PTC THERAPEUTICS, INC.
Form 10-K
March 06, 2014

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended: December 31, 2013

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

Commission file number: 001-35969

PTC THERAPEUTICS, INC.

(Exact Name of Registrant as Specified in its Charter)

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

(908) 222-7000

(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

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

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

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes o No ý

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes o No ý

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ý No o

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. o

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

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

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

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

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on the NASDAQ Global Select Market on June 28, 2013, the last business day of the registrant's most recently completed second fiscal quarter, was $260,280,900. For purposes of this calculation, shares of Common Stock held by directors, officers and 10% stockholders known to the registrant have been treated as shares held by affiliates.

As of March 4, 2014, the registrant had 30,076,773 shares of Common Stock, $0.001 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Part III of this Annual Report incorporates by reference information from the definitive Proxy Statement for the registrant's 2014 Annual Meeting of Shareholders which is expected to be filed with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year ended December 31, 2013.

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PTC Therapeutics, Inc.

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FORWARD-LOOKING STATEMENTS

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

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

- the timing and conduct of our clinical trials of 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;

- our expectations with respect to development and regulatory status of our program directed against spinal muscular atrophy in collaboration with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., which we refer to collectively as Roche, and the Spinal Muscular Atrophy Foundation, or the SMA Foundation, and our estimates regarding future revenues from achievement of milestones in that program;

- 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;

the impact of government laws and regulations;

our competitive position; and

our estimates regarding expenses, future revenues, capital requirements and needs for additional financing.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included

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in this Annual Report on Form 10-K, particularly in Part I, Item 1A. Risk Factors, that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

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

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

All website addresses given in this prospectus are for information only and are not intended to be an active link or to incorporate any website information into this document.

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PART I

Item 1. Business

Overview

We are a 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 hold worldwide commercialization rights to ataluren for all indications in all territories.

We have initiated a confirmatory Phase 3 clinical trial of ataluren for the treatment of Duchenne muscular dystrophy caused by nonsense mutations, or nmDMD. We refer to this trial as the Ataluren Confirmatory Trial in DMD, or ACT DMD. We dosed the first patient in this trial in 2013 and expect to complete enrollment in mid-2014. 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. In January 2014, EMA's Committee for Medicinal Products for Human Use, or CHMP, adopted a negative opinion recommending the refusal of the granting of the conditional marketing authorization for ataluren for the treatment of nmDMD. We have requested a re-examination of the CHMP opinion and currently expect a final outcome in the second quarter of 2014. 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 dosing patients in this trial in the first half of 2014. In addition, we are pursuing early access programs for ataluren for nmDMD patients in selected territories that support reimbursement for such programs. 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. We also plan to pursue additional indications for ataluren beyond nmDMD and nmCF and expect to initiate a proof-of-concept study for a third indication in 2014.

We continue to advance the development of our spinal muscular atrophy collaboration with F. Hoffman-La Roche Ltd and Hoffman-La Roche Inc., which we refer to collectively as Roche, and the Spinal Muscular Atrophy Foundation, or SMA Foundation. A development candidate for the program was selected in August 2013, and a Phase 1 clinical program was initiated in healthy volunteers in January 2014. Each of these events triggered a milestone payment to us from Roche.

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

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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 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 initiated our confirmatory Phase 3 ACT DMD clinical trial 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. During the review process, the EMA informed us of major objections that would preclude a recommendation for marketing authorization unless adequately addressed. These major objections related 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, and uncertainties about the effective dose. The EMA also questioned whether our confirmatory Phase 3 ACT DMD clinical trial could be completed if the EMA granted conditional approval. In December 2013, the EMA convened a scientific advisory group, or SAG, meeting as part of the regulatory review process followed by the oral explanation meeting with the CHMP. We believe that both the SAG and oral explanation meetings allowed us and independent experts in the DMD field to provide information to the SAG and CHMP members about important aspects of our clinical data and trial design.

In January 2014, the CHMP adopted a negative opinion recommending the refusal of the granting of the conditional marketing authorization for ataluren for the treatment of nmDMD. The CHMP stated that a principal reason for the negative opinion was that our prior Phase 2b clinical trial had failed to demonstrate in the primary analysis that patients taking ataluren could walk a greater distance than patients taking placebo in six minutes, the primary endpoint. Additionally, the CHMP noted that

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other measures of efficacy provided only limited supportive evidence of the beneficial effects of ataluren. The CHMP acknowledged to us that the retrospective analyses that we presented to the CHMP were performed in line with the most current knowledge about the natural history of the disease and that our definition of the subgroups in the analyses were both clinically and scientifically justified. However, the CHMP concluded that we did not provide sufficiently compelling evidence of efficacy to justify conditional approval. In addition, the CHMP considered that we had not provided sufficient data to determine how ataluren works in the body and how its effects change with dose. Finally, the CHMP expressed concern that the conduct of the confirmatory Phase 3 ACT DMD clinical trial might be affected by the availability of an authorized product and therefore potentially jeopardize the feasibility of completing the trial. As a result, despite divergent minority positions, the CHMP concluded a favorable risk-benefit balance could not be established at that time and adopted a negative opinion. We have requested a re-examination of the CHMP opinion and currently expect a final outcome in the second quarter of 2014. Based upon the timelines for a re-examination process, we believe that our confirmatory Phase 3 ACT DMD clinical trial will be substantially enrolled at the time the CHMP would consider a revision of their initial opinion as part of the re-examination process.

We continue to believe that completion of our confirmatory Phase 3 ACT DMD clinical trial and submission of data to the regulatory authorities is the more likely path to obtain marketing approval of ataluren. There is substantial risk that the EMA will not grant us conditional approval upon re-examination of the original CHMP negative opinion. 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 ACT DMD clinical trial. We plan to complete our confirmatory Phase 3 ACT DMD clinical trial before applying for marketing approval from the FDA. In designing our confirmatory Phase 3 ACT DMD 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 have concluded discussions with regulatory authorities concerning our proposed trial protocol for a confirmatory Phase 3 clinical trial of ataluren for nmCF. We plan to begin dosing patients in this trial in the first half of 2014. 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. Our interactions with the FDA regarding the clinical development design options which would have the potential to support an NDA in 2013 did not achieve a consensus between the EMA and FDA views. However, based on these interactions, we nonetheless intend to proceed with our confirmatory Phase 3 clinical trial of ataluren in nmCF in the first half of 2014 consistent with feedback from the EMA on our trial design. Following the conclusion of the re-examination process for our MAA for conditional approval of ataluren in nmDMD, we plan to evaluate the benefit and timing for a potential MAA submission to the EMA for the conditional approval of ataluren in nmCF. There also is substantial risk that the EMA will not grant us conditional approval of ataluren for the treatment of nmCF.

We continue to advance the development of our spinal muscular atrophy collaboration with Roche and the SMA Foundation. The collaboration was initially funded in part by the SMA Foundation. In December 2011, we announced a collaboration with Roche which provided us with an upfront payment of $30 million, the potential for up to $460 million in milestone payments and royalties on any future sales. In August 2013, a development candidate for the program was selected which triggered a $10 million milestone payment to us from Roche. In January 2014, a Phase 1 clinical program was initiated which triggered a $7.5 million milestone payment to us from Roche. Roche is responsible for pursuing clinical development of compounds from the program consistent with a governance structure

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that includes representation from us and the SMA Foundation and then commercialization of these compounds.

In addition, 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.

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 our confirmatory Phase 3 ACT DMD clinical trial and are pursuing a re-examination of our application for conditional approval to market ataluren for the treatment of nmDMD 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. We plan to evaluate the benefit and timing for a potential MAA submission to the EMA for the conditional approval of ataluren in nmCF and, in the first half of 2014, to begin dosing patients for a confirmatory Phase 3 clinical trial of ataluren for the treatment of nmCF.

Maximize commercial potential of ataluren. We hold 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. We plan to initiate a proof-of-concept study for a third indication for ataluren in 2014.

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

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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 ACT DMD clinical trial ongoing	PTC
Ataluren for nmCF	Phase 3 clinical trial completed Confirmatory Phase 3 clinical trial patient dosing planned for first half of 2014	PTC
Spinal muscular atrophy	Development candidate selected Phase 1 clinical program initiated	Roche
Oncology BMI1	Preclinical Lead development compound selected IND-enabling studies ongoing	PTC
Antibacterial		PTC

	Preclinical
	Optimization of development compounds ongoing

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 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.

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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.

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.

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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, nmDMD-007 or nmDMD-008)	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, nmDMD-007, or nmDMD-008)	Ongoing	Initiated in May 2012
nmDMD-020 (ACT DMD)	Confirmatory Phase 3, double-blind, placebo controlled, planned as Australia, Canada, European Union, Israel, South America, South Korea, Switzerland, Turkey, United States	Approximately 220	Ongoing	Initiated in April 2013
nmDMD-020e	Phase 3 extension, open label, planned as Australia, Canada, European Union, Israel, South America, South Korea, Switzerland, Turkey, United States	Approximately 220 (patients previously in nmDMD-020)	Planned	Plan to begin dosing in the first half of 2014

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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)	Completed	August 2010 to December 2013
nmCF-021	Confirmatory Phase 3, double-blind, placebo controlled, global trial sites planned	Approximately 210	Planned	Plan to begin dosing patients in the first half of 2014
nmCF-023	Phase 3 open label planned in Canada, European Union, Israel, United States	80 (patients previously in nmCF-009 not using chronic inhaled aminoglycosides)	Planned	Plan to begin enrolling trial sites in the first quarter of 2014

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 initiated our confirmatory Phase 3 ACT DMD clinical trial in April 2013 and expect to initiate an open label extension study to obtain additional safety and efficacy data in patients who completed the double-blind confirmatory Phase 3 ACT DMD clinical trial. We are also 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 dosing patients in our confirmatory Phase 3 clinical trial of ataluren for the treatment of nmCF in the first half of 2014. We expect to initiate a separate open label, trial extension study to obtain additional safety and efficacy information in patients who completed the double-blind Phase 3 clinical trial and are not receiving chronic inhaled aminoglycoside antibiotics.

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. Duchenne muscular dystrophy occurs when a mutation in the dystrophin gene prevents the

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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.

ACT DMD Phase 3 clinical trial of ataluren for nmDMD

We have initiated our confirmatory Phase 3 ACT DMD clinical trial to evaluate the efficacy and safety of ataluren in patients with nmDMD as confirmed by gene sequencing. This is a multicenter, randomized, double-blind, placebo controlled Phase 3 clinical trial. We dosed the first patient in this trial in April 2013, with enrollment expected to be completed in mid-2014. 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

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6-minute walk test has become the most common primary endpoint currently used in Duchenne muscular dystrophy clinical trials.

Supportive analyses of ambulation in our trial protocol 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.

We are employing 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;

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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 enrollment for this trial in mid-2014 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 ACT DMD clinical trial.

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

The study population and ou