CYTOKINETICS INC
Form 10-K
March 03, 2016
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UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

(Mark One)

þ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended December 31, 2015

or

¨ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
From the transition period from_____ to _____

Commission file number: 000-50633

CYTOKINETICS, INCORPORATED

(Exact name of registrant as specified in its charter)

Delaware	**94-3291317**
(State or other jurisdiction of incorporation or organization)	*(I.R.S. Employer Identification No.)*
280 East Grand Avenue	
South San Francisco, CA	**94080**
(Address of principal executive offices)	*(Zip Code)*

(650) 624-3000

(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	The NASDAQ Capital Market

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

None

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

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

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 þ No ¨

Indicate by check mark whether the Registrant has submitted electronically and posted on its corporate Website, 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 þ No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of the 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. þ

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 the definitions of large accelerated filer, accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act.

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

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

The aggregate market value of the voting and non-voting common equity held by non-affiliates was $259.6 million, computed by reference to the last sales price of $6.72 as reported by the NASDAQ Market as of June 30, 2015. This calculation does not reflect a determination that certain persons are affiliates of the Registrant for any other purpose. The number of shares of common stock held by non-affiliates excluded 96,371 shares of common stock held by directors, officers and affiliates of directors. The number of shares owned by affiliates of directors was determined based upon information supplied by such persons and upon Schedules 13D and 13G, if any, filed with the SEC. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the Registrant, that such person is controlled by or under common control with the Registrant, or that such persons are affiliates for any other purpose.

The number of shares outstanding of the Registrant s common stock on February 26, 2016 was 39,592,808 shares.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant s Proxy Statement for its 2016 Annual Meeting of Stockholders to be filed with the Securities and Exchange Commission, no later than 120 days after the end of the fiscal year, are incorporated by reference into Part III of this Annual Report on Form 10-K.

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CYTOKINETICS, INCORPORATED

FORM 10-K

Year Ended December 31, 2015

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PART I

This report contains forward-looking statements indicating expectations about future performance and other forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the Securities Act), Section 21E of the Securities Exchange Act of 1934, as amended (the Exchange Act), and the Private Securities Litigation Reform Act of 1995, that involve risks and uncertainties. We intend that such statements be protected by the safe harbor created thereby. Forward-looking statements involve risks and uncertainties and our actual results and the timing of events may differ significantly from the results discussed in the forward-looking statements. Examples of such forward-looking statements include, but are not limited to, statements about or relating to:

guidance concerning revenues, research and development expenses and general and administrative expenses for 2016;

the sufficiency of existing resources to fund our operations for at least the next 12 months;

our capital requirements and needs for additional financing;

the initiation, design, conduct, enrollment, progress, timing and scope of clinical trials and development activities for our drug candidates conducted by ourselves or our partners, Amgen Inc. and Astellas Pharma Inc. (Astellas), including the anticipated timing for initiation of clinical trials, anticipated rates of enrollment for clinical trials and anticipated timing of results becoming available or being announced from clinical trials;

the results from the clinical trials and non-clinical and preclinical studies of our drug candidates and other compounds, and the significance and utility of such results;

anticipated interactions with regulatory authorities;

the further development of tirasemtiv for the potential treatment of amyotrophic lateral sclerosis (ALS);

the expected acceptability by regulatory authorities of the effects of tirasemtiv on slow vital capacity or other measures of clinical benefit related to respiratory function in patients with ALS as a Phase 3 clinical trial endpoint to support the registration of tirasemtiv as a treatment for ALS;

our and our partners plans or ability to conduct the continued research and development of our drug candidates and other compounds;

the potential advancement of omecamtiv mecarbil into Phase 3 clinical development;

our expected roles in research, development or commercialization under our strategic alliances with Amgen and Astellas;

the properties and potential benefits of, and the potential market opportunities for, our drug candidates and other compounds, including the potential indications for which they may be developed;

the sufficiency of the clinical trials conducted with our drug candidates to demonstrate that they are safe and efficacious;

our receipt of milestone payments, royalties, reimbursements and other funds from current or future partners under strategic alliances, such as with Amgen or Astellas;

our ability to continue to identify additional potential drug candidates that may be suitable for clinical development;

our plans or ability to commercialize drugs with or without a partner, including our intention to develop sales and marketing capabilities;

the focus, scope and size of our research and development activities and programs;

the utility of our focus on the biology of muscle function, and our ability to leverage our experience in muscle contractility to other muscle functions;

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our ability to protect our intellectual property and avoid infringing the intellectual property rights of others;

expected future sources of revenue and capital;

losses, costs, expenses and expenditures;

future payments under loan and lease obligations;

potential competitors and competitive products;

retaining key personnel and recruiting additional key personnel;

expected timing for recognition of compensation cost related to unvested stock options; and

the potential impact of recent accounting pronouncements on our financial position or results of operations.

Such forward-looking statements involve risks and uncertainties, including, but not limited to:

further clinical development of tirasemtiv for the potential treatment of ALS will require significant additional funding and we may be unable to obtain such additional funding on acceptable terms, if at all;

the U.S. Food and Drug Administration (FDA) and/or other regulatory authorities may not accept effects on respiratory function, including slow vital capacity, as an appropriate clinical trial endpoint to support the registration of tirasemtiv for the treatment of ALS;

Amgen s decisions with respect to the timing, design and conduct of research and development activities for omecamtiv mecarbil and related compounds, including decisions to postpone or discontinue research or development activities relating to omecamtiv mecarbil and related compounds;

Astellas decisions with respect to the timing, design and conduct of research and development activities for CK-2127107 and other skeletal muscle activators, including decisions to postpone or discontinue research or development activities relating to CK-2127107 and other skeletal muscle activators;

our ability to enter into strategic partnership agreements for any of our programs on acceptable terms and conditions or in accordance with our planned timelines;

our ability to obtain additional financing on acceptable terms, if at all;

our receipt of funds and access to other resources under our current or future strategic alliances;

difficulties or delays in the development, testing, manufacturing or commercialization of our drug candidates;

difficulties or delays, or slower than anticipated patient enrollment, in our or partners clinical trials;

difficulties or delays in the manufacture and supply of clinical trial materials;

failure by our contract research organizations, contract manufacturing organizations and other vendors to properly fulfill their obligations or otherwise perform as expected;

results from non-clinical studies that may adversely impact the timing or the further development of our drug candidates and other compounds;

the possibility that the FDA or foreign regulatory agencies may delay or limit our or our partners ability to conduct clinical trials or may delay or withhold approvals for the manufacture and sale of our products;

changing standards of care and the introduction of products by competitors or alternative therapies for the treatment of indications we target that may limit the commercial potential of our drug candidates;

difficulties or delays in achieving market access and reimbursement for our drug candidates and the potential impacts of health care reform;

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changes in laws and regulations applicable to drug development, commercialization or reimbursement;

the uncertainty of protection for our intellectual property, whether in the form of patents, trade secrets or otherwise;

potential infringement or misuse by us of the intellectual property rights of third parties;

activities and decisions of, and market conditions affecting, current and future strategic partners;

accrual information provided by our contract research organizations and other vendors;

potential ownership changes under Internal Revenue Code Section 382; and

the timeliness and accuracy of information filed with the U.S. Securities and Exchange Commission (the SEC) by third parties.

In addition such statements are subject to the risks and uncertainties discussed in the Risk Factors section and elsewhere in this document. Such statements speak only as of the date on which they are made, and, except as required by law, we undertake no obligation to update any forward-looking statement to reflect events or circumstances after the date on which the statement is made or to reflect the occurrence of unanticipated events. New factors emerge from time to time, and it is not possible for us to predict which factors will arise. In addition, we cannot assess the impact of each factor on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements.

Item 1. ***Business***

Overview

We were incorporated in Delaware in August 1997 as Cytokinetics, Incorporated. We are a late-stage biopharmaceutical company focused on the discovery and developments of first-in-class muscle activators as potential treatment for debilitating diseases in which muscle performance is compromised and/or declining. Our research and development activities relating to the biology of muscle function have evolved from our knowledge and expertise regarding the cytoskeleton, a complex biological infrastructure that plays a fundamental role within every human cell. Our most advanced research and development programs relate to the biology of muscle function and are directed to small molecule modulators of the contractility of skeletal or cardiac muscle. We are also conducting earlier-stage research directed to other compounds with the potential to modulate muscle contractility and other muscle functions, such as growth, energetics and metabolism.

Our lead drug candidate from our skeletal muscle contractility program, tirasemtiv (formerly known as CK-2017357), is a fast skeletal muscle troponin activator. Cytokinetics retains exclusive rights to tirasemtiv and is independently developing this drug candidate for the potential treatment of ALS. We conducted a Phase 2 clinical trials program for tirasemtiv, including a Phase 2b clinical trial in patients with ALS, known as BENEFIT-ALS (Blinded Evaluation of Neuromuscular Effects and Functional Improvement with Tirasemtiv in ALS). Based on the results of BENEFIT-ALS, we started a Phase 3 clinical development program for tirasemtiv in patients with ALS in July 2015 known as VITALITY-ALS (Ventilatory Investigation of Tirasemtiv and Assessment of Longitudinal Indices after Treatment for a Year in ALS). Tirasemtiv has been granted orphan drug designation and fast track status by the FDA and orphan medicinal product designation by the European Medicines Agency, in each case for the potential treatment of ALS.

We are also developing CK-2127107, a structurally distinct fast skeletal muscle troponin activator, under a strategic alliance with Astellas established in June 2013 and expanded in December 2014. Astellas holds an exclusive license to develop and commercialize CK-2127107 worldwide, subject to our development and commercialization participation rights. Under this strategic alliance, Cytokinetics conducted five Phase 1 clinical trials of CK-2127107 and started a Phase 2 clinical trial of CK-2127107 in patients with spinal muscular atrophy (SMA) in December 2015. CK-2127107 is also being evaluated for the potential use in other indications

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associated with muscle weakness. We expect that Astellas will initiate a Phase 2 clinical trial in patients with chronic obstructive pulmonary disease (COPD) in the first half of 2016. We are also conducting joint research with Astellas directed to next-generation skeletal muscle activators. Further details regarding our strategic alliance with Astellas can be found below in Item 1 of this report under Research and Development Programs Skeletal Muscle Contractility Program CK-2127107 and Other Skeletal Muscle Activators Astellas Strategic Alliance.

Our lead drug candidate from our cardiac muscle contractility program, omecamtiv mecarbil (formerly known as CK-1827452), is a novel cardiac muscle myosin activator that is being developed under a strategic alliance with Amgen. Amgen holds an exclusive license to develop and commercialize omecamtiv mecarbil worldwide, subject to our development and commercialization participation rights.

Omecamtiv mecarbil has been the subject of an extensive Phase 1 and Phase 2 clinical trials program. In October 2015, we announced the results of COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure), the last planned Phase 2 trial of omecamtiv mecarbil to be completed prior to a decision regarding the potential advancement of this drug candidate to Phase 3. COSMIC-HF was designed to assess the pharmacokinetics and tolerability of omecamtiv mecarbil dosed orally in patients with heart failure and left ventricular systolic dysfunction and its effects on echocardiographic measures of cardiac function. An intravenous formulation of omecamtiv mecarbil was studied in a Phase 2b clinical trial known as ATOMIC-AHF (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure), which was designed to evaluate the safety and efficacy of omecamtiv mecarbil in patients with left ventricular systolic dysfunction who are hospitalized with acute heart failure. We expect to continue our joint research with Amgen directed to next-generation compounds in our cardiac muscle contractility program in 2016. Further details regarding our strategic alliance with Amgen can be found below in Item 1 of this report under Research and Development Programs Cardiac Muscle Contractility Program Amgen Strategic Alliance.

All of our drug candidates have demonstrated evidence of potentially clinically relevant pharmacodynamic activity in humans. In 2016, we expect to continue to focus on translating the observed pharmacodynamic activity of these compounds into potentially meaningful clinical benefits for patients.

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Following is a summary of the planned clinical development activities for our drug candidates:

Drug Candidate (Mechanism of Action)	Partnership Status	Potential Indication(s)	Stage of Development	Development Status and Planned Development Activities
Skeletal Muscle Contractility Program				
Tirasemtiv (fast skeletal muscle troponin activator)	Cytokinetics developing independently	ALS	Phase 3	We started a Phase 3 clinical development program for tirasemtiv in patients with ALS in the third quarter of 2015. We anticipate that the trial will be fully enrolled in the first half of 2016.
CK-2127107 (fast skeletal muscle troponin activator)	Partnered with Astellas	SMA COPD	Phase 2	We started a Phase 2 clinical trial in patients with SMA in December 2015. We anticipate that the trial will complete enrollment in the second half of 2016. We anticipate that in the first half of 2016, Astellas will initiate a Phase 2 clinical trial in patients with chronic obstructive pulmonary disease (COPD)
Cardiac Muscle Contractility Program				
Omecamtiv mecarbil (cardiac muscle myosin activator)	Partnered with Amgen	heart failure (oral administration)	Phase 2	We reported results from COSMIC-HF in November 2015. Expect to make a decision regarding the potential advancement to Phase 3 in the coming months.
Omecamtiv mecarbil (cardiac muscle myosin activator)	Partnered with Amgen	heart failure (IV administration)	Phase 2	ATOMIC-HF completed in 2013.

All of our drug candidates have arisen from our cytoskeletal research activities. Our focus on the biology of the cytoskeleton distinguishes us from other biopharmaceutical companies, and potentially positions us to discover and develop novel therapeutics that may be useful for the treatment of severe diseases and medical conditions. Each of our drug candidates has a novel mechanism of action compared to currently marketed drugs, which we believe validates our focus on the cytoskeleton as a productive area for drug discovery. We intend to leverage our experience in muscle contractility in order to expand our current pipeline, and expect to identify additional potential drug candidates that may be suitable for clinical development.

Corporate Strategy

We are a late-stage biopharmaceutical company focused on discovering, developing and commercializing first-in-class muscle activators as potential treatments for debilitating diseases in which muscle performance is compromised and/or declining. As a leader in muscle biology and the mechanics of muscle performance, the company is developing small molecule drug candidates specifically engineered to increase muscle function and contractility. Over the next 5 years, our goal is to discover, develop and commercialize novel drug products that modulate muscle function in ways that may benefit people living with serious diseases or medical conditions, with the intent of establishing a fully integrated biopharmaceutical company.

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The five key components of our Corporate Strategy, Vision 2020: Empowering Our Future, are:

Conduct late-stage clinical development of novel, first-in-class muscle activators for the potential treatment of ALS, SMA, heart failure and other diseases impacting muscle function. As we enter 2016, our portfolio consists of three products that are in mid-late stage clinical development in three therapeutic areas, namely ALS, SMA and heart failure. We believe that by focusing on these disease areas characterized by well-organized physician-investigator groups, significant unmet clinical needs, and strong patient and disease advocacy, we may enhance our effectiveness in enrolling and conducting clinical trials that may answer important questions about the dosing, tolerability, pharmacokinetics and pharmacodynamics as well as the potential safety and efficacy of our drug candidates. We believe that our considered clinical trial designs and well-executed development programs can improve our ability to realize value from our and our partners clinical development activities. As we advance our drug candidates into later-stage clinical development, we extensively evaluate previous clinical trial designs and results to assess key learnings that may be applied to our late-stage clinical development activities. We believe this may result in more successful later-stage clinical development activities that may increase the likelihood of achieving our objectives to develop effective therapies that may address the needs of people living with these devastating diseases.

Collaborate with patient communities to support the urgent development of new medicines for diseases of impaired muscle function with pressing unmet medical needs. Central to our corporate strategy are the people living with a disease or medical condition characterized by impaired muscle function. We focused our development and commercialization activities on diseases that lack effective therapies and, in some cases, those with no approved medicines. We recognize that by applying our extensive knowledge of muscle biology towards the development of novel therapies for the people living with these diseases, not only patients but their caregivers and families, we aim to improve their lives. As such, we need to collaborate with these individuals and their communities to ensure our therapeutics are addressing their urgent needs and that we understand and appreciate the issues associated with these diseases and conditions. We work collaboratively with entities, such as patient advocacy groups, that are focused on policies, guidelines and practices to accelerate development and commercialization of novel therapies, where possible and appropriate, and on ensuring that the voice of their constituency is heard.

Mature our company operations to enable development, registration and commercialization of muscle biology drug candidates across North America and Europe. With a focus on disease areas for which there are serious unmet medical needs, we direct our activities to potential commercial opportunities in concentrated and tractable customer segments, such as hospital specialists and disease-specific centers of excellence, which may be addressed by a smaller, targeted sales force. In preparing for the potential commercialization of our drug candidates directed to these markets, we are focusing our activities on a broad range of issues facing patients and payors, including the principal drivers of clinical and economic burdens associated with these diseases. We also seek to focus on opportunities that the multiple constituencies and stakeholders for these markets may recognize as creating value. Accordingly, targeting unmet medical needs in these areas may provide us competitive opportunities and support development of a franchise in diseases involving muscle weakness, wasting and fatigue. In these markets, we believe that a company with limited resources may be able to compete effectively against larger, more established companies with greater financial and commercial resources. For these opportunities, we intend to develop clinical development and sales and marketing capabilities in North America and Europe with the goal of becoming a fully integrated biopharmaceutical company.

Advance next-generation skeletal and cardiac muscle activator compounds into clinical development by leveraging existing research collaborations. We take a purpose-driven approach by leveraging our extensive muscle biology expertise to engineer compounds with specific characteristics aimed at treating diseases that impact muscle function. By increasing muscle strength and performance, the potential treatments we are developing may preserve and extend independence and self-reliance in people suffering from debilitating diseases. We have established select strategic alliances to support our drug development programs while preserving significant development and commercialization rights. We believe that such

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alliances may allow us to obtain financial support and to capitalize on the therapeutic area expertise and resources of our partners that can potentially accelerate the development and commercialization of our drug candidates. Where we deem appropriate, we plan to retain certain rights to participate in the development of drug candidates and commercialization of potential drugs arising from our programs and alliances, so that we can expand and capitalize on our own internal development capabilities and build our commercialization capabilities.

Progress proprietary research programs focused on muscle metabolism, growth and energetics into development under new collaborations. We believe that our extensive understanding of muscle biology and our proprietary research technologies should enable us to discover and potentially to develop drug candidates with novel mechanisms of action that may offer potential benefits not provided by existing drugs and which may have application across a broad array of diseases and medical conditions. We expect that we may be able to leverage our expertise in muscle contractility to expand programs related to other areas of muscle function and which may extend to the potential treatment of other serious medical diseases and conditions. Progressing related programs in parallel may afford us an opportunity to build a broader business that could benefit from multiple products that serve related clinical and commercial needs associated with impaired muscle function, muscle weakness and fatigue. In addition, this strategy may enable us to diversify certain technical, financial and operating risks by advancing several drug candidates in parallel.

Research and Development Programs

Our long-standing interest in the cytoskeleton has led us to focus our research and development activities on the biology of muscle function, and in particular, small molecule modulation of muscle contractility. We believe that our expertise in the modulation of muscle contractility is an important differentiator for us. Our preclinical and clinical experience in muscle contractility may position us to discover and develop additional novel therapies that have the potential to improve the health of patients with severe and debilitating diseases or medical conditions.

Small molecules that affect muscle contractility may have several applications for a variety of serious diseases and medical conditions. For example, certain diseases and medical conditions associated with muscle weakness may be amenable to treatment by enhancing the contractility of skeletal muscle. Similarly, heart failure is a disease often characterized by impaired cardiac muscle contractility which may be treated by modulating the contractility of cardiac muscle. Because the modulation of the contractility of different types of muscle, such as cardiac and skeletal muscle, may be relevant to multiple diseases or medical conditions, we believe we can leverage our expertise in these areas to more efficiently discover and develop potential drug candidates that modulate the applicable muscle type for multiple indications.

We are currently developing a number of small molecule compounds arising from our muscle contractility programs.

Tirasemtiv is our lead drug candidate from our skeletal muscle contractility program. Potential indications for which this drug candidate may be useful include skeletal muscle weakness associated with neuromuscular diseases, such as ALS. We have conducted a Phase 2 clinical trials program for tirasemtiv, and started a Phase 3 clinical development program of this drug candidate in patients with ALS in the July 2015.

CK-2127107, another drug candidate from this program, is partnered with Astellas world-wide for the potential treatment of SMA and potentially other neuromuscular and non-neuromuscular indications associated with muscle weakness. We conducted a Phase 1 clinical trials program for CK-2127107 under this collaboration. We started a Phase 2 clinical trial of CK-2127107 in patients with SMA in December 2015. We anticipate that in the first half of 2016, Astellas will initiate a Phase 2 clinical trial in patients with chronic obstructive pulmonary disease (COPD). Cytokinetics and Astellas continue to evaluate other indications which may be suitable for CK-2127107 or other skeletal sarcomere activators under the collaboration.

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Omecamtiv mecarbil, a novel cardiac muscle myosin activator, is partnered with Amgen world-wide for the potential treatment of heart failure. Phase 2 clinical trials were conducted with both intravenous and oral formulations of omecamtiv mecarbil. An intravenous formulation of omecamtiv mecarbil was studied in ATOMIC-AHF, a Phase 2b clinical trial in patients with acute heart failure, and an oral formulation of omecamtiv mecarbil was studied in COSMIC-HF, a Phase 2 clinical trial in patients with heart failure.

We are continuing to conduct discovery, characterization and lead optimization activities for other compounds with the potential to modulate muscle contractility and other muscle functions, such as growth, energetics and metabolism.

Research and Development Expense. Our research and development expenses were $46.4 million, $44.4 million and $49.5 million for 2015, 2014 and 2013, respectively.

Skeletal Muscle Contractility Program

Overview. Our skeletal muscle contractility program is focused on the activation of the skeletal sarcomere, the basic unit of skeletal muscle contraction. The skeletal sarcomere is a highly ordered cytoskeletal structure composed of skeletal muscle myosin, actin, and a set of regulatory proteins, which include the troponins and tropomyosin. This program leverages our expertise developed in our ongoing discovery and development of cardiac sarcomere activators, including the cardiac muscle myosin activator omecamtiv mecarbil.

We believe that our skeletal sarcomere activators may lead to new therapeutic options for diseases and medical conditions associated with aging, muscle weakness and wasting and neuromuscular dysfunction. The clinical effects of muscle weakness and wasting, fatigue and loss of mobility can range from decreased quality of life to, in some instances, life-threatening complications. By directly improving skeletal muscle function, a small molecule activator of the skeletal sarcomere potentially could enhance functional performance and quality of life in patients suffering from diseases or medical conditions characterized or complicated by muscle weakness or wasting. These may include diseases and medical conditions associated with skeletal muscle weakness or wasting, such as ALS, claudication, myasthenia gravis, sarcopenia (general frailty associated with aging), post-surgical rehabilitation and cachexia in connection with heart failure or cancer.

Tirasemtiv is the lead drug candidate from this program. We retain exclusive rights to tirasemtiv. We have conducted a Phase 2 clinical development program for tirasemtiv, and we started a Phase 3 clinical trial for this drug candidate in patients with ALS in July 2015. We are also developing another drug candidate from this program, CK-2127107, which has been evaluated in Phase 1 clinical trials in collaboration with Astellas for potential indications associated with muscle weakness. We started a Phase 2 clinical trial for CK-2127107 in patients with SMA in December 2015 Tirasemtiv and CK-2127107 are structurally distinct and selective small molecules that activate the fast skeletal muscle troponin complex in the sarcomere by increasing its sensitivity to calcium, leading to an increase in skeletal muscle contractility. Each of tirasemtiv and CK-2127107 has demonstrated pharmacological activity in preclinical models and evidence of potentially clinically relevant pharmacodynamic effects in humans. We are evaluating other potential indications for which tirasemtiv and CK-2127107 may be useful.

Tirasemtiv. Tirasemtiv, a fast skeletal troponin activator, is the lead drug candidate from our skeletal muscle contractility program. We conducted three evidence of effect Phase 2a clinical trials, including two Phase 2 dosing trials, of tirasemtiv. These evidence of effect clinical trials were randomized, double-blind, placebo-controlled, three-period cross-over studies of single doses of tirasemtiv administered to patients with impaired muscle function. These studies were intended to translate the mechanism of action of tirasemtiv into potentially clinically relevant pharmacodynamic effects. The first of these trials was conducted in patients with ALS, a chronic and progressive disease in which the motor neurons die, thus denervating skeletal muscles and causing them to atrophy. This leads to weakness, fatigue, and eventually complete paralysis and death, primarily from respiratory complications. The second of these trials was conducted in patients with myasthenia gravis, a

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chronic, autoimmune, neuromuscular disease which is the most common primary disorder of neuromuscular transmission. The third of these trials was conducted in patients with symptoms of claudication, which is pain or cramping in the leg muscles due to inadequate blood flow during exercise, associated with peripheral artery disease. Evidence of potentially clinically relevant pharmacodynamic effects was observed in each of these trials.

In 2014, we completed BENEFIT-ALS (Blinded Evaluation of Neuromuscular Effects and Functional Improvement with Tirasemtiv in ALS), a Phase 2b clinical trial of tirasemtiv in patients with ALS and reported the results from BENEFIT-ALS in April 2014. We concluded that in this trial effects observed on slow vital capacity (SVC), a measure of the strength of the skeletal muscles responsible for breathing, in patients treated with tirasemtiv were robust and potentially clinically meaningful and support further evaluation of tirasemtiv in a Phase 3 clinical trial, known as VITALITY-ALS (Ventilatory Investigation of Tirasemtiv and Assessment of Longitudinal Indices after Treatment for a Year in ALS).

Tirasemtiv Clinical Development

BENEFIT-ALS (Blinded Evaluation of Neuromuscular Effects and Functional Improvement with Tirasemtiv in ALS). In 2012, we initiated BENEFIT-ALS, a Phase 2b, multi-national, double-blind, randomized, placebo-controlled, clinical trial designed to evaluate the safety, tolerability and efficacy of tirasemtiv in patients with ALS.

In 2014, BENEFIT-ALS results were presented at the 66th Annual Meeting of the American Academy of Neurology. BENEFIT-ALS did not achieve its primary efficacy endpoint, the mean change from baseline in the ALS Functional Rating Scale in its revised form (ALSFRS-R; $p = 0.11$). Treatment with tirasemtiv resulted in a statistically significant and potentially clinically meaningful reduction in the decline of slow vital capacity (SVC), a measure of the strength of the skeletal muscles responsible for breathing. SVC has been shown to be an important predictor of disease progression and survival in prior trials of patients with ALS. At week 12, the decline in SVC from baseline was -3.12 for patients receiving tirasemtiv versus -8.66 for those receiving placebo ($p < 0.0001$). From week 0 to week 12, the slope of decline in SVC measured as percentage points per day was -0.0394 for patients receiving tirasemtiv versus -0.0905 for those receiving placebo ($p = 0.0006$).

The analyses of other pre-specified secondary efficacy endpoints in BENEFIT-ALS produced mixed results. The muscle strength mega-score, a measure of strength combining the data from several muscle groups in each patient, declined more slowly on tirasemtiv versus placebo. The difference in the rate of decline for sniff nasal inspiratory pressure (SNIP) was not statistically significant); however, SNIP decreased more on tirasemtiv compared with placebo in a statistically significant manner at 4 and 12 weeks. No differences in maximum voluntary ventilation and hand grip fatigue were observed on tirasemtiv versus placebo.

Serious adverse events (SAEs) during double-blind treatment were more frequent on tirasemtiv than on placebo (9.0% vs. 5.4%). The most common SAE was respiratory failure which occurred in 1 patient on tirasemtiv and 3 patients on placebo. Confusional state and delirium occurred in 2 patients on tirasemtiv and no patients on placebo. More patients on tirasemtiv withdrew from the trial following randomization than on placebo (99 vs. 33 patients, respectively). Adverse events more common on tirasemtiv than on placebo (>10% difference) were dizziness, fatigue, and nausea.

Throughout the remainder of 2014, we presented further results from BENEFIT-ALS. These results indicated that:

- Differences in the decline in SVC on tirasemtiv versus placebo observed after 12 weeks of double-blind treatment were maintained for up to 4 weeks after discontinuation of treatment;
- The reduced decline in SVC on tirasemtiv versus placebo was observed consistently across all subgroups of patients in BENEFIT-ALS that were examined;
- The effects of tirasemtiv on SVC were observed at all doses studied and the concentration-response relationship was flat; and

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Riluzole did not increase plasma concentrations nor impact the tolerability of tirasemtiv.

Later in 2014, we announced that we had completed our review of results from BENEFIT-ALS and concluded that effects observed on SVC in patients treated with tirasemtiv were robust and potentially clinically meaningful. We engaged with regulatory authorities in the U.S. and Europe regarding results from BENEFIT-ALS and have advanced tirasemtiv into Phase 3 clinical development.

VITALITY-ALS (Ventilatory Investigation of Tirasemtiv and Assessment of Longitudinal Indices after Treatment for a Year in ALS): In July 2015, we started VITALITY-ALS, a Phase 3 clinical trial designed to assess the effects of tirasemtiv versus placebo on slow vital capacity and other measures of respiratory function in patients with ALS. VITALITY-ALS is designed to confirm and extend the results observed in BENEFIT-ALS.

VITALITY-ALS is a multi-national, randomized, double-blind, placebo-controlled trial that was originally designed to enroll 445 patients with possible, probable or definite ALS diagnosed within 24 months, and with a baseline vital capacity > 70 % of predicted, based on age, sex, and height. Patients may be enrolled whether or not they are on riluzole therapy. The primary endpoint of the trial will assess change from baseline in SVC, to be assessed after 24 weeks of double-blind, placebo-controlled treatment. Secondary endpoints include time to decline from baseline in percent predicted SVC by ³ 20 percentage points or the onset of respiratory insufficiency or death; time to decline from baseline in percent predicted SVC to £ 50 percent predicted or the onset of respiratory insufficiency or death; time to first occurrence of any use of assisted ventilation or death; time to decline in any of the three respiratory domains of the ALSFRS-R or death; and change in the Mega-Score of muscle strength.

Patients enrolled in VITALITY-ALS will receive two-weeks of open-label treatment with tirasemtiv administered at 250 mg/day and will then be randomized to double-blind treatment with placebo or one of three target tirasemtiv dose levels (250 mg/day, 375 mg/day, 500 mg/day) in a 3:2:2:2 ratio for a total of 48 weeks of randomized, double-blind, placebo-controlled treatment. Then in a four-week double-blind, tirasemtiv withdrawal phase, patients on tirasemtiv will be randomized either to continue the double-blind tirasemtiv dose they were receiving or to be withdrawn to placebo in a 1:1 ratio. Patients who had been receiving placebo during the 48 weeks of double-blind, placebo-controlled treatment will continue to receive placebo. We expect VITALITY-ALS to be conducted in more than 75 centers in 11 countries in North America and Europe and to include most of the sites who participated in BENEFIT-ALS.

The design of VITALITY-ALS addresses certain observations from BENEFIT-ALS. VITALITY-ALS provides for a longer open label phase (one week in BENEFIT-ALS versus two weeks in VITALITY-ALS) prior to patient randomization. The longer open label phase in VITALITY-ALS provides more time for patients to acclimate to potential side effects of tirasemtiv to potentially reduce the rate of early termination on study medication post randomization as compared to BENEFIT-ALS. In addition, VITALITY-ALS randomizes patients to three different target dose levels to evaluate the potential effect of dose on the safety, tolerability and efficacy of tirasemtiv. Patients in BENEFIT-ALS were randomized to one target dose level of 500 mg/day and investigators were encouraged to up-titrate patients to their maximally tolerated dose levels. In addition in VITALITY-ALS, patients are up-titrated more slowly (two weeks at each dose level before up-titration in VITALITY-ALS versus one week in BENEFIT-ALS). We believe these and other design changes in VITALITY-ALS may decrease the rate of early terminations on tirasemtiv after randomization compared to the rate we observed after randomization in BENEFIT-ALS.

In 2015, we focused on the start-up phase of VITALITY-ALS, activating and initiating patient enrollment in a majority of the clinical trial sites in North America that are expected to participate in the trial. In the first quarter of 2016, we expect to activate other clinical trial sites in North America and Europe. VITALITY-ALS is expected to complete enrollment in the first half of 2016 with results anticipated in the third quarter of 2017.

In January 2016, we amended the protocol of VITALITY-ALS to provide for an increase in the number of patients to be enrolled in the clinical trial from approximately 445 patients to approximately 600 patients.

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Increasing the number of patients enrolled in VITALITY-ALS will increase the statistical power to detect a difference in the primary efficacy endpoint (change from baseline in SVC at 24 weeks) between *tirasemtiv* and placebo.

Also in January 2016, in collaboration with Knopp Biosciences, we presented exploratory analyses of data from patients with ALS combined from three different sources: First, the placebo data from EMPOWER, the Phase 3 clinical trial of Knopp s dexpramipexole in patients with ALS, second, the placebo data from Cytokinetics Phase 2b study of tirasemtiv in patients with ALS, BENEFIT-ALS, and finally, the open-access Pro-Act database. These combined databases included multiple observations of SVC over time from over 900 patients with ALS. Our analyses of this combined database demonstrated that the rate of decline of SVC predicts the risk of meaningful clinical events, including a decline in any one of the three respiratory questions of the ALSFRS-R, as well as the time to the first occurrence of respiratory insufficiency, tracheostomy or death.

In July 2015, we were awarded a $1.5 million grant from The ALS Association (the ALSA Grant) to support the conduct of VITALITY-ALS as well as the collection of clinical data and plasma samples from patients in VITALITY-ALS in order to help advance the discovery of potentially useful biomarkers in ALS. The grant provides funding for collaboration among Cytokinetics, The ALS Association and the Barrow Neurological Institute to enable plasma samples collected from patients enrolled in VITALITY-ALS to be added to The Northeastern ALS Consortium (NEALS) Repository, a resource for the academic research community to identify biomarkers that may help to assess disease progression and underlying disease mechanisms in ALS. On August 28, 2015 Cytokinetics achieved its first milestone under the ALSA Grant which triggered a payment of $0.5 million in accordance with the ALSA Grant. We recorded $0.1 million as grant revenue as qualified expenses were incurred and approved by management. At December 31, 2015, we had $0.4 million of deferred revenue under the ALSA Grant, reflecting the unrecognized portion of the grant revenue.

Tirasemtiv Strategic and Commercial Planning. During 2015, we continued preparing for t