus Directive") was implemented in that Relevant Member State (the "Relevant Implementation Date") an offer of securities described in this prospectus may not be made to the public in that Relevant Member State prior to the publication of a prospectus in relation to the shares which has been approved by the competent authority in that Relevant Member State or, where appropriate, approved in another Relevant Member State and notified to the competent authority in that

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Relevant Member State, all in accordance with the E.U. Prospectus Directive, except that, with effect from and including the Relevant Implementation Date, an offer of securities described in this prospectus may be made to the public in that Relevant Member State at any time:

to any legal entity which is a qualified investor as defined under the E.U. Prospectus Directive;

to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150 natural or legal persons (other than qualified investors as defined in the E.U. Prospectus Directive); or

in any other circumstances falling within Article 3(2) of the E.U. Prospectus Directive, provided that no such offer of securities described in this prospectus shall result in a requirement for the publication by us of a prospectus pursuant to Article 3 of the E.U. Prospectus Directive.

For the purposes of this provision, the expression an "offer of securities to the public" in relation to any securities in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and the securities to be offered so as to enable an investor to decide to purchase or subscribe for the securities, as the same may be varied in that Member State by any measure implementing the E.U. Prospectus Directive in that Member State. The expression "E.U. Prospectus Directive" means Directive 2003/71/EC (and any amendments thereto, including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member State) and includes any relevant implementing measure in each Relevant Member State, and the expression "2010 PD Amending Directive" means Directive 2010/73/EU.

United Kingdom

Each of the underwriters has:

(1) only communicated or caused to be communicated and will only communicate or cause to be communicated an invitation or inducement to engage in investment activity (within the meaning of Section 21 of the Financial Services and Markets Act 2000, or FSMA, received by it in connection with the issue or sale of the securities in circumstances in which Section 21(1) of the FSMA does not apply to us; and

(2) complied and will comply with all applicable provisions of the FSMA with respect to anything done by it in relation to the securities in, from or otherwise involving the United Kingdom.

Switzerland

The shares may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange, or SIX, or on any other stock exchange or regulated trading facility in Switzerland. This document has been prepared without regard to the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or regulated trading facility in Switzerland. Neither this document nor any other offering or marketing material relating to the shares or the offering may be publicly distributed or otherwise made publicly available in Switzerland.

Neither this document nor any other offering or marketing material relating to the offering, the Company, the shares have been or will be filed with or approved by any Swiss regulatory authority. In particular, this document will not be filed with, and the offer of shares will not be supervised by, the Swiss Financial Market Supervisory Authority FINMA, or FINMA, and the offer of shares has not been and will not be authorized under the Swiss Federal Act on Collective Investment Schemes, or CISA. The investor protection

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afforded to acquirers of interests in collective investment schemes under the CISA does not extend to acquirers of shares.

United Arab Emirates

This prospectus relates to an Exempt Offer in accordance with the Offered Securities Rules of the Dubai Financial Services Authority, or DFSA. This prospectus is intended for distribution only to persons of a type specified in the Offered Securities Rules of the DFSA. It must not be delivered to, or relied on by, any other person. The DFSA has no responsibility for reviewing or verifying any documents in connection with Exempt Offers. The DFSA has not approved this prospectus nor taken steps to verify the information set forth herein and has no responsibility for the prospectus. The shares to which this prospectus relates may be illiquid and/or subject to restrictions on their resale. Prospective purchasers of the shares offered should conduct their own due diligence on the shares. If you do not understand the contents of this prospectus you should consult an authorized financial advisor.

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Legal matters

The validity of the shares of our common stock offered hereby is being passed upon for us by Wilmer Cutler Pickering Hale and Dorr LLP. Davis Polk & Wardwell LLP is acting as counsel for the underwriters in connection with this offering.

Experts

Ernst & Young LLP, independent registered public accounting firm, has audited our financial statements at December 31, 2011 and 2012 and for each of the two years in the period ended December 31, 2012, as set forth in their report. We have included our financial statements in this prospectus and elsewhere in this registration statement in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

Where you can find more information

We have filed with the SEC a registration statement on Form S-1 under the Securities Act with respect to the shares of our common stock we are offering to sell. This prospectus, which constitutes part of the registration statement, does not include all of the information contained in the registration statement and the exhibits, schedules and amendments to the registration statement. For further information with respect to us and our common stock, we refer you to the registration statement and to the exhibits and schedules to the registration statement. Statements contained in this prospectus about the contents of any contract, agreement or other document are not necessarily complete, and, in each instance, we refer you to the copy of the contract, agreement or other document filed as an exhibit to the registration statement. Each of these statements is qualified in all respects by this reference to such contract, agreement or document.

You may read and copy the registration statement of which this prospectus is a part at the SEC's public reference room, which is located at 100 F Street, N.E., Room 1580, Washington, DC 20549. You can request copies of the registration statement by writing to the Securities and Exchange Commission and paying a fee for the copying cost. Please call the SEC at 1-800-SEC-0330 for more information about the operation of the SEC's public reference room. In addition, the SEC maintains an Internet website, which is located at www.sec.gov, that contains reports, proxy and information statements and other information regarding issuers that file electronically with the SEC. You may access the registration statement of which this prospectus is a part at the SEC's Internet website. Upon completion of this offering, we will be subject to the information reporting requirements of the Securities Exchange Act of 1934, and we will file reports, proxy statements and other information with the SEC.

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PTC Therapeutics, Inc.
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Report of independent registered accounting firm

The Board of Directors and Stockholders
PTC Therapeutics, Inc.

We have audited the accompanying balance sheets of PTC Therapeutics, Inc. (the Company) as of December 31, 2011 and 2012, and the related statements of operations, comprehensive income (loss), statements of convertible preferred stock and stockholders' deficit, and cash flows for each of the two years in the period ended December 31, 2012. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. We were not engaged to perform an audit of the Company's internal control over financial reporting. Our audit included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the financial position of PTC Therapeutics, Inc. at December 31, 2011 and 2012 and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2012, in conformity with U.S. generally accepted accounting principles.

/s/ ERNST & YOUNG LLP

Metro Park, New Jersey
March 15, 2013

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PTC Therapeutics, Inc.
Balance sheets

	December 31	
	2011	2012
Assets		
Current assets:		
Cash and cash equivalents	$28,431,410	$ 2,725,702
Prepaid expenses and other current assets	3,379,199	855,750
Grant and collaboration receivables, net	1,244,128	1,013,813
Total current assets	33,054,737	4,595,265
Fixed assets, net	10,795,507	8,280,037
Deposits and other assets	297,916	197,050
Total assets	$44,148,160	$13,072,352
Liabilities convertible preferred stocks and stockholders' deficit		
Current liabilities:		
Accounts payable and accrued expenses	$13,049,454	$ 7,023,971
Current portion of long-term debt	7,139,975	4,444,171
Deferred revenue	22,955,901	16,690,747
Total current liabilities	43,145,330	28,158,889
Deferred revenue, less current portion	16,448,656	741,667
Long-term debt, less current portion	4,549,332	438,810
Other long-term liabilities	4,229,617	2,549,719
Total liabilities	68,372,935	31,889,085
Commitments and contingencies *(Note 12)*		
Series One convertible preferred stock, designated 2,000,000 shares; issued and outstanding 1,483,337 shares at December 31, 2012		62,263,852
Series Two convertible preferred stock, designated 13,750,000 shares; issued and outstanding 10,701,405 shares at December 31, 2012		18,182,129
Series Three convertible preferred stock, designated 13,750,000 shares; issued and outstanding 2,853,517 shares at December 31, 2012		377,787
Series A G Convertible preferred stock:		
Preferred stock, $0.001 par value. Authorized 156,995,095 shares:		
Series A convertible preferred stock, designated 750,000 shares; issued and outstanding 750,000 shares at December 31, 2011 (liquidation preference of $750,000)	750,000	
Series B convertible preferred stock, designated 187,500 shares; issued and outstanding 187,500 shares at December 31, 2011 (liquidation preference of $375,000)	364,524	
	14,117,089	

Series C convertible preferred stock, designated 6,295,000 shares; issued and outstanding 6,000,000 shares at December 31, 2011 (liquidation preference of $15,000,000)	
Series D convertible preferred stock, designated 13,769,935 shares; issued and outstanding 13,095,769 shares at December 31, 2011 (liquidation preference of $42,561,249)	39,282,460
Series E convertible preferred stock, designated 126,735,022 shares; issued and outstanding 125,740,607 shares at December 31, 2011 (liquidation preference of $49,999,998)	49,048,047
Series E-2 convertible preferred stock, designated 3,670,138 shares; issued and outstanding 3,670,138 shares at December 31, 2011 (liquidation preference of $26,645,187)	26,509,451
Series F convertible preferred stock, designated 675,000 shares; issued and outstanding 625,000 shares at December 31, 2011 (liquidation preference of $10,000,000)	10,000,000
Series F-2 convertible preferred stock, designated 1,612,500 shares; issued and outstanding 1,515,503 shares at December 31, 2011 (liquidation preference of $24,248,048)	24,114,456
Series G convertible preferred stock, designated 3,300,000 shares; issued and outstanding 3,143,750 shares at December 31, 2011 (liquidation preference of $50,300,000)	50,193,887
Stockholders' deficit:	
Common stock, $0.001 par value. Authorized 216,666 shares; issued and outstanding 1,083 shares at December 31, 2011 and 4,52	