

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)**

**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**  
*(State or other jurisdiction of  
incorporation or organization)*

**94-3291317**  
*(I.R.S. Employer  
Identification No.)*

**280 East Grand Avenue**  
**South San Francisco, CA**  
*(Address of principal executive offices)*

**(650) 624-3000**

**94080**  
*(Zip Code)*

*(Registrant's telephone number, including area code)*

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## 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

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

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

Indicate by check mark 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  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.

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  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

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**

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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;

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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;

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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:

<b>Drug</b>	<b>Partnership</b>	<b>Potential</b>	<b>Stage of</b>	<b>Development Status and</b>
<b>Candidate</b>	<b>Status</b>	<b>Indication(s)</b>	<b>Development</b>	<b>Planned Development Activities</b>
<b>(Mechanism of Action)</b>		<b>Skeletal Muscle</b>	<b>Contractility Program</b>	
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 )
<b>Cardiac Muscle Contractility Program</b>				
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 66<sup>th</sup> 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 <sup>3</sup> 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 dexamipexole 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 the potential commercialization of *tirasemtiv*. These activities included interactions with manufacturers, and corporate development and commercial planning activities to support various scenarios. We expect to continue to engage extensively with ALS experts, both neuromuscular and pulmonary, and with payors, regulatory authorities and patient advocacy groups as we develop plans for the potential commercialization of *tirasemtiv* as a treatment for patients living with ALS. These commercialization plans will include market assessment and corporate development activities to support the launch of *tirasemtiv* in the U.S. and Europe, if appropriate.

Background on ALS Market. Limited options exist for the treatment of patients with ALS, which affects as many as 30,000 Americans, with an estimated 5,600 new cases diagnosed each year in the U.S. Based on our primary market research, the per capita prevalence and incidence appears similar in the major European markets. ALS is 20% more common in men than women; however, with increasing age, the prevalence becomes more equal between men and women. The life expectancy of an ALS patient averages two to five years from the time of diagnosis, mostly due to respiratory issues. Of the patients diagnosed with ALS, 5 to 10% have a family history of the disease (familial ALS) and remaining 90 to 95% have the sporadic form. The majority of patients with ALS in the U.S. and Europe receive treatment at multidisciplinary centers that specialize in the unique needs of these patients. In the U.S., there are approximately 104 ALS centers of excellence, according to either the ALS Association or the Muscular Dystrophy Association. For most patients with ALS, death is usually due to respiratory failure because of diminished strength in the skeletal muscles responsible for breathing. We believe that the majority of ALS patients in the U.S. and Europe are treated at ALS centers of excellence; therefore, it is a concentrated market. We believe that there is a need for novel therapies to address the urgent unmet medical issues of this patient population which could be addressed by a small, targeted sales force. If *tirasemtiv* is approved by regulatory authorities in the U.S. or Europe for commercialization for ALS, we believe that we may be able to independently commercialize *tirasemtiv* in these concentrated markets.

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**CK-2127107 and Other Skeletal Muscle Activators**

*Astellas Strategic Alliance.* CK-2127107 is being developed jointly by Cytokinetics and Astellas. In December 2014, we entered into an Amended and Restated License and Collaboration Agreement with Astellas (the Amended Astellas Agreement). This agreement superseded the License and Collaboration Agreement between Cytokinetics and Astellas of June 2013 (the Original Astellas Agreement). The Amended Astellas Agreement expanded the objective of the collaboration of advancing novel therapies for diseases and medical conditions associated with muscle weakness to include SMA and potentially other neuromuscular indications for CK-2127107 and other fast skeletal troponin activators, in addition to the non-neuromuscular indications provided for in the Original Astellas Agreement.

Under the Amended Astellas Agreement, we expanded the exclusive license previously granted Astellas under the Original Astellas Agreement to co-develop and commercialize CK-2127107 for potential application in non-neuromuscular indications worldwide to include certain neuromuscular indications as well. Concurrent with the expanded collaboration, the companies agreed to advance CK-2127107 into Phase 2 clinical development. Cytokinetics started a Phase 2 clinical trial of CK-2127107 in patients with SMA in December 2015. The development program may include other neuromuscular indications as the companies may agree. Cytokinetics and Astellas will jointly develop and may jointly commercialize CK-2127107 and other fast skeletal troponin activators in neuromuscular indications. Astellas will be responsible for the costs associated with the development of all collaboration products, including CK-2127107, subject to Cytokinetics' option to co-fund certain development costs as described below.

Under the Amended Astellas Agreement, the parties extended through 2016 their joint research program to identify next-generation skeletal muscle activators to be nominated as potential drug candidates. This research will be conducted at Astellas' expense. Under the Amended Astellas Agreement, Astellas has exclusive rights to co-develop and commercialize CK-2127107 and other fast skeletal troponin activators in SMA and potentially other indications and other novel mechanism skeletal muscle activators in all indications, subject to certain Cytokinetics development and commercialization rights. Cytokinetics may co-promote and conduct certain commercial activities in the U.S., Canada and Europe under agreed scenarios.

Cytokinetics retains an option to conduct early-stage development for certain agreed indications at its initial expense, subject to reimbursement if development continues under the collaboration. Under the Amended Astellas Agreement, Cytokinetics also retains an option to co-promote collaboration products containing fast skeletal muscle activators for neuromuscular indications in the U.S., Canada and Europe, in addition to its option to co-promote other collaboration products in the U.S. and Canada as provided for in the Original Astellas Agreement. Astellas will reimburse Cytokinetics for certain expenses associated with its co-promotion activities. The Amended Astellas Agreement also provides for Cytokinetics to lead certain activities relating to the commercialization of collaboration products for neuromuscular indications in the U.S., Canada and Europe under particular scenarios.

Cytokinetics received a non-refundable upfront payment of \$30.0 million in connection with the execution of the Amended Astellas Agreement. Also, in conjunction with the execution of the Amended Astellas Agreement, we entered into a common stock purchase agreement which provided for the sale of 2,040,816 shares of our common stock to Astellas at a price per share of \$4.90 and an aggregate purchase price of \$10.0 million, which was received in December 2014. Pursuant to this agreement, Astellas agreed to certain trading and other restrictions with respect to our common stock. Concurrently, Cytokinetics earned a \$15.0 million milestone payment relating to Astellas' decision to advance CK-2127107 into Phase 2 clinical development. Cytokinetics is also eligible to potentially receive over \$20.0 million in reimbursement of sponsored research and development activities during the two years of the collaboration following the execution of the Amended Astellas Agreement.

Based on the achievement of pre-specified criteria, Cytokinetics may receive over \$600.0 million in milestone payments relating to the development and commercial launch of collaboration products, including up

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to \$112.0 million (of which Cytokinetics has now received \$17.0 million) relating to early development of CK-2127107 and for later-stage development and commercial launch milestones for CK-2127107 in non-neuromuscular indications, and over \$100.0 million in development and commercial launch milestones for CK-2127107 in each of SMA and other neuromuscular indications. Cytokinetics may also receive up to \$200.0 million in payments for achievement of pre-specified sales milestones related to net sales of all collaboration products under the Amended Astellas Agreement. If Astellas commercializes any collaboration products, Cytokinetics will also receive royalties on sales of such collaboration products, including royalties ranging from the high single digits to the high teens on sales of products containing CK-2127107. Cytokinetics also holds an option to co-fund certain development costs for CK-2127107 and other compounds in exchange for increased milestone payments and royalties; such royalties may increase under certain scenarios to exceed twenty percent. In addition to the foregoing development, commercial launch and sales milestones, Cytokinetics may also receive payments for the achievement of pre-specified milestones relating to the joint research program.

Cytokinetics retains the exclusive right to develop and commercialize tirasemtiv for the potential treatment of ALS and certain other neuromuscular disorders independently from the Amended Astellas Agreement.

*CK-2127107 Clinical Development*

**Phase 1 Clinical Trials Program:** We completed five Phase 1 clinical trials evaluating safety, tolerability and pharmacokinetics and pharmacodynamics of CK-2127107 in both oral tablet and liquid suspension formulations in healthy volunteers. These include a single ascending dose study (Study CY 5011), a multiple ascending dose study in young vs. elderly subjects (CY 5012), a PK/PD study (CY 5013), a formulation study (CY 5014) and a food effect study (CY 5015). The Phase 1 clinical trials demonstrated that CK-2127107 appeared well-tolerated in healthy volunteers and that exposures generally increased across the dose ranges studied. CK-2127107 increased the response of muscle to neuromuscular input in a dose and plasma concentration related fashion in healthy volunteers consistent with preclinical observations. In addition, an oral tablet formulation of CK-2127107 appears appropriate for use in Phase 2 clinical trials.

**Phase 2 Clinical Development:** Cytokinetics started a Phase 2 clinical trial of CK-2127107 in patients with SMA (CY 5021) in December 2015. The clinical trial is designed to assess effects of CK-2127107 on multiple measures of muscle function in both ambulatory and non-ambulatory patients with SMA, a severe, genetic neuromuscular disease that leads to debilitating muscle wasting and progressive, often fatal, muscle weakness. The primary objective of this double-blind, randomized, placebo-controlled clinical trial is to determine the potential pharmacodynamic effects of a suspension formulation of CK-2127107 following multiple oral doses in patients with Type II, Type III, or Type IV SMA. Secondary objectives are to evaluate the safety, tolerability and pharmacokinetics of CK-2127107. The trial will enroll seventy-two patients in two sequential, ascending dose cohorts (two cohorts of 36 patients each, stratified half ambulatory and half non- ambulatory).

The first cohort of patients will receive 150 mg of CK-2127107 dosed twice daily for eight weeks; the second cohort of patients will receive 450 mg of CK-2127107 dosed twice daily or a lower dose, depending on the data from the first cohort. At the conclusion of the trial, approximately 24 patients will have been randomized to placebo, approximately 24 patients to 150 mg of CK-2127107 twice daily and approximately 24 patients to 450 mg of CK-2127107 twice daily (or a lower dose, pending the review of data from the first cohort). In each of these three treatment groups of approximately 24 patients each, roughly half will be ambulatory and half will be non-ambulatory. Multiple assessments of skeletal muscle function and fatigability will be performed including respiratory assessments, upper limb strength and functionality for non-ambulatory patients, as well as six-minute walk and timed-up-and-go for ambulatory patients.

An additional Phase 2 clinical trial to be conducted by Astellas in collaboration with Cytokinetics, will study CK-2127107 in patients with chronic obstructive pulmonary disorder ( COPD ) and is expected to be initiated in the first half of 2016.

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**Background on SMA Market:** Spinal muscular atrophy (SMA) is a severe neuromuscular disease that occurs in 1 in every 6,000 to 10,000 live births each year resulting in a prevalence of 10,000 to 25,000 patients in the U.S., and is one of the most common fatal genetic disorders. SMA manifests in various degrees of severity as progressive muscle weakness resulting in respiratory and mobility impairment. There are four types of SMA, distinguished by the time of the initial onset of muscle weakness and the severity of related symptoms: Type I (severe), Type II (intermediate), Type III (juvenile) and Type IV (adult onset). Life expectancy and disease severity varies by type of SMA from Type I, who have the worst prognosis and a life expectancy of approximately two years from birth, to Type IV, who have a normal life span but with gradual weakness in the proximal muscles of the extremities resulting in mobility issues. Type II, III and IV patients are often characterized by their ambulatory status as it is an important driver of clinical decisions and care. Few treatment options exist for these patients, resulting in a high unmet need for new therapeutic options to ameliorate symptoms, improve muscle function and modify disease progression.

**Ongoing Research in Skeletal Muscle Activators.** Our research on the direct activation of skeletal muscle continues in two areas. We are conducting translational research in preclinical models of disease and muscle function with fast skeletal muscle troponin activators to explore the potential clinical applications of this novel mechanism in diseases or conditions associated with skeletal muscle dysfunction. We also intend to conduct preclinical research on other chemically and pharmacologically distinct mechanisms to activate the skeletal sarcomere. We are conducting a joint research program with Astellas directed to the discovery of next-generation skeletal muscle activators. Under the Amended Astellas Agreement, the joint research program will continue through 2016 and Astellas will reimburse us for certain research activities we perform.

### ***Cardiac Muscle Contractility Program***

**Overview.** Our cardiac muscle contractility program is focused on the cardiac sarcomere, the basic unit of muscle contraction in the heart. The cardiac sarcomere is a highly ordered cytoskeletal structure composed of cardiac muscle myosin, actin and a set of regulatory proteins. This program is currently directed towards the discovery and development of small molecule cardiac muscle myosin activators with the goal of developing novel drugs to treat acute and chronic heart failure. Cardiac muscle myosin is the cytoskeletal motor protein in the cardiac muscle cell. It is directly responsible for converting chemical energy into the mechanical force, resulting in cardiac muscle contraction. This program is based on the hypothesis that activators of cardiac muscle myosin may address certain adverse properties of existing positive inotropic agents. Current positive inotropic agents, such as beta-adrenergic receptor agonists or inhibitors of phosphodiesterase activity, increase the concentration of intracellular calcium, thereby increasing cardiac sarcomere contractility. The effect on calcium levels, however, also has been linked to potentially life-threatening side effects. In contrast, our novel cardiac muscle myosin activators work by a mechanism that directly stimulates the activity of the cardiac muscle myosin motor protein, without increasing the intracellular calcium concentration. They accelerate the rate-limiting step of the myosin enzymatic cycle and shift it in favor of the force-producing state. Rather than increasing the velocity of cardiac contraction, this mechanism instead lengthens the systolic ejection time, which results in increased cardiac function in a potentially more oxygen-efficient manner.

**Amgen Strategic Alliance.** In December 2006, we entered into a collaboration and option agreement with Amgen to discover, develop and commercialize novel small molecule therapeutics, including omecamtiv mecarbil, that activate cardiac muscle contractility for potential applications in the treatment of heart failure (the Amgen Agreement ). The agreement granted Amgen an option to obtain an exclusive license worldwide, except Japan, to develop and commercialize omecamtiv mecarbil and other drug candidates arising from the collaboration. In May 2009, Amgen exercised its option. As a result, Amgen became responsible for the development and commercialization of omecamtiv mecarbil and related compounds at its expense worldwide (excluding Japan), subject to our development and commercialization participation rights. Amgen reimburses us for certain research and development activities we perform under the collaboration.

In June 2013, Cytokinetics and Amgen executed an amendment to the Amgen Agreement to include Japan, resulting in a worldwide collaboration (the Amgen Agreement Amendment ). Under the terms of the Amgen

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Agreement Amendment, we received a non-refundable upfront license fee of \$15.0 million in June 2013. Under the Amgen Agreement Amendment, we conducted a Phase 1 pharmacokinetic study intended to support inclusion of Japan in a potential Phase 3 clinical development program and potential global registration dossier for omecamtiv mecarbil. Amgen reimbursed us for the costs of this study. In addition, we are eligible to receive additional pre-commercialization milestone payments relating to the development of omecamtiv mecarbil in Japan of up to \$50.0 million, and royalties on sales of omecamtiv mecarbil in Japan. In conjunction with the Amgen Agreement Amendment, we also entered into a common stock purchase agreement which provided for the sale of 1,404,100 shares of our common stock to Amgen at a price per share of \$7.12 and an aggregate purchase price of \$10.0 million which was received in June 2013. Pursuant to this agreement, Amgen agreed to certain trading and other restrictions with respect to our common stock.

Under the Amgen Agreement as amended we are eligible for potential pre-commercialization and commercialization milestone payments of over \$650.0 million in the aggregate on omecamtiv mecarbil and other potential products arising from research under the collaboration, and royalties that escalate based on increasing levels of annual net sales of products commercialized under the agreement. The Amgen Agreement also provides for us to receive increased royalties by co-funding Phase 3 development costs of omecamtiv mecarbil and other drug candidates under the collaboration. If we elect to co-fund such costs, we would be entitled to co-promote the co-funded drug in North America and participate in agreed commercialization activities in institutional care settings, at Amgen's expense.

In July 2013, Amgen announced that it had granted an option to commercialize omecamtiv mecarbil in Europe to Servier, with Cytokinetics consent. The option and, if the option is exercised, the resulting commercialization sublicense to Servier, is subject to the terms and conditions of the Amgen Agreement. Amgen remains responsible for the performance of its obligations under the Amgen Agreement relating to Europe, including the payment of milestones and royalties relating to the development and commercialization of omecamtiv mecarbil in Europe.

*Omecamtiv Mecarbil.* Our lead drug candidate from this program is omecamtiv mecarbil, a novel cardiac muscle myosin activator. We expect omecamtiv mecarbil to be developed as a potential treatment across the continuum of care in heart failure both for use in the hospital setting and for use in the outpatient setting.

*Omecamtiv Mecarbil Clinical Development*

Phase 2 Clinical Development Program

COSMIC-HF. COSMIC-HF is a Phase 2, double-blind, randomized, placebo-controlled, multicenter, clinical trial designed to assess the pharmacokinetics and tolerability of *omecmtiv mecarbil* dosed orally in patients with heart failure and left ventricular systolic dysfunction as well as its effects on echocardiographic measures of cardiac function. COSMIC-HF was conducted by Amgen in collaboration with Cytokinetics. The study began with two dose escalation cohorts of 40 patients each, randomized 1:1:1 to placebo or one of three different modified release oral formulations of *omecmtiv mecarbil* for seven days. The *omecmtiv mecarbil* dose in the first of these two dose escalation cohorts was 25 mg twice daily; in the second, it was 50 mg twice daily. The purpose of the dose escalation cohorts was to select one of the three modified release oral formulations of *omecmtiv mecarbil* for further evaluation in a larger group of patients treated for a longer period of time.

The expansion phase of COSMIC-HF was designed to evaluate the pharmacokinetics, pharmacodynamics, safety and tolerability of the modified release oral formulation *omecmtiv mecarbil* selected based on the results of the two dose escalation cohorts in 448 patients with chronic heart failure and left ventricular systolic dysfunction. Patients were randomized 1:1:1 to receive either placebo or treatment with *omecmtiv mecarbil* 25 mg twice daily or a dose titration group where 25 mg twice daily dosing could be increased to 50 mg twice daily depending on plasma concentrations of *omecmtiv mecarbil* after two weeks of treatment with the 25 mg dose.

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In November 2015, we announced the results from the expansion phase of COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) that were presented at American Heart Association in Orlando, Florida. Data from the expansion phase showed that dose titration controlled patient exposure to omecamtiv mecarbil. Approximately 60 percent of patients in the dose titration group escalated dosing to 50 mg twice daily. The study met its primary pharmacokinetics objective.

Following 20 weeks of treatment, statistically significant improvements were observed in pre-specified secondary endpoint measures of cardiac function in the dose titration group, compared to placebo. Systolic ejection time increased by 25.0 msec ( $p<0.001$ ), stroke volume increased by 3.63 mL ( $p=0.022$ ) and heart rate decreased by 2.97 beats per min ( $p=0.007$ ). Left ventricular end-systolic and end-diastolic dimensions decreased by 1.79 mm ( $p=0.003$ ) and 1.29 mm ( $p=0.013$ ), respectively, and were associated with statistically significant reductions in left ventricular end-systolic and end-diastolic volumes. N-terminal pro-brain natriuretic peptide (NT-proBNP) decreased by 970 pg/mL ( $p=0.007$ ). Additionally, in the 25 mg twice daily group, there were statistically significant increases in systolic ejection time and stroke volume and a decrease in NT-proBNP. All changes are from baseline compared to placebo. The pharmacodynamic effects of *omecmtiv mecarbil* were generally dose dependent and larger in patients that received oral dosing with 50 mg twice daily.

Adverse events (AEs), including serious AEs, in patients on *omecmtiv mecarbil* were comparable to placebo. The incidence of adjudicated deaths (2.7 percent died on placebo, 1.4 percent died on *omecmtiv mecarbil*), myocardial infarction (1.34 percent on placebo, 0.34 percent on *omecmtiv mecarbil*) and unstable angina (0 percent on placebo, 0.34 percent on *omecmtiv mecarbil*) was similar. Other cardiac AEs were generally balanced between placebo and active treatment groups. In the *omecmtiv mecarbil* groups, compared to placebo, cardiac troponin increased by 0.001 ng/mL and 0.006 ng/mL (median change from baseline at week 20) in the 25 mg twice daily group and dose titration group, respectively. Events of increased troponin ( $n=278$  across all treatment groups) were independently adjudicated and none were determined to be myocardial ischemia or infarction.

**ATOMIC-AHF.** ATOMIC-AHF (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure) was an international, randomized, double-blind, placebo-controlled, Phase 2b clinical trial of intravenous omecamtiv mecarbil in patients with left ventricular systolic dysfunction hospitalized with acutely decompensated heart failure, completed in 2013. ATOMIC-AHF was conducted by Amgen in collaboration with Cytokinetics. This clinical trial enrolled over 600 patients in three sequential, ascending-dose cohorts. In each cohort, patients were randomized to receive omecamtiv mecarbil or placebo. The primary efficacy objective of this trial was to evaluate the effect of 48 hours of intravenous omecamtiv mecarbil compared to placebo on dyspnea (shortness of breath). The secondary objectives were to assess the safety and tolerability of three dose levels of intravenous omecamtiv mecarbil compared with placebo and to evaluate the effects of 48 hours of treatment with intravenous omecamtiv mecarbil on additional measures of dyspnea, patients' global assessments, change in N-terminal pro brain-type natriuretic peptide (a biomarker associated with the severity of heart failure) and short-term clinical outcomes in these patients. In addition, the trial evaluated the relationship between plasma concentrations of omecamtiv mecarbil and echocardiographic parameters in patients with acute heart failure.

The primary efficacy endpoint of dyspnea symptom response was not met; however, the study demonstrated favorable trends between the dose and plasma concentration of *omecmtiv mecarbil* and dyspnea response. The incidence of worsening heart failure within seven days of initiating treatment appeared lower in each of the cohorts on *omecmtiv mecarbil* compared to the pooled placebo group of patients. Rates of adverse events (AEs), serious AEs, adjudicated deaths and hospitalizations were similar between *omecmtiv mecarbil* and placebo groups. Omecamtiv mecarbil was not associated with an increased incidence of tachyarrhythmias nor were heart rate or blood pressure adversely affected.

**Prior Clinical Experience with Omecamtiv Mecarbil.** Nine Phase 1 clinical trials of omecamtiv mecarbil have been conducted in healthy subjects: five conducted by Cytokinetics and four conducted by Amgen in collaboration with Cytokinetics. Cytokinetics has also conducted two Phase 2a clinical trials of omecamtiv

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mecarbil. These clinical trials were designed to evaluate the safety, tolerability, pharmacodynamic and pharmacokinetic profiles of both intravenous and oral formulations in a diversity of patients, including patients with stable heart failure and patients with ischemic cardiomyopathy. In these trials, omecamtiv mecarbil exhibited generally linear, dose-proportional pharmacokinetics across the dose ranges studied. The adverse effects observed at intolerable doses in humans appeared similar to the adverse findings which occurred in preclinical safety studies at similar plasma concentrations. These effects are believed to be related to the mechanism of action of this drug candidate which, at intolerable doses, resulted in an excessive prolongation of the systolic ejection time (i.e., the time in which the heart is contracting). However, these effects resolved promptly with discontinuation of the infusions of omecamtiv mecarbil.

*Ongoing Research in Cardiac Muscle Contractility.* We agreed with Amgen to additional research activities conducted in 2014 and 2015 under the research plan directed to next-generation compounds in our cardiac muscle contractility program. We expect to continue our joint research program with Amgen in 2016. Under the Amgen Agreement, Amgen reimburses us for certain research activities we perform.

*Background on Heart Failure Market.* Heart failure is a widespread and debilitating syndrome affecting millions of people in the United States. The high and rapidly growing prevalence of heart failure translates into significant hospitalization rates and associated societal costs. About 6.4 million people in the United States have heart failure, resulting in nearly one million hospital discharges with the primary diagnosis of heart failure and approximately 300,000 deaths each year. For people over 65 years of age, heart failure incidences approach 10 per 1000 and approximately 50% of people diagnosed with heart failure will die within 5 years of diagnosis. These numbers are increasing due to the aging of the U.S. population and an increased likelihood of survival following acute myocardial infarctions. The costs to society attributable to the prevalence of heart failure are high, especially as many chronic heart failure patients suffer repeated acute episodes. Despite currently available therapies, readmission rates for heart failure patients remain high. In general, the mortality following hospitalization for patients with heart failure is 10.4% at 30 days, 22% at one year and 42.3% at 5 years, despite the availability of therapeutic alternatives for treatment of these patients. These poor outcomes in the setting of current therapies points to the need for novel therapeutics that may offer further reductions in morbidity and mortality. The annual cost of heart failure to the U.S. health care system is estimated to be \$32 billion and is predicted to grow 120% to almost \$70 billion by the year 2030. Today, a portion of that cost is attributable to drugs used to treat each of chronic and acute heart failure. Approximately 70% of those costs are due to hospitalization, home health and physician care. In the U.S., Medicare is one of the largest payors for heart failure related costs. Approximately 50% of Medicare beneficiaries with heart failure are concentrated in the top 20% of the hospital referral regions in the U.S, which generally include 5 to 10 hospitals in a geographic area. New drug therapies that could reduce the number of hospitalizations could decrease the cost to the health care system.

**Beyond Muscle Contractility**

We developed preclinical expertise in the mechanics of skeletal, cardiac and smooth muscle that extends from proteins to tissues to intact animal models. Our translational research in muscle contractility has enabled us to better understand the potential impact of small molecule compounds that increase skeletal or cardiac muscle contractility and to apply those findings to the further evaluation of our drug candidates in clinical populations. In addition to contractility, the other major functions of muscle include metabolism, growth and energetics, with each of these functions playing a role in certain diseases that could benefit from novel mechanism treatments. Accordingly, our knowledge of muscle contractility may serve as an entry point to the discovery of novel treatments for disorders involving muscle functions other than muscle contractility. We are leveraging our current understandings of muscle biology to investigate new ways of modulating these other aspects of muscle function for other potential therapeutic applications. For example, we are conducting research with compounds that affect muscle growth and that may have applications for serious diseases and medical conditions such as cachexia. Cachexia is a condition that can be associated with cancer, heart failure, chronic obstructive pulmonary disease or other conditions. This syndrome is characterized by the loss of muscle mass and may lead to weakness



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and disability. We are performing research on compounds that may increase muscle mass and which may impact patient functionality or potentially alter the course of diseases associated with muscle wasting.

### **Intellectual Property**

Our policy is to seek patent protection for the technologies, inventions and improvements that we develop that we consider important to the advancement of our business. As of December 31, 2015, we owned or controlled 91 issued U.S. patents and over 125 additional pending U.S. and foreign patent applications. We also rely on trade secrets, technical know-how and continuing innovation to develop and maintain our competitive position. Our commercial success will depend on obtaining and maintaining patent protection and trade secret protection for our drug candidates and technologies and our successfully defending these patents against third-party challenges. We will only be able to protect our technologies from unauthorized use by third parties to the extent that valid and enforceable patents cover them or we maintain them as trade secrets.

With regard to our drug candidates directed to muscle biology targets, we have a U.S. patent covering omecamtiv mecarbil and U.S. patents covering our skeletal muscle sarcomere activators including, but not limited to, tirasemtiv and CK-2127107, each of which will expire in 2027, 2027 and 2031, respectively, unless extended. We also have additional U.S. and foreign patent applications pending for each of our drug candidates. It is not known or determinable whether other patents will issue from any of our other pending applications or what the expiration dates would be for any other patents that do issue.

All of our drug candidates are still in clinical development and have not yet been approved by the FDA. If any of these drug candidates is approved, then pursuant to federal law, we may apply for an extension of the U.S. patent term for one patent covering the approved drug, which could extend the term of the applicable patent by up to a maximum of five additional years.

The degree of future protection of our proprietary rights is uncertain because legal means may not adequately protect our rights or permit us to gain or keep our competitive advantage. Due to evolving legal standards relating to the patentability, validity and enforceability of patents covering pharmaceutical inventions and the claim scope of these patents, our ability to enforce our existing patents and to obtain and enforce patents that may issue from any pending or future patent applications is uncertain and involves complex legal, scientific and factual questions. The standards that the U.S. Patent and Trademark Office and its foreign counterparts use to grant patents are not always applied predictably or uniformly and are subject to change. To date, no consistent policy has emerged regarding the breadth of claims allowed in biotechnology and pharmaceutical patents. Thus, we cannot be sure that any patents will issue from any pending or future patent applications owned by or licensed to us. Even if patents do issue, we cannot be sure that the claims of these patents will be held valid or enforceable by a court of law, will provide us with any significant protection against competitive products, or will afford us a commercial advantage over competitive products. For example:

we or our licensors might not have been the first to make the inventions covered by each of our pending patent applications and issued patents;

we or our licensors might not have been the first to file patent applications for the inventions covered by our pending patent applications and issued patents;

others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights;

some or all of our or our licensors' pending patent applications may not result in issued patents or the claims that issue may be narrow in scope and not provide us with competitive advantages;

our and our licensors' issued patents may not provide a basis for commercially viable drugs or therapies or may be challenged and invalidated by third parties;

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our or our licensors' patent applications or patents may be subject to interference, opposition or similar administrative proceedings that may result in a reduction in their scope or their loss altogether;

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we may not develop additional proprietary technologies or drug candidates that are patentable; or

the patents of others may prevent us or our partners from discovering, developing or commercializing our drug candidates.

The defense and prosecution of intellectual property infringement suits, interferences, oppositions and related legal and administrative proceedings are costly, time-consuming to pursue and divert resources. The outcome of these types of proceedings is uncertain and could significantly harm our business.

Our ability to commercialize drugs depends on our ability to use, manufacture and sell those drugs without infringing the patents or other proprietary rights of third parties. U.S. and foreign issued patents and pending patent applications owned by third parties exist that may be relevant to the therapeutic areas and chemical compositions of our drug candidates. While we are aware of certain relevant patents and patent applications owned by third parties, there may be issued patents or pending applications of which we are not aware that could cover our drug candidates. Because patent applications are often not published immediately after filing, there may be currently pending applications, unknown to us, which could later result in issued patents that our activities with our drug candidates could infringe.

The development of our drug candidates and the commercialization of any resulting drugs may be impacted by patents of companies engaged in competitive programs with significantly greater resources. This could result in the expenditure of significant legal fees and management resources.

We also rely on trade secrets to protect our technology, especially where we do not believe patent protection is appropriate or obtainable. However, trade secrets are often difficult to protect, especially outside of the United States. While we believe that we use reasonable efforts to protect our trade secrets, our employees, consultants, contractors, partners and other advisors may unintentionally or willfully disclose our trade secrets to competitors. Enforcing a claim that a third party illegally obtained and is using our trade secrets would be expensive and time-consuming, and the outcome would be unpredictable. Even if we are able to maintain our trade secrets as confidential, our competitors may independently develop information that is equivalent or similar to our trade secrets.

We seek to protect our intellectual property by requiring our employees, consultants, contractors and other advisors to execute nondisclosure and invention assignment agreements upon commencement of their employment or engagement, through which we seek to protect our intellectual property. Agreements with our employees also preclude them from bringing the proprietary information or materials of third parties to us. We also require confidentiality agreements or material transfer agreements from third parties that receive our confidential information or materials.

For further details on the risks relating to our intellectual property, please see the risk factors under Item 1A of this report, including, but not limited to, the risk factors entitled "Our success depends substantially upon our ability to obtain and maintain intellectual property protection relating to our drug candidates and research technologies" and "If we are sued for infringing third party intellectual property rights, it will be costly and time-consuming, and an unfavorable outcome would have a significant adverse effect on our business."

## **Government Regulation**

The FDA and comparable regulatory agencies in state and local jurisdictions and in foreign countries impose substantial requirements upon the clinical development, manufacture, marketing and distribution of drugs. These agencies and other federal, state and local entities regulate research and development activities and the testing, manufacture, quality control, labeling, storage, record keeping, approval, advertising and promotion of our drug candidates and drugs.

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In the United States, the FDA regulates drugs under the Federal Food, Drug and Cosmetic Act and implementing regulations. The process required by the FDA before our drug candidates may be marketed in the United States generally involves the following:

completion of extensive preclinical laboratory tests, preclinical animal studies and formulation studies, all performed in accordance with the FDA's good laboratory practice regulations;

submission to the FDA of an investigational new drug application ( IND ), which must become effective before clinical trials may begin;

performance of adequate and well-controlled clinical trials to establish the safety and efficacy of the drug candidate for each proposed indication in accordance with good clinical practices;

submission of a new drug application ( NDA ) to the FDA, which must usually be accompanied by payment of a substantial user fee;

satisfactory completion of an FDA preapproval inspection of the manufacturing facilities at which the product is produced to assess compliance with current good manufacturing practice ( cGMP ) regulations and FDA audits of select clinical investigator sites to assess compliance with good clinical practices ( GCP ); and

FDA review and approval of the NDA prior to any commercial marketing, sale or shipment of the drug.

Similar regulatory procedures generally apply in countries outside of the United States. This testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our drug candidates will be granted on a timely basis, if at all.

Nonclinical tests include laboratory evaluation of product chemistry, formulation and stability, and studies to evaluate toxicity and pharmacokinetics in animals. The results of nonclinical tests, together with manufacturing information and analytical data, are submitted as part of an IND application to the FDA. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day period, raises concerns or questions about the conduct of the clinical trial, including concerns that human research subjects may be exposed to unreasonable health risks. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. Our submission of an IND or a foreign equivalent, or those of our collaborators, may not result in authorization from the FDA or its foreign equivalent to commence a clinical trial. A separate submission to an existing IND must also be made for each successive clinical trial conducted during product development. Further, an independent institutional review board ( IRB ) or its foreign equivalent for each medical center proposing to conduct the clinical trial must review and approve the plan for any clinical trial before it commences at that center and it must monitor the clinical trial until completed. The FDA, the IRB or their foreign equivalents, or the clinical trial sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk.

*Clinical Trials.* For purposes of an NDA or equivalent submission and approval, clinical trials are typically conducted in the following three sequential phases, which may overlap:

*Phase 1:* Phase 1 includes the initial introduction of a drug candidate into humans. These studies may be conducted in patients, but are usually conducted in healthy volunteer subjects. These studies are designed to determine the metabolic and pharmacologic actions of the drug candidate in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug candidate's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 trials.

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*Phase 2:* Phase 2 includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug candidate for a particular indication or indications in patients with the disease or condition. This phase of testing also helps determine the common short-term side effects and risks associated with the drug candidate. These clinical trials are generally conducted in a limited

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patient population to identify possible adverse effects and safety risks, to make an initial determination of potential efficacy of the drug candidate for specific targeted indications and to determine dose tolerance and optimal dosage. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more expensive Phase 3 clinical trials. Phase 2a clinical trials generally are designed to study the pharmacokinetic or pharmacodynamic properties and to conduct a preliminary assessment of safety of the drug candidate over a measured dose response range. In some cases, a sponsor may decide to conduct a Phase 2b clinical trial, which is a second, typically larger, confirmatory Phase 2 trial that could, if positive and accepted by a regulatory authority, support approval of a drug candidate.

*Phase 3:* If the Phase 2 clinical trials demonstrate that a dose range of the drug candidate is potentially effective and has an acceptable safety profile, Phase 3 clinical trials are then undertaken in large patient populations to further evaluate dosage, to provide substantial evidence of clinical efficacy and to further test for safety in an expanded and diverse patient population at multiple, geographically dispersed clinical trial sites. Phase 3 trials are also intended to provide an adequate basis for extrapolating the results to the general population and transmitting that information in the drug labeling. Phase 3 studies usually include several hundred to several thousand people.

At any time during the conduct of a clinical trial, the FDA or a foreign equivalent can impose a clinical hold on the trial if it believes the trial is unsafe or that the protocol is clearly deficient in design in meeting its stated objectives, which requires the conduct of the trial to cease until the clinical hold is removed. In some cases, the FDA or foreign equivalent may condition approval of marketing approval for a drug candidate on the sponsor's agreement to conduct additional clinical trials to further assess the drug's safety and effectiveness after marketing approval, known as Phase 4 clinical trials.

The clinical trials we conduct for our drug candidates, both before and after approval, and the results of those trials, are generally required to be included in a clinical trials registry database that is available and accessible to the public via the internet. A failure by us to properly participate in the clinical trial database registry could subject us to significant civil monetary penalties.

Health care providers in the United States, including research institutions from which we or our partners obtain patient information, are subject to privacy rules under the Health Insurance Portability and Accountability Act of 1996 and state and local privacy laws. In the European Union, these entities are subject to the Directive 95/46-EC of the European Parliament on the protection of individuals with regard to the processing of personal data and individual European Union member states implementing additional legislation. Other countries have similar privacy legislation. We could face substantial penalties if we knowingly receive individually identifiable health information from a health care provider that has not satisfied the applicable privacy laws. In addition, certain privacy laws and genetic testing laws may apply directly to our operations and/or those of our partners and may impose restrictions on the use and dissemination of individuals' health information and use of biological samples.

*New Drug/Marketing Approval Application.* The results of drug candidate development, preclinical testing and clinical trials are submitted to the FDA as part of an NDA. The NDA also must contain extensive manufacturing information. In addition, the FDA may require that a proposed Risk Evaluation and Mitigation Strategy, also known as a REMS, be submitted as part of the NDA if the FDA determines that it is necessary to ensure that the benefits of the drug outweigh its risks. Similar, and in some cases additional, requirements apply in foreign jurisdictions for marketing approval applications for drugs in those jurisdictions. The FDA may refer the NDA to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. The FDA often, but not always, follows the advisory committee's recommendations. The FDA may deny approval of an NDA by issuing a complete response letter if the applicable regulatory criteria are not satisfied, or it may require additional clinical data, including data in a pediatric population, or an additional Phase 3 clinical trial or impose other conditions that must be met in order to secure final approval for an NDA.

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Even if such data are submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. Data from clinical trials are not always conclusive and the FDA may interpret data differently than we or our partners do. Once issued, the FDA or foreign equivalent may withdraw a drug approval if ongoing regulatory requirements are not met or if safety problems occur after the drug reaches the market. In addition, the FDA or its foreign counterparts may require further testing, including Phase 4 clinical trials, and surveillance or restrictive distribution programs to monitor the effect of approved drugs which have been commercialized. The FDA and its foreign counterparts have the power to prevent or limit further marketing of a drug based on the results of these post-marketing programs. Drugs may be marketed only for the approved indications and in accordance with the provisions of the approved label. Further, if there are any modifications to a drug, including changes in indications, labeling or manufacturing processes or facilities, we may be required to submit and obtain prior FDA approval of a new NDA or NDA supplement, or the foreign equivalent, which may require us to develop additional data or conduct additional preclinical studies and clinical trials.

Satisfaction of FDA regulations and requirements or similar requirements of state, local and foreign regulatory agencies typically takes several years. The actual time required may vary substantially based upon the type, complexity and novelty of the drug candidate or disease. Typically, if a drug candidate is intended to treat a chronic disease, as is the case with some of our drug candidates, safety and efficacy data must be gathered over an extended period of time. Government regulation may delay or prevent marketing of drug candidates for a considerable period of time and impose costly procedures upon our activities. The FDA or any other regulatory agency may not grant approvals for new indications for our drug candidates on a timely basis, if at all. Even if a drug candidate receives regulatory approval, the approval may be significantly limited to specific disease states, patient populations and dosages or restrictive distribution programs. Further, even after regulatory approval is obtained, later discovery of previously unknown problems with a drug may result in restrictions on the drug or even complete withdrawal of the drug from the market. Delays in obtaining, or failures to obtain, regulatory approvals for any of our drug candidates would harm our business. In addition, we cannot predict what future U.S. or foreign governmental regulations may be implemented.

*Orphan Drug Designation.* Some jurisdictions, including the United States, may designate drugs for relatively small patient populations as orphan drugs. The FDA grants orphan drug designation to drugs intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States. For example, the FDA has granted tirasemtiv an orphan drug designation for the treatment of ALS. In addition, the European Medicines Agency has granted tirasemtiv orphan medicinal product status for the treatment of ALS.

An FDA orphan drug designation does not shorten the duration of the regulatory review and approval process. If a drug candidate that has an orphan drug designation receives the first FDA marketing approval for the indication for which the designation was granted, then the approved drug is entitled to orphan drug exclusivity. This means that the FDA may not approve another company's application to market the same drug for the same indication for a period of seven years, except in certain circumstances, such as a showing of clinical superiority to the drug with orphan exclusivity or if the holder of the orphan drug designation cannot assure the availability of sufficient quantities of the orphan drug to meet the needs of patients with the disease or condition for which the designation was granted. Competitors may receive approval of different drugs or biologics for the indications for which the orphan drug has exclusivity.

*Fast Track Designation.* Fast track is a process designed by the FDA to facilitate the development and expedite the review of drugs to treat serious diseases and fill an unmet medical need. Tirasemtiv has been granted fast track designation by the FDA for the treatment of ALS. Although fast track designation does not affect the standards for approval, the benefits of this designation include scheduled meetings to seek FDA input into development plans, the option of submitting an NDA in sections rather than all components simultaneously, and the potential eligibility for priority review if supported by clinical data.

*Other Regulatory Requirements.* Any drugs manufactured or distributed by us or our partners pursuant to FDA approvals or their foreign counterparts are subject to continuing regulation by the applicable regulatory

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authority, including recordkeeping requirements and reporting of adverse experiences associated with the drug. Drug manufacturers and their subcontractors are required to register their establishments with the FDA and other applicable regulatory authorities, and are subject to periodic unannounced inspections by these regulatory authorities for compliance with ongoing regulatory requirements, including cGMPs, which impose certain procedural and documentation requirements upon us and our third-party manufacturers. Failure to comply with the statutory and regulatory requirements can subject a manufacturer to possible legal or regulatory action, such as warning letters, suspension of manufacturing, seizure of product, injunctive action or possible civil penalties. We cannot be certain that we or our present or future third-party manufacturers or suppliers will be able to comply with the cGMP regulations and other ongoing FDA and other regulatory requirements. If our present or future third-party manufacturers or suppliers are not able to comply with these requirements, the FDA or its foreign counterparts may halt our or our partners' clinical trials, require us to recall a drug from distribution, or withdraw approval of the NDA for that drug.

For further details on the risks relating to government regulation of our business, please see the risk factors under Item 1A of this report, including, but not limited to, the risk factor entitled "The regulatory approval process is expensive, time-consuming and uncertain and may prevent our partners or us from obtaining approvals to commercialize some or all of our drug candidates."

**Competition**

We compete in the segments of the pharmaceutical, biotechnology and other related markets that address neuromuscular and cardiovascular diseases and other diseases relating to muscle dysfunction, each of which is highly competitive. We face significant competition from most pharmaceutical companies and biotechnology companies that are also researching and selling products designed to address cardiovascular diseases and diseases and medical conditions associated with skeletal muscle weakness and wasting. Many of our competitors have significantly greater financial, manufacturing, marketing and drug development resources than we do. Large pharmaceutical companies in particular have extensive experience in clinical testing and in obtaining regulatory approvals for drugs. These companies also have significantly greater research capabilities than we do. In addition, many universities and private and public research institutes are active in research of neuromuscular and cardiovascular diseases and other diseases where there is muscle dysfunction, some in direct competition with us.

We believe that our ability to successfully compete will depend on, among other things:

our drug candidates' efficacy, safety and tolerability;

the speed and cost-effectiveness with which we develop our drug candidates;

the selection of suitable indications for which to develop our drug candidates;

the successful completion of clinical development and laboratory testing of our drug candidates;

the timing and scope of any regulatory approvals we or our partners obtain for our drug candidates;

our or our partners' ability to manufacture and sell commercial quantities of our approved drugs to meet market demand;

acceptance of our drugs by physicians and other health care providers;

the willingness of third party payors to provide reimbursement for the use of our drugs;



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

the quality and breadth of our technology;

our employees' skills and our ability to recruit and retain skilled employees;

our cash flows under existing and potential future arrangements with licensees, partners and other parties; and

the availability of substantial capital resources to fund development and commercialization activities.

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Our competitors may develop drug candidates and market drugs that are less expensive and more effective than our future drugs or that may render our drugs obsolete. Our current or future competitors may also commercialize competing drugs before we or our partners can launch any drugs developed from our drug candidates. These organizations also compete with us to attract qualified personnel and potential parties for acquisitions, joint ventures or other strategic alliances.

If tirasemtiv is approved for marketing by the FDA or other regulatory authorities for the treatment of ALS, it may then compete with other potential new therapies for ALS that are currently being developed by companies such as Neuraltus Pharmaceuticals, Inc., Ionis Pharmaceuticals, Inc. (in collaboration with Biogen), Genervon Biopharmaceuticals, LLC, Orion Pharmaceuticals, Orphazyme, Mitsubishi Tanabe Pharma Corporation, Eisai Co., Ltd., and MediciNova, Inc. In addition, BrainStorm Cell Therapeutics and Neuralstem, Inc. are each conducting clinical development of stem cell therapies for the potential treatment of ALS.

If CK-2127107 is approved by the FDA or other regulatory authorities for the potential treatment of SMA, potential competitors include Roche (in collaboration with PTC Therapeutics), AveXis, Inc., Pfizer Inc., Ionis Pharmaceuticals, Inc. (in collaboration with Biogen), and Bioblast Pharma, Ltd. Drugs that could compete with CK-2127107 could also compete against tirasemtiv in ALS or other neuromuscular diseases, should the appropriate clinical trials be conducted. If CK-2127107 is approved by the FDA for the potential treatment of non-neuromuscular indications associated with muscle weakness, potential competitors include Ligand Pharmaceuticals, Inc., which is developing LGD-4033, a selective androgen receptor modulator, for muscle wasting; and GTX, Inc., which is developing ostarine, a selective androgen receptor modulator, for cancer cachexia and potentially other indications; Regeneron Pharmaceuticals, Inc. (in collaboration with Sanofi), which is developing SAR391786, a monoclonal antibody targeted to GDF8, for sarcopenia; Eli Lilly & Company, which is developing LY2495655, a monoclonal antibody targeted to myostatin, for muscular atrophy after hip arthroplasty; Acceleron Pharma, which is developing ACE-083 for diseases such as inclusion body myositis and certain forms of muscular dystrophy; Stealth Biotherapeutics, which is developing Bendavia for skeletal muscle disorders; Scholar Rock, which is developing SRK-015, a specific and local inhibitor of the activation of latent myostatin for the potential treatment of primary myopathies and Pfizer Inc., which is developing PF-06252616, a monoclonal antibody targeted to myostatin, in Duchenne muscular dystrophy. Novartis (in collaboration with Morphosys AG), is conducting clinical development with an activin type-IIb receptor antagonist, bimagrumab, to evaluate its ability to treat diseases involving the loss of muscle mass, strength and function.

If omecamtiv mecarbil is approved for marketing by the FDA or other regulatory authorities for the treatment of heart failure, it would compete against other drugs used for the treatment of acute and chronic heart failure. These include generic drugs, such as milrinone, dobutamine or digoxin and branded drugs such as Natrecor (nesiritide) Corlanor (ivabradine) and Entresto (LCZ696). Omecamtiv mecarbil could also potentially compete against other novel drug candidates and therapies in development, such as Gencaro (bucindolol), which is being developed by ARCA biopharma, Inc.; Reasanz (serelaxin) and Tekturna, which are being developed by Novartis; finerenone which is being developed by Bayer, cenderitide (CD-NP), which is being developed by Carpikor Therapeutics, Inc., TRV-027, which is being developed by Trevena; ularitide, which is being developed by Cardiorientis Ltd.; ONO-4232 which is being developed by Ono Pharmaceutical Company; JVS-100, a gene therapy being developed by Juventas Therapeutics; aladorian, which is being developed by ARMGO Pharma, Inc; TRV027, which is being developed by Trevena, Inc. in partnership with Forest Laboratories, Inc.; certain cardioprotectants which are being developed by Cardioxyl Pharmaceuticals, Inc.; Neurocardin, which is being developed by Zensun Sci & Tech, Ltd; and levosimendan, which was acquired for development by Tenax Therapeutics (formerly known as Oxygen Biotherapeutics, Inc.). In addition, there are a number of medical devices both marketed and in development for the potential treatment of heart failure.

For further details on the risks relating to our competitors, please see the risk factors under Item 1A of this report, including, but not limited to, the risk factor entitled Our competitors may develop drugs that are less expensive, safer or more effective than ours, which may diminish or eliminate the commercial success of any drugs that we may commercialize.

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### **Employees**

As of December 31, 2015, our workforce consisted of 100 full-time employees, 28 of whom hold Ph.D. or M.D. degrees, or both, and 22 of whom hold other advanced degrees. Of our total full-time employees, 68 are engaged in research and development and 32 are engaged in business and new product development, finance and administration functions

We have no collective bargaining agreements with our employees, and we have not experienced any work stoppages. We believe that our relations with our employees are good.

### **Investor Information**

We file electronically with the SEC our annual reports on Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K pursuant to Section 13 or 15(d) of the Exchange Act. The public may read or copy any materials we file with the SEC at the SEC's Public Reference Room at 100 F Street, NE, Washington, DC 20549. The public may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC maintains an Internet site that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC. The address of that site is [www.sec.gov](http://www.sec.gov).

You may obtain a free copy of our annual reports on Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K and amendments to those reports on the day of filing with the SEC on our website at [www.cytokinetics.com](http://www.cytokinetics.com) or by contacting the Investor Relations Department at our corporate offices by calling 650-624-3060. The information found on our website is not part of this or any other report filed with or furnished to the SEC.

### **Item 1A. Risk Factors**

*In evaluating our business, you should carefully consider the following risks in addition to the other information in this report. Any of the following risks could materially and adversely affect our business, results of operations, financial condition or your investment in our securities, and many are beyond our control. The risks and uncertainties described below are not the only ones facing us. Additional risks and uncertainties not presently known to us, or that we currently see as immaterial, may also adversely affect our business.*

#### **Risks Related To Our Business**

*We have a history of significant losses and may not achieve or sustain profitability and, as a result, you may lose all or part of your investment.*

We have generally incurred operating losses in each year since our inception in 1997, due to costs incurred in connection with our research and development activities and general and administrative costs associated with our operations. Our drug candidates are all in early and mid-stage clinical testing, and we and our partners must conduct significant additional clinical trials before we and our partners can seek the regulatory approvals necessary to begin commercial sales of our drugs. We expect to incur increasing losses for at least several more years, as we continue our research activities and conduct development of, and seek regulatory approvals for, our drug candidates, and commercialize any approved drugs. If our drug candidates fail or do not gain regulatory approval, or if our drugs do not achieve market acceptance, we will not be profitable. If we fail to become and remain profitable, or if we are unable to fund our continuing losses, you could lose all or part of your investment.

*We will need substantial additional capital in the future to sufficiently fund our operations.*

We have consumed substantial amounts of capital to date, and our operating expenditures will increase over the next several years if we expand our research and development activities. We have funded all of our

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operations and capital expenditures with proceeds from private and public sales of our equity securities, strategic alliances with Amgen, Astellas and others, long term debt, equipment financings, interest on investments, government grants and other grants. We believe that our existing cash and cash equivalents, short-term investments and interest earned on investments should be sufficient to meet our projected operating requirements for at least the next 12 months. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we currently expect. Because of the numerous risks and uncertainties associated with the development of our drug candidates and other research and development activities, including risks and uncertainties that could impact the rate of progress of our development activities, we are unable to estimate with certainty the amounts of capital outlays and operating expenditures associated with these activities.

For the foreseeable future, our operations will require significant additional funding, in large part due to our research and development expenses and the absence of any revenues from product sales. For example, we will require significant additional funding to enable us to conduct further development of tirasemtiv for the potential treatment of ALS, including any additional Phase 3 clinical trials that may be required by regulatory authorities to receive marketing approval for tirasemtiv. Until we can generate a sufficient amount of product revenue, we expect to raise future capital through strategic alliance and licensing arrangements, public or private equity offerings and debt financings. We do not currently have any commitments for future funding other than reimbursements, milestone and royalty payments that we may receive under our collaboration agreements with Amgen and Astellas. We may not receive any further funds under those agreements. Our ability to raise funds may be adversely impacted by current economic conditions. As a result of these and other factors, we do not know whether additional financing will be available when needed, or that, if available, such financing would be on terms favorable to our stockholders or us.

To the extent that we raise additional funds through strategic alliances or licensing and other arrangements with third parties, we will likely have to relinquish valuable rights to our technologies, research programs or drug candidates, or grant licenses on terms that may not be favorable to us. To the extent that we raise additional funds by issuing equity securities, our stockholders will experience additional dilution and our share price may decline. To the extent that we raise additional funds through debt financing, the financing may involve covenants that restrict our business activities. In addition, funding from any of these sources, if needed, may not be available to us on favorable terms, or at all, or in accordance with our planned timelines.

If we cannot raise the funds we need to operate our business, we will need to delay or discontinue certain research and development activities. For example, if we cannot raise the funds necessary to enable the conduct of further development for tirasemtiv for the potential treatment of ALS, our ability to continue the development of tirasemtiv will be delayed or suspended. If we delay or discontinue research and development activities, our stock price may be negatively affected.

***Covenants in our loan and security agreement restrict our business and operations in many ways and if we do not effectively manage our covenants, our financial conditions and results of operations could be adversely affected. In addition, our operations may not provide sufficient revenue to meet the condition required in order to access the final loan available under the agreement and may also not provide sufficient cash to meet the repayment obligations of our debt incurred under the loan and security agreement.***

Our loan and security agreement with Oxford Finance LLC and Silicon Valley Bank provides for up to \$40.0 million in term loans due on October 1, 2020, of which \$30.0 million in term loans has been borrowed to date. All of our current and future assets, except for intellectual property, are secured for our borrowings under the loan and security agreement. The loan and security agreement requires that we comply with certain covenants applicable to us, including among other things, covenants restricting dispositions, changes in business, management, ownership or business locations, mergers or acquisitions, indebtedness, encumbrances, distributions, investments, transactions with affiliates and subordinated debt, any of which could restrict our business and operations, particularly our ability to respond to changes in our business or to take specified actions

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to take advantage of certain business opportunities that may be presented to us. Our failure to comply with any of the covenants could result in a default under the loan and security agreement, which could permit the lenders to declare all or part of any outstanding borrowings to be immediately due and payable, or to refuse to permit additional borrowings under the loan and security agreement. If we are unable to repay those amounts, the lenders under the loan and security agreement could proceed against the collateral granted to them to secure that debt, which would seriously harm our business. In addition, should we be unable to comply with these covenants or if we default on any portion of our outstanding borrowings, the lenders can also impose a 5.0% penalty and restrict access to additional borrowings under the loan and security agreement. Moreover, our ability to access any additional term loans under the loan and security agreement is subject to our ability to achieve a certain conditions, including certain clinical development milestones, which conditions we may not be able to meet and which and could adversely affect our liquidity. In addition, although we expect to borrow additional funds under the loan and security agreement, before we do so, we must first satisfy ourselves that we will have access to future alternate sources of capital, including cash flow from our own operations, equity capital markets or debt capital markets in order to repay any principal borrowed, which we may be unable to do, in which case, our liquidity and ability to fund our operations may be substantially impaired.

*We have never generated, and may never generate, revenues from commercial sales of our drugs and we will not have drugs to market for at least several years, if ever.*

We currently have no drugs for sale and we cannot guarantee that we will ever develop or obtain approval to market any drugs. To receive marketing approval for any drug candidate, we must demonstrate that the drug candidate satisfies rigorous standards of safety and efficacy to the FDA in the United States and other regulatory authorities abroad. We and our partners will need to conduct significant additional research and preclinical and clinical testing before we or our partners can file applications with the FDA or other regulatory authorities for approval of any of our drug candidates. In addition, to compete effectively, our drugs must be easy to use, cost-effective and economical to manufacture on a commercial scale, compared to other therapies available for the treatment of the same conditions. We may not achieve any of these objectives. Currently, our only drug candidates in clinical development are omeamtiv mecarbil for the potential treatment of heart failure, tirasemtiv for the potential treatment of ALS, and CK-2127107 for the potential treatment of SMA and potentially other neuromuscular and non-neuromuscular indications associated with muscle weakness. We cannot be certain that the clinical development of these or any future drug candidates will be successful, that they will receive the regulatory approvals required to commercialize them, that they will ultimately be accepted by prescribers or reimbursed by insurers or that any of our other research programs will yield a drug candidate suitable for clinical testing or commercialization. Our commercial revenues, if any, will be derived from sales of drugs that we do not expect to be commercially marketed for at least several years, if at all. The development of any one or all of these drug candidates may be discontinued at any stage of our clinical trials programs and we may not generate revenue from any of these drug candidates.

*Clinical trials may fail to demonstrate the desired safety and efficacy of our drug candidates, which could prevent or significantly delay completion of clinical development and regulatory approval.*

Prior to receiving approval to commercialize any of our drug candidates, we or our partners must adequately demonstrate to the satisfaction of FDA and foreign regulatory authorities that the drug candidate is sufficiently safe and effective with substantial evidence from well-controlled clinical trials. We or our partners will need to demonstrate efficacy in clinical trials for the treatment of specific indications and monitor safety throughout the clinical development process and following approval. None of our drug candidates have yet met the safety and efficacy standards required for regulatory approval for commercialization and they may never do so. In addition, for each of our preclinical compounds, we or our partners must adequately demonstrate satisfactory chemistry, formulation, stability and toxicity in order to submit an investigational new drug application ( IND ) to the FDA, or an equivalent application in foreign jurisdictions, that would allow us to advance that compound into clinical trials. Furthermore, we or our partners may need to submit separate INDs (or foreign equivalent) to different divisions within the FDA (or foreign regulatory authorities) in order to pursue clinical trials in different therapeutic areas. Each new IND (or foreign equivalent) must be reviewed by the new division before the clinical

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trial under its jurisdiction can proceed, entailing all the risks of delay inherent to regulatory review. If our or our partners' current or future preclinical studies or clinical trials are unsuccessful, our business will be significantly harmed and our stock price could be negatively affected.

All of our drug candidates are prone to the risks of failure inherent in drug development. Preclinical studies may not yield results that would adequately support the filing of an IND (or a foreign equivalent) with respect to our potential drug candidates. Even if the results of preclinical studies for a drug candidate are sufficient to support such a filing, the results of preclinical studies do not necessarily predict the results of clinical trials. As an example, because the physiology of animal species used in preclinical studies may vary substantially from other animal species and from humans, it may be difficult to assess with certainty whether a finding from a study in a particular animal species will result in similar findings in other animal species or in humans. For any of our drug candidates, the results from Phase 1 clinical trials in healthy volunteers and clinical results from Phase 1 and 2 trials in patients are not necessarily indicative of the results of later and larger clinical trials that are necessary to establish whether the drug candidate is safe and effective for the applicable indication. Likewise, interim results from a clinical trial may not be indicative of the final results from that trial, and results from early Phase 2 clinical trials may not be indicative of the results from later clinical trials. For example, early Phase 2 clinical trials of tirasemtiv in patients with ALS showed encouraging dose-related trends in measurements of the ALS Functional Rating Scale in its revised form (ALSFRS-R), a clinically validated instrument designed to measure disease progression and changes in functional status, for patients receiving tirasemtiv compared to those receiving placebo. However, BENEFIT-ALS, a Phase 2b clinical trial of tirasemtiv in patients with ALS, did not achieve its primary efficacy endpoint, the mean change from baseline in the ALSFRS-R for patients receiving tirasemtiv compared to those receiving placebo.

In addition, while the clinical trials of our drug candidates are designed based on the available relevant information, such information may not accurately predict what actually occurs during the course of the trial itself, which may have consequences for the conduct of an ongoing clinical trial or for the eventual results of that trial. For example, the number of patients planned to be enrolled in a placebo-controlled clinical trial is determined in part by estimates relating to expected treatment effect and variability about the primary endpoint. These estimates are based upon earlier nonclinical and clinical studies of the drug candidate itself and clinical trials of other drugs thought to have similar effects in a similar patient population. If information gained during the conduct of the trial shows these estimates to be inaccurate, we may elect to adjust the enrollment accordingly, which may cause delays in completing the trial, additional expense or a statistical penalty to apply to the evaluation of the trial results.

Furthermore, in view of the uncertainties inherent in drug development, such clinical trials may not be designed with focus on indications, patient populations, dosing regimens, endpoints, safety, efficacy or pharmacokinetic parameters or other variables that will provide the necessary safety or efficacy data to support regulatory approval to commercialize the resulting drugs. For example, we believe that effects on respiratory function, including slow vital capacity (SVC), may be appropriate as a clinical endpoint for tirasemtiv; however, regulatory authorities may not accept these effects as a clinical endpoint to support registration of tirasemtiv for the treatment of ALS. Clinical trials of our drug candidates are designed based on guidance or advice from regulatory agencies, which is subject to change during the development of the drug candidate at any time. Such a change in a regulatory agency's guidance or advice may cause that agency to deem results from trials to be insufficient to support approval of the drug candidate and require further clinical trials of that drug candidate to be conducted. In addition, individual patient responses to the dose administered of a drug may vary in a manner that is difficult to predict. Also, the methods we select to assess particular safety, efficacy or pharmacokinetic parameters may not yield the same statistical precision in estimating our drug candidates' effects as may other methodologies. Even if we believe the data collected from clinical trials of our drug candidates are promising, these data may not be sufficient to support approval by the FDA or foreign regulatory authorities. Non-clinical and clinical data can be interpreted in different ways. Accordingly, the FDA or foreign regulatory authorities could interpret these data in different ways from us or our partners, which could delay, limit or prevent regulatory approval.

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Administering any of our drug candidates or potential drug candidates may produce undesirable side effects, also known as adverse events. Toxicities and adverse events observed in preclinical studies for some compounds in a particular research and development program may also occur in preclinical studies or clinical trials of other compounds from the same program. Potential toxicity issues may arise from the effects of the active pharmaceutical ingredient itself or from impurities or degradants that are present in the active pharmaceutical ingredient or could form over time in the formulated drug candidate or the active pharmaceutical ingredient. These toxicities or adverse events could delay or prevent the filing of an IND (or a foreign equivalent) with respect to our drug candidates or potential drug candidates or cause us, our partners or the FDA or foreign regulatory authorities to modify, suspend or terminate clinical trials with respect to any drug candidate at any time during the development program. Further, the administration of two or more drugs contemporaneously can lead to interactions between them, and our drug candidates may interact with other drugs that trial subjects are taking. For example, co-administration of tirasemtiv and riluzole (an approved treatment for ALS) approximately doubles the average maximum riluzole plasma level. If the adverse events are severe or frequent enough to outweigh the potential efficacy of a drug candidate, the FDA or other regulatory authorities could deny approval of that drug candidate for any or all targeted indications. Even if one or more of our drug candidates were approved for sale as drugs, the occurrence of even a limited number of toxicities or adverse events when used in large populations may cause the FDA or foreign regulatory authorities to impose restrictions on, or stop, the further marketing of those drugs. Indications of potential adverse events or toxicities which do not seem significant during the course of clinical trials may later turn out to actually constitute serious adverse events or toxicities when a drug is used in large populations or for extended periods of time.

We have observed certain adverse events in the clinical trials conducted with our drug candidates. For example, in BENEFIT-ALS, adverse events of dizziness, fatigue, nausea, confusional state, muscle spasms, somnolence (sleepiness), decreased appetite, headache, insomnia, dyspnea (difficulty breathing) and dysathria (difficulty speaking) occurred more frequently during treatment with tirasemtiv than with placebo. In addition, weight loss was significantly greater in patients with gastrointestinal adverse events (e.g., nausea and decreased appetite), which occurred more frequently on tirasemtiv than on placebo. In clinical trials of omecamtiv mecarbil, adverse events of chest discomfort, palpitations, dizziness and feeling hot, increases in heart rate, declines in blood pressure, electrocardiographic changes consistent with acute myocardial ischemia and transient rises in the MB fraction of creatine kinase and cardiac troponins I and T, which are indicative of myocardial infarction were observed during treatment with omecamtiv mecarbil.

In addition, clinical trials of tirasemtiv and omecamtiv mecarbil enroll patients who typically suffer from serious diseases which put them at increased risk of death. These patients may die while receiving our drug candidates. In such circumstances, it may not be possible to exclude with certainty a causal relationship to our drug candidate, even though the responsible clinical investigator may view such an event as not study drug-related.

Any failure or significant delay in completing preclinical studies or clinical trials for our drug candidates, or in receiving and maintaining regulatory approval for the sale of any resulting drugs, may significantly harm our business and negatively affect our stock price.

***The failure of a number of Phase 3 clinical trials evaluating other compounds as potential treatments for patients with ALS may suggest an increased risk that our planned Phase 3 clinical development program of tirasemtiv in patients with ALS will also fail.***

The FDA has not approved any drug for the treatment of ALS since its approval of riluzole in 1995. In recent years, a number of Phase 3 clinical trials of potential treatments for ALS have failed to demonstrate the requisite efficacy for approval or for their continued development. These include Biogen Idec's trial of dexpramipexole, known as EMPOWER, the National Institute of Neurological Disorders and Stroke's trial of ceftriaxone, and Trophos SA's trial of olesoxime. Tirasemtiv, like these compounds, may fail in Phase 3 clinical development if it does not show a statistically significant level of clinical efficacy or if the adverse event profile

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is too great compared to its benefits. Further, even if we believe the data collected from our planned Phase 3 clinical development program of tirasemtiv are promising and should support approval, the FDA or other regulatory authorities may not deem these data to be sufficient to support approval.

*We have never before conducted a Phase 3 clinical trial nor submitted an application for marketing authorization to regulatory authorities, and may be unable to do so for tirasemtiv or any other drug candidates we are developing.*

We are conducting VITALITY-ALS, a Phase 3 clinical trial, designed to assess the effects of tirasemtiv versus placebo on slow vital capacity ( SVC ) and other measure of respiratory function in patients with ALS. Conducting Phase 3 clinical trials and submitting a successful application for marketing authorization is complex, time consuming and expensive. We have not previously conducted a Phase 3 clinical trial and have limited experience in preparing, submitting and prosecuting a marketing authorization. Consequently, we may be unable to effectively and efficiently execute and complete the trial in a manner that leads to the submission to and approval by regulatory authorities of a marketing application for tirasemtiv. We may require more time and incur greater costs than our competitors and may not succeed in obtaining regulatory approvals of products that we develop. Failure to commence or complete, or delays in, our planned clinical trials, would prevent us from or delay us in commercializing tirasemtiv, and other product candidates we are developing.

*Neither the FDA nor European regulatory authorities has accepted the primary endpoint in our Phase 3 clinical trial in patients with ALS (a statistically significant reduction in the decline in SVC) as a sufficient measure of clinical significance alone to support regulatory approval of tirasemtiv for the treatment of ALS.*

To commercialize tirasemtiv, we must first demonstrate to the satisfaction of the FDA or foreign regulatory authorities that tirasemtiv is sufficiently safe and effective. To date, neither the FDA nor European regulatory authorities has indicated that the primary end point that we have specified in our Phase 3 clinical trial in patients with ALS (change from baseline to 24 weeks in SVC) is, in and of itself, a sufficient measure of clinical significance to establish the efficacy of tirasemtiv. Our Phase 3 clinical trial will also be measuring secondary endpoints of respiratory function and patient condition to provide further evidence of the potential clinical significance of a treatment effect. However, there is no assurance as to which of these secondary endpoints (if any) will be affected even if treatment with tirasemtiv achieves the primary efficacy objective of the trial. Further, there is no assurance as to whether regulatory authorities would accept the outcome of the trial as being a sufficient demonstration of clinical efficacy even if the primary endpoint and all secondary endpoints are achieved. We will continue interactions with regulatory authorities regarding the appropriate assessment(s) of the clinical meaningfulness and potential efficacy of therapy in the ALS population. If the results of our Phase 3 clinical trial in ALS are not sufficient to persuade regulatory authorities of the safety and efficacy of tirasemtiv, either because of a failure to achieve pre-specified endpoints or because the authorities do not accept such endpoints as being sufficient, then we would be required to conduct successfully one or more additional Phase 3 clinical trials, prior to receiving marketing authorization, which would be expensive, time consuming and uncertain.

*It is not known whether the FDA or other regulatory authorities would accept a single Phase 3 clinical trial as being adequate to support marketing approval of tirasemtiv, even if the results of such trial are positive.*

The conventional standard for granting marketing authorization of a new investigational medicine is the demonstration of safety and efficacy in two large, well-controlled Phase 3 clinical trials. The Phase 3 trial of tirasemtiv in ALS that we are currently conducting will be the first Phase 3 trial of this drug candidate. In the case of diseases with high unmet medical need, such as ALS, regulatory authorities may exercise their discretion to approve a new pharmaceutical on the basis of a single outcomes trial (sometimes subject to the conduct of subsequent confirmatory trial(s)). However, this is always within the judgment of the regulatory authorities and is dependent on their assessment of the degree of success achieved in the clinical trial as balanced by the potential risks associated with treatment. Even if our first Phase 3 trial of tirasemtiv shows positive results,



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regulatory authorities may require us to successfully conduct one or more additional Phase 3 clinical trials prior to receiving marketing authorization, which would be expensive, time consuming and uncertain.

*Clinical trials are expensive, time-consuming and subject to delay.*

Clinical trials are subject to rigorous regulatory requirements and are very expensive, difficult and time-consuming to design and implement. The length of time and number of trial sites and patients required for clinical trials vary substantially based on the type, complexity, novelty, intended use of the drug candidate and safety concerns. We estimate that the clinical trials of our current drug candidates will each continue for several more years. However, the clinical trials for all or any of our drug candidates may take significantly longer to complete. The commencement and completion of our or our partners' clinical trials could be delayed or prevented by many factors, including, but not limited to:

delays in obtaining, or inability to obtain, regulatory or other approvals to commence and conduct clinical trials in the manner we or our partners deem necessary for the appropriate and timely development of our drug candidates and commercialization of any resulting drugs;

delays in identifying and reaching agreement, or inability to identify and reach agreement, on acceptable terms, with prospective clinical trial sites and other entities involved in the conduct of our or our partners' clinical trials;

delays or additional costs in developing, or inability to develop, appropriate formulations of our drug candidates for clinical trial use, including an appropriate modified release oral formulation for omecamtiv mecarbil;

slower than expected rates of patient recruitment and enrollment, including as a result of competition for patients with other clinical trials; limited numbers of patients that meet the enrollment criteria; patients', investigators' or trial sites' reluctance to agree to the requirements of a protocol; or the introduction of alternative therapies or drugs by others;

for those drug candidates that are the subject of a strategic alliance, delays in reaching agreement with our partner as to appropriate development strategies;

a regulatory authority may require changes to a protocol for a clinical trial that then may require approval from regulatory agencies in other jurisdictions where the trial is being conducted;

an institutional review board ( IRB ) or its foreign equivalent may require changes to a protocol that then require approval from regulatory agencies and other IRBs and their foreign equivalents, or regulatory authorities may require changes to a protocol that then require approval from the IRBs or their foreign equivalents;

for clinical trials conducted in foreign countries, the time and resources required to identify, interpret and comply with foreign regulatory requirements or changes in those requirements, and political instability or natural disasters occurring in those countries;

lack of effectiveness of our drug candidates during clinical trials;

unforeseen safety issues;

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inadequate supply, or delays in the manufacture or supply, of clinical trial materials;

uncertain dosing issues;

failure by us, our partners, or clinical research organizations, investigators or site personnel engaged by us or our partners to comply with good clinical practices and other applicable laws and regulations, including those concerning informed consent;

inability or unwillingness of investigators or their staffs to follow clinical protocols;

failure by our clinical research organizations, clinical manufacturing organizations and other third parties supporting our or our partners clinical trials to fulfill their obligations;

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inability to monitor patients adequately during or after treatment;

introduction of new therapies or changes in standards of practice or regulatory guidance that render our drug candidates or their clinical trial endpoints obsolete; and

results from non-clinical studies that may adversely impact the timing or further development of our drug candidates.

We do not know whether planned clinical trials will begin on time, or whether planned or currently ongoing clinical trials will need to be restructured or will be completed on schedule, if at all. Significant delays in clinical trials will impede our ability to commercialize our drug candidates and generate revenue and could significantly increase our development costs.

***We depend on Amgen for the conduct and funding of the development and commercialization of omecamtiv mecarbil.***

Under our strategic alliance, Amgen holds an exclusive license to our drug candidate omecamtiv mecarbil worldwide. As a result, Amgen is responsible for the development and obtaining and maintaining regulatory approval of omecamtiv mecarbil for the potential treatment of heart failure worldwide.

We do not control the development activities being conducted or that may be conducted in the future by Amgen, including, but not limited to, the timing of initiation, termination or completion of clinical trials, the analysis of data arising out of those clinical trials or the timing of release of data concerning those clinical trials, which may impact our ability to report on Amgen's results. Amgen may conduct these activities more slowly or in a different manner than we would if we controlled the development of omecamtiv mecarbil. Amgen is responsible for filing future applications with the FDA or other regulatory authorities for approval of omecamtiv mecarbil and will be the owner of any marketing approvals issued by the FDA or other regulatory authorities for omecamtiv mecarbil. If the FDA or other regulatory authorities approve omecamtiv mecarbil, Amgen will also be responsible for the marketing and sale of the resulting drug, subject to our right to co-promote omecamtiv mecarbil in North America if we exercise our option to co-fund Phase 3 development costs of omecamtiv mecarbil under the collaboration. However, we cannot control whether Amgen will devote sufficient attention and resources to the development of omecamtiv mecarbil or will proceed in an expeditious manner, even if we do exercise our option to co-fund the development of omecamtiv mecarbil. Even if the FDA or other regulatory agencies approve omecamtiv mecarbil, Amgen may elect not to proceed with the commercialization of the resulting drug in one or more countries.

If the results of one or more clinical trials with omecamtiv mecarbil do not meet Amgen's expectations at any time, Amgen may elect to terminate further development of omecamtiv mecarbil or certain of the potential clinical trials for omecamtiv mecarbil, even if the actual number of patients treated at that time is relatively small. In addition, Amgen generally has discretion to elect whether to pursue or abandon the development of omecamtiv mecarbil and may terminate our strategic alliance for any reason upon six months prior notice. If Amgen abandons omecamtiv mecarbil, it would result in a delay in or could prevent us from commercializing omecamtiv mecarbil, and would delay and could prevent us from obtaining revenues for this drug candidate. Disputes may arise between us and Amgen, which may delay or cause the termination of any omecamtiv mecarbil clinical trials, result in significant litigation or cause Amgen to act in a manner that is not in our best interest. If development of omecamtiv mecarbil does not progress for these or any other reasons, we would not receive further milestone payments or royalties on product sales from Amgen with respect to omecamtiv mecarbil. If Amgen abandons development of omecamtiv mecarbil prior to regulatory approval or if it elects not to proceed with commercialization of the resulting drug following regulatory approval, we would have to seek a new partner for development or commercialization, curtail or abandon that development or commercialization, or undertake and fund the development of omecamtiv mecarbil or commercialization of the resulting drug ourselves. If we seek a new partner but are unable to do so on acceptable terms, or at all, or do not have sufficient funds to conduct the development or commercialization of omecamtiv mecarbil ourselves, we would have to curtail or abandon that development or commercialization, which could harm our business.

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***We depend on Astellas for the conduct and funding of the development and commercialization of CK-2127107.***

In December 2014, we expanded our strategic alliance with Astellas focused on the research, development and commercialization of skeletal muscle activators, other than tirasemtiv and certain related compounds. The primary objective of the strategic alliance is to advance novel therapies for indications associated with muscle weakness.

Under this strategic alliance, we have granted Astellas an exclusive license to co-develop and commercialize CK-2127107 for potential application in spinal muscular atrophy (SMA) and potentially other indications worldwide. We have initiated a Phase 2 clinical trial of CK-2127107 in patients with SMA. Unless otherwise agreed by the parties, Astellas will be primarily responsible for the conduct of subsequent development and commercialization activities for CK-2127107.

We do not control the development activities that may be conducted by Astellas, including, but not limited to, the timing of initiation, termination or completion of clinical trials, the analysis of data arising out of those clinical trials or the timing of release of data concerning those clinical trials, which may impact our ability to report on Astellas' results. Astellas may conduct these activities more slowly or in a different manner than we would. In general, Astellas is responsible for filing future applications with the FDA or other regulatory authorities for approval of CK-2127107 and will be the owner of any marketing approvals issued by the FDA or other regulatory authorities for CK-2127107. If the FDA or other regulatory authorities approve CK-2127107, Astellas will also be responsible for the marketing and sale of the resulting drug, subject to our right to co-promote the drug in the United States, Canada and, for neuromuscular indications, Europe. However, we cannot control whether Astellas will devote sufficient attention and resources to the development of CK-2127107 or will proceed in an expeditious manner. Even if the FDA or other regulatory agencies approve CK-2127107, Astellas may elect not to proceed with the commercialization of the resulting drug in one or more countries.

If the results of one or more clinical trials with CK-2127107 do not meet Astellas' expectations at any time, Astellas may elect to terminate further development of CK-2127107 or certain of the potential clinical trials for CK-2127107, even if the actual number of patients treated at that time is relatively small. In addition, Astellas generally has discretion to elect whether to pursue or abandon the development of CK-2127107. Astellas may terminate our strategic alliance in whole or in part for any reason upon six months prior notice at any time following expiration of the strategic alliance's research term, which will expire December 31, 2016. If Astellas abandons CK-2127107, it would result in a delay in or could prevent us from further developing or commercializing CK-2127107, and would delay and could prevent us from obtaining revenues for this drug candidate. Disputes may arise between us and Astellas, which may delay or cause the termination of any CK-2127107 clinical trials, result in significant litigation or cause Astellas to act in a manner that is not in our best interest. If development of CK-2127107 does not progress for these or any other reasons, we would not receive further milestone payments or royalties on product sales from Astellas with respect to CK-2127107. If Astellas abandons development of CK-2127107 prior to regulatory approval or if it elects not to proceed with commercialization of the resulting drug following regulatory approval, we would have to seek a new partner for development or commercialization, curtail or abandon that development or commercialization, or undertake and fund the development of CK-2127107 or commercialization of the resulting drug ourselves. If we seek a new partner but are unable to do so on acceptable terms, or at all, or do not have sufficient funds to conduct the development or commercialization of CK-2127107 ourselves, we would have to curtail or abandon that development or commercialization, which could harm our business.

***If we do not enter into strategic alliances for our unpartnered drug candidates or research and development programs or fail to successfully maintain our current or future strategic alliances, we may have to reduce, delay or discontinue our advancement of our drug candidates and programs or expand our research and development capabilities and increase our expenditures.***

Drug development is complicated and expensive. We currently have limited financial and operational resources to carry out drug development. Our strategy for developing, manufacturing and commercializing our

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drug candidates currently requires us to enter into and successfully maintain strategic alliances with pharmaceutical companies or other industry participants to advance our programs and reduce our expenditures on each program. Accordingly, the success of our development activities depends in large part on our current and future strategic partners' performance, over which we have little or no control.

We have retained exclusive rights to develop and commercialize tirasemtiv. We currently do not have a strategic partner for this drug candidate. We may seek one or more strategic partners or other arrangements with third parties to support further clinical development and commercialization of tirasemtiv. However, we may not be able to negotiate and enter into such strategic alliances or arrangements on acceptable terms, if at all, or in accordance with our planned timelines. If we are unable to enter into a strategic alliance for tirasemtiv, we will be unable to conduct further clinical development of tirasemtiv for the potential treatment of ALS unless we are able to acquire the funding to do so from another source.

Our ability to commercialize drugs that we develop with our partners and that generate royalties from product sales depends on our partners' abilities to assist us in establishing the safety and efficacy of our drug candidates, obtaining and maintaining regulatory approvals and achieving market acceptance of the drugs once commercialized. Our partners may elect to delay or terminate development of one or more drug candidates, independently develop drugs that could compete with ours or fail to commit sufficient resources to the marketing and distribution of drugs developed through their strategic alliances with us. Our partners may not proceed with the development and commercialization of our drug candidates with the same degree of urgency as we would because of other priorities they face. In addition, new business combinations or changes in a partner's business strategy may adversely affect its willingness or ability to carry out its obligations under a strategic alliance.

If we are not able to successfully maintain our existing strategic alliances or establish and successfully maintain additional strategic alliances, we will have to limit the size or scope of, or delay or discontinue, one or more of our drug development programs or research programs, or undertake and fund these programs ourselves. Alternatively, if we elect to continue to conduct any of these drug development programs or research programs on our own, we will need to expand our capability to conduct clinical development by bringing additional skills, technical expertise and resources into our organization. This would require significant additional funding, which may not be available to us on acceptable terms, or at all.

***To the extent we elect to fund the development of a drug candidate, such as omecamtiv mecarbil, tirasemtiv or CK-2127107, or the commercialization of a drug at our expense, we will need substantial additional funding.***

The discovery, development and commercialization of new drugs is costly. As a result, to the extent we elect to fund the development of a drug candidate, such as omecamtiv mecarbil, tirasemtiv or CK-2127107, or the commercialization of a drug, we will need to raise additional capital to:

fund clinical trials and seek regulatory approvals;

expand our development capabilities;

engage third party manufacturers for such drug candidate or drug;

build or access commercialization capabilities;

implement additional internal systems and infrastructure;

maintain, defend and expand the scope of our intellectual property; and

hire and support additional management and scientific personnel.

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Our future funding requirements will depend on many factors, including, but not limited to:

the rate of progress and costs of our or our partners' clinical trials and other research and development activities;

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the costs and timing of seeking and obtaining regulatory approvals;

the costs associated with establishing manufacturing and commercialization capabilities;

the costs of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights;

the costs of acquiring or investing in businesses, products and technologies;

the effect of competing technological and market developments; and

the status of, payment and other terms, and timing of any strategic alliance, licensing or other arrangements that we have entered into or may establish.

Until we can generate a sufficient amount of product revenue to finance our cash requirements, which we may never do, we expect to continue to finance our future cash needs primarily through strategic alliances, public or private equity offerings and debt financings. We cannot be certain that additional funding will be available on acceptable terms, or at all. If we are not able to secure additional funding when needed, we may have to delay, reduce the scope of or eliminate one or more of our clinical trials or research and development programs or future commercialization initiatives.

***We depend on contract research organizations to conduct our clinical trials and have limited control over their performance.***

We have used and intend to continue to use contract research organizations ( CROs ) within and outside of the United States to conduct clinical trials of our drug candidates, such as tirasemtiv, CK-2127107 and omecamtiv mecarbil, and related activities. We do not have control over many aspects of our CROs activities, and cannot fully control the amount, timing or quality of resources that they devote to our programs. CROs may not assign as high a priority to our programs or pursue them as diligently as we would if we were undertaking these programs ourselves. The activities conducted by our CROs therefore may not be completed on schedule or in a satisfactory manner. CROs may also give higher priority to relationships with our competitors and potential competitors than to their relationships with us. Outside of the United States, we are particularly dependent on our CROs expertise in communicating with clinical trial sites and regulatory authorities and ensuring that our clinical trials and related activities and regulatory filings comply with applicable laws.

Our CROs failure to carry out development activities on our behalf as agreed and in accordance with our and the FDA s or other regulatory agencies requirements and applicable U.S. and foreign laws, or our failure to properly coordinate and manage these activities, could increase the cost of our operations and delay or prevent the development, approval and commercialization of our drug candidates. For example, in June 2013, we learned from our data management vendor for our BENEFIT-ALS clinical trial that a programming error in the electronic data capture system controlling study drug assignment caused 58 patients initially randomized to and treated with tirasemtiv to receive placebo instead at a certain trial visit and for the remainder of the trial. In order to maintain the originally intended statistical power of the trial, we amended the protocol to permit enrollment of approximately 680 patients, or 180 patients in addition to the 500 patients allowed under the existing protocol. This protocol amendment resulted in additional costs and delays in conducting BENEFIT-ALS. In addition, if a CRO fails to perform as agreed, our ability to collect damages may be contractually limited. If we fail to effectively manage the CROs carrying out the development of our drug candidates or if our CROs fail to perform as agreed, the commercialization of our drug candidates will be delayed or prevented.

***We have no manufacturing capacity and depend on our strategic partners and contract manufacturers to produce our clinical trial materials, including our drug candidates, and anticipate continued reliance on contract manufacturers for the development and commercialization of our potential drugs.***

We do not currently operate manufacturing facilities for clinical or commercial production of our drug candidates. We have limited experience in drug formulation and manufacturing, and we lack the resources and

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the capabilities to manufacture any of our drug candidates on a clinical or commercial scale. Amgen has assumed responsibility to conduct these activities for the ongoing development of omecamtiv mecarbil worldwide. Following our conduct of the early development of CK-2127107, including the ongoing Phase 2 clinical trial in patients with SMA, Astellas will assume primary responsibility to conduct the manufacturing for the ongoing development of CK-2127107 worldwide. For tirasemtiv, we rely on a limited number of contract manufacturers. In particular, we rely on single-source contract manufacturers for the active pharmaceutical ingredient and the drug product supply for our clinical trials, as well as other materials required to conduct our clinical trials. We expect to rely on contract manufacturers to supply all future drug candidates for which we conduct development, as well as other materials required to conduct our clinical trials. If any of our existing or future contract manufacturers fail to perform satisfactorily, it could delay development or regulatory approval of our drug candidates or commercialization of our drugs, producing additional losses and depriving us of potential product revenues. In addition, if a contract manufacturer fails to perform as agreed, our ability to collect damages may be contractually limited.

Our drug candidates require precise high-quality manufacturing. The failure to achieve and maintain high manufacturing standards, including failure to detect or control anticipated or unanticipated manufacturing errors or the frequent occurrence of such errors, could result in patient injury or death, discontinuance or delay of ongoing or planned clinical trials, delays or failures in product testing or delivery, cost overruns, product recalls or withdrawals and other problems that could seriously hurt our business. Contract drug manufacturers often encounter difficulties involving production yields, quality control and quality assurance and shortages of qualified personnel. These manufacturers are subject to stringent regulatory requirements, including the FDA's current good manufacturing practices regulations and similar foreign laws and standards. Each contract manufacturer must pass a pre-approval inspection before we can obtain marketing approval for any of our drug candidates and following approval will be subject to ongoing periodic unannounced inspections by the FDA, the U.S. Drug Enforcement Agency and other regulatory agencies, to ensure strict compliance with current good manufacturing practices and other applicable government regulations and corresponding foreign laws and standards. We seek to ensure that our contract manufacturers comply fully with all applicable regulations, laws and standards. However, we do not have control over our contract manufacturers' compliance with these regulations, laws and standards. If one of our contract manufacturers fails to pass its pre-approval inspection or maintain ongoing compliance at any time, the production of our drug candidates could be interrupted, resulting in delays or discontinuance of our clinical trials, additional costs and potentially lost revenues. In addition, failure of any third party manufacturers or us to comply with applicable regulations, including pre- or post-approval inspections and the current good manufacturing practice requirements of the FDA or other comparable regulatory agencies, could result in sanctions being imposed on us. These sanctions could include fines, injunctions, civil penalties, failure of regulatory authorities to grant marketing approval of our products, delay, suspension or withdrawal of approvals, license revocation, product seizures or recalls, operational restrictions and criminal prosecutions, any of which could significantly and adversely affect our business.

In addition, our existing and future contract manufacturers may not perform as agreed or may not remain in the contract manufacturing business for the time required to successfully produce, store and distribute our drug candidates. If a natural disaster, business failure, strike or other difficulty occurs, we may be unable to replace these contract manufacturers in a timely or cost-effective manner and the production of our drug candidates would be interrupted, resulting in delays and additional costs.

Switching manufacturers or manufacturing sites would be difficult and time-consuming because the number of potential manufacturers is limited. In addition, before a drug from any replacement manufacturer or manufacturing site can be commercialized, the FDA and, in some cases, foreign regulatory agencies, must approve that site. These approvals would require regulatory testing and compliance inspections. A new manufacturer or manufacturing site also would have to be educated in, or develop substantially equivalent processes for, production of our drugs and drug candidates. It may be difficult or impossible to transfer certain elements of a manufacturing process to a new manufacturer or for us to find a replacement manufacturer on



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acceptable terms quickly, or at all, either of which would delay or prevent our ability to develop drug candidates and commercialize any resulting drugs.

***We may not be able to successfully scale-up manufacturing of our drug candidates in sufficient quality and quantity, which would delay or prevent us from developing our drug candidates and commercializing resulting approved drugs, if any.***

To date, our drug candidates have been manufactured in small quantities for preclinical studies and early and mid-stage clinical trials. In order to conduct larger scale or late-stage clinical trials for a drug candidate and for commercialization of the resulting drug if that drug candidate is approved for sale, we will need to manufacture it in larger quantities. We may not be able to successfully increase the manufacturing capacity for any of our drug candidates, whether in collaboration with third-party manufacturers or on our own, in a timely or cost-effective manner or at all. If a contract manufacturer makes improvements in the manufacturing process for our drug candidates, we may not own, or may have to share, the intellectual property rights to those improvements. Significant scale-up of manufacturing may require additional validation studies, which are costly and which regulatory authorities must review and approve. In addition, quality issues may arise during those scale-up activities because of the inherent properties of a drug candidate itself or of a drug candidate in combination with other components added during the manufacturing and packaging process, or during shipping and storage of the finished product or active pharmaceutical ingredients. If we are unable to successfully scale-up manufacture of any of our drug candidates in sufficient quality and quantity, the development of that drug candidate and regulatory approval or commercial launch for any resulting drugs may be delayed or there may be a shortage in supply, which could significantly harm our business. In addition, data demonstrating the stability of both drug substance and drug product, using the commercial manufacturing process and at commercial scale, are required for marketing applications. Failure to produce drug substance and drug products in a timely manner and obtain stability data could result in delay of submission of marketing applications.

***The mechanisms of action of our drug candidates are unproven, and we do not know whether we will be able to develop any drug of commercial value.***

We have discovered and are currently developing drug candidates that have what we believe are novel mechanisms of action directed against cytoskeletal targets, and intend to continue to do so. Because no currently approved drugs appear to operate via the same biochemical mechanisms as our compounds, we cannot be certain that our drug candidates will result in commercially viable drugs that safely and effectively treat the indications for which we intend to develop them. The results we have seen for our compounds in preclinical models may not translate into similar results in humans, and results of early clinical trials in humans may not be predictive of the results of larger clinical trials that may later be conducted with our drug candidates. Even if we are successful in developing and receiving regulatory approval for a drug candidate for the treatment of a particular disease, we cannot be certain that it will be accepted by prescribers or be reimbursed by insurers or that we will also be able to develop and receive regulatory approval for that or other drug candidates for the treatment of other diseases. If we or our partners are unable to successfully develop and commercialize our drug candidates, our business will be materially harmed.

***Our success depends substantially upon our ability to obtain and maintain intellectual property protection relating to our drug candidates, compounds and research technologies.***

We own, or hold exclusive licenses to, a number of U.S. and foreign patents and patent applications directed to our drug candidates, compounds and research technologies. Our success depends on our ability to obtain patent protection both in the United States and in other countries for our drug candidates, their methods of manufacture and use, and our technologies. Our ability to protect our drug candidates, compounds and technologies from unauthorized or infringing use by third parties depends substantially on our ability to obtain and enforce our patents. If our issued patents and patent applications, if granted, do not adequately describe, enable or otherwise provide coverage of our technologies and drug candidates, including omeamtiv mecarbil,

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tirasemtiv and CK-2127107, we or our licensees would not be able to exclude others from developing or commercializing these drug candidates. Furthermore, the degree of future protection of our proprietary rights is uncertain because legal means may not adequately protect our rights or permit us to gain or keep our competitive advantage.

Due to evolving legal standards relating to the patentability, validity and enforceability of patents covering pharmaceutical inventions and the claim scope of these patents, our ability to enforce our existing patents and to obtain and enforce patents that may issue from any pending or future patent applications is uncertain and involves complex legal, scientific and factual questions. The standards which the U.S. Patent and Trademark Office and its foreign counterparts use to grant patents are not always applied predictably or uniformly and are subject to change. To date, no consistent policy has emerged regarding the breadth of claims allowed in biotechnology and pharmaceutical patents. Thus, we cannot be sure that any patents will issue from any pending or future patent applications owned by or licensed to us. Even if patents do issue, we cannot be sure that the claims of these patents will be held valid or enforceable by a court of law, will provide us with any significant protection against competitive products, or will afford us a commercial advantage over competitive products. In particular:

we or our licensors might not have been the first to make the inventions covered by each of our pending patent applications and issued patents;

we or our licensors might not have been the first to file patent applications for the inventions covered by our pending patent applications and issued patents;

others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights;

some or all of our or our licensors' pending patent applications may not result in issued patents or the claims that issue may be narrow in scope and not provide us with competitive advantages;

our and our licensors' issued patents may not provide a basis for commercially viable drugs or therapies or may be challenged and invalidated by third parties;

our or our licensors' patent applications or patents may be subject to interference, opposition or similar administrative proceedings that may result in a reduction in their scope or their loss altogether;

we may not develop additional proprietary technologies or drug candidates that are patentable; or

the patents of others may prevent us or our partners from discovering, developing or commercializing our drug candidates. Patent protection is afforded on a country-by-country basis. Some foreign jurisdictions do not protect intellectual property rights to the same extent as in the United States. Many companies have encountered significant difficulties in protecting and defending intellectual property rights in foreign jurisdictions. Some of our development efforts are performed in countries outside of the United States through third party contractors. We may not be able to effectively monitor and assess intellectual property developed by these contractors. We therefore may not be able to effectively protect this intellectual property and could lose potentially valuable intellectual property rights. In addition, the legal protection afforded to inventors and owners of intellectual property in countries outside of the United States may not be as protective of intellectual property rights as in the United States. Therefore, we may be unable to acquire and protect intellectual property developed by these contractors to the same extent as if these development activities were being conducted in the United States. If we encounter difficulties in protecting our intellectual property rights in foreign jurisdictions, our business prospects could be substantially harmed.

## Edgar Filing: CYTOKINETICS INC - Form 10-K

We rely on intellectual property assignment agreements with our corporate partners, employees, consultants, scientific advisors and other collaborators to grant us ownership of new intellectual property that is developed. These agreements may not result in the effective assignment to us of that intellectual property. As a result, our ownership of key intellectual property could be compromised.

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Changes in either the patent laws or their interpretation in the United States or other countries may diminish the value of our intellectual property or our ability to obtain patents. For example, the America Invents Act of 2011 may affect the scope, strength and enforceability of our patent rights in the United States or the nature of proceedings which may be brought by us related to our patent rights in the United States.

If one or more products resulting from our drug candidates is approved for sale by the FDA and we do not have adequate intellectual property protection for those products, competitors could duplicate them for approval and sale in the United States without repeating the extensive testing required of us or our partners to obtain FDA approval. Regardless of any patent protection, under current law, an application for a generic version of a new chemical entity cannot be approved until at least five years after the FDA has approved the original product. When that period expires, or if that period is altered, the FDA could approve a generic version of our product regardless of our patent protection. An applicant for a generic version of our product may only be required to conduct a relatively inexpensive study to show that its product is bioequivalent to our product, and may not have to repeat the lengthy and expensive clinical trials that we or our partners conducted to demonstrate that the product is safe and effective. In the absence of adequate patent protection for our products in other countries, competitors may similarly be able to obtain regulatory approval in those countries of generic versions of our products.

We also rely on trade secrets to protect our technology, particularly where we believe patent protection is not appropriate or obtainable. However, trade secrets are often difficult to protect, especially outside of the United States. While we endeavor to use reasonable efforts to protect our trade secrets, our or our partners' employees, consultants, contractors or scientific and other advisors may unintentionally or willfully disclose our information to competitors. In addition, confidentiality agreements, if any, executed by those individuals may not be enforceable or provide meaningful protection for our trade secrets or other proprietary information in the event of unauthorized use or disclosure. Pursuing a claim that a third party had illegally obtained and was using our trade secrets would be expensive and time-consuming, and the outcome would be unpredictable. Even if we are able to maintain our trade secrets as confidential, if our competitors independently develop information equivalent or similar to our trade secrets, our business could be harmed.

If we are not able to defend the patent or trade secret protection position of our technologies and drug candidates, then we will not be able to exclude competitors from developing or marketing competing drugs, and we may not generate enough revenue from product sales to justify the cost of development of our drugs or to achieve or maintain profitability.

***If we are sued for infringing third party intellectual property rights, it will be costly and time-consuming, and an unfavorable outcome could have a significant adverse effect on our business.***

Our ability to commercialize drugs depends on our ability to use, manufacture and sell those drugs without infringing the patents or other proprietary rights of third parties. Numerous U.S. and foreign issued patents and pending patent applications owned by third parties exist in the therapeutic areas in which we are developing drug candidates and seeking new potential drug candidates. In addition, because patent applications can take several years to issue, there may be currently pending applications, unknown to us, which could later result in issued patents that our activities with our drug candidates could infringe. There may also be existing patents, unknown to us, that our activities with our drug candidates could infringe.

Other future products of ours may be impacted by patents of companies engaged in competitive programs with significantly greater resources. Further development of these products could be impacted by these patents and result in significant legal fees.

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If a third party claims that our actions infringe its patents or other proprietary rights, we could face a number of issues that could seriously harm our competitive position, including, but not limited to:

infringement and other intellectual property claims that, even if meritless, can be costly and time-consuming to litigate, delay the regulatory approval process and divert management's attention from our core business operations;

substantial damages for past infringement which we may have to pay if a court determines that our drugs or technologies infringe a third party's patent or other proprietary rights;

a court prohibiting us from selling or licensing our drugs or technologies unless the holder licenses the patent or other proprietary rights to us, which it is not required to do; and

if a license is available from a holder, we may have to pay substantial royalties or grant cross-licenses to our patents or other proprietary rights.

If any of these events occur, it could significantly harm our business and negatively affect our stock price.

***We may undertake infringement or other legal proceedings against third parties, causing us to spend substantial resources on litigation and exposing our own intellectual property portfolio to challenge.***

Third parties may infringe our patents. To prevent infringement or unauthorized use, we may need to file infringement suits, which are expensive and time-consuming. In an infringement proceeding, a court may decide that one or more of our patents is invalid, unenforceable, or both. In this case, third parties may be able to use our technology without paying licensing fees or royalties. Even if the validity of our patents is upheld, a court may refuse to stop the other party from using the technology at issue on the ground that the other party's activities are not covered by our patents. Policing unauthorized use of our intellectual property is difficult, and we may not be able to prevent misappropriation of our proprietary rights, particularly in countries where the laws may not protect such rights as fully as in the United States. In addition, third parties may affirmatively challenge our rights to, or the scope or validity of, our patent rights.

***We may become involved in disputes with our strategic partners over intellectual property ownership, and publications by our research collaborators and clinical investigators could impair our ability to obtain patent protection or protect our proprietary information, either of which would have a significant impact on our business.***

Inventions discovered under our current or future strategic alliance agreements may become jointly owned by our strategic partners and us in some cases, and the exclusive property of one of us in other cases. Under some circumstances, it may be difficult to determine who owns a particular invention or whether it is jointly owned, and disputes could arise regarding ownership or use of those inventions. These disputes could be costly and time-consuming, and an unfavorable outcome could have a significant adverse effect on our business if we were not able to protect or license rights to these inventions. In addition, our research collaborators and clinical investigators generally have contractual rights to publish data arising from their work. Publications by our research collaborators and clinical investigators relating to our research and development programs, either with or without our consent, could benefit our current or potential competitors and may impair our ability to obtain patent protection or protect our proprietary information, which could significantly harm our business.

***We may be subject to claims that we or our employees have wrongfully used or disclosed trade secrets of their former employers.***

Many of our employees were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although no claims against us are currently pending, we may be subject to claims that these employees or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former employers. Litigation may be necessary to

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defend against these claims. If we fail in defending these claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. A loss of key research personnel or their work product could hamper or prevent our ability to develop and commercialize certain potential drugs, which could significantly harm our business. Even if we are successful in defending against these claims, litigation could result in substantial costs and distract management.

*Our competitors may develop drugs that are less expensive, safer or more effective than ours, which may diminish or eliminate the commercial success of any drugs that we may commercialize.*

We compete with companies that have developed drugs or are developing drug candidates for cardiovascular diseases, diseases and conditions associated with muscle weakness or wasting and other diseases for which our drug candidates may be useful treatments. For example, if tirasemtiv is approved for marketing by the FDA or other regulatory authorities for the treatment of ALS, it may then compete with other potential new therapies for ALS that are currently being developed by companies such as Neuraltus Pharmaceuticals, Inc., Isis Pharmaceuticals, Inc., Genervon Biopharmaceuticals, LLC, and GlaxoSmithKline plc. In addition, BrainStorm Cell Therapeutics and Neuralstem, Inc. are each conducting clinical development of stem cell therapies for the potential treatment of ALS.

If CK-2127107 is approved by the FDA or other regulatory authorities for the potential treatment of SMA, potential competitors include Roche (in collaboration with PTC Therapeutics), AveXis, Inc., Pfizer Inc., Isis Pharmaceuticals, Inc., Trophos SA, and Bioblast Pharma, Ltd. Drugs that could compete with CK-2127107 could also compete against tirasemtiv in ALS or other neuromuscular diseases, should the appropriate clinical trials be conducted. If CK-2127107 is approved by the FDA for the potential treatment of non-neuromuscular indications associated with muscle weakness, potential competitors include Ligand Pharmaceuticals, Inc., which is developing LGD-4033, a selective androgen receptor modulator, for muscle wasting; and GTx, Inc., which is developing ostarine, a selective androgen receptor modulator, for cancer cachexia and potentially other indications; Regeneron Pharmaceuticals, Inc. (in collaboration with Sanofi), which is developing SAR391786, a monoclonal antibody targeted to GDF8, for sarcopenia; Eli Lilly & Company, which is developing LY2495655, a monoclonal antibody targeted to myostatin, for muscular atrophy after hip arthroplasty; Acceleron Pharma, which is developing ACE-083 for diseases such as inclusion body myositis and certain forms of muscular dystrophy; and Pfizer Inc., which is developing PF-06252616, a monoclonal antibody targeted to myostatin, in Duchenne muscular dystrophy. Novartis (in collaboration with Morphosys AG), is conducting clinical development with an activin type-IIb receptor antagonist, bimagrumab, to evaluate its ability to treat diseases involving the loss of muscle mass, strength and function.

If omecamtiv mecarbil is approved for marketing by the FDA or other regulatory authorities for the treatment of heart failure, it would compete against other drugs used for the treatment of acute and chronic heart failure. These include generic drugs, such as milrinone, dobutamine or digoxin and branded drugs such as Natrecor (nesiritide) and Procoralan (ivabradine). Omecamtiv mecarbil could also potentially compete against other novel drug candidates and therapies in development, such as bucindolol, which is being developed by ARCA biopharma, Inc.; Reasanz (serelaxin) and LCZ-696, which are being developed by Novartis; cenderitide (CD-NP), which is being developed by Carpacor Therapeutics, Inc., TRV-027, which is being developed by Trevena; ularitide, which is being developed by Cardiorientis Ltd.; aladorian, which is being developed by ARMGO Pharma, Inc; TRV027, which is being developed by Trevena, Inc. in partnership with Forest Laboratories, Inc.; certain cardioprotectants which are being developed by Cardioxyl Pharmaceuticals, Inc.; glial growth factor (GGF-2) which is being developed by Acorda Therapeutics, Inc.; Neurocardin, which is being developed by Zensun Sci & Tech, Ltd; Mydicar, a genetically-targeted enzyme replacement therapy for advanced heart failure which is being developed by Celladon Corporation; and levosimendan, which was acquired for development by Oxygen Biotherapeutics, Inc. In addition, there are a number of medical devices being developed for the potential treatment of heart failure.

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Our competitors may:

develop drug candidates and market drugs that are less expensive or more effective than our future drugs;

commercialize competing drugs before we or our partners can launch any drugs developed from our drug candidates;

hold or obtain proprietary rights that could prevent us from commercializing our products;

initiate or withstand substantial price competition more successfully than we can;

more successfully recruit skilled scientific workers and management from the limited pool of available talent;

more effectively negotiate third-party licenses and strategic alliances;

take advantage of acquisition or other opportunities more readily than we can;

develop drug candidates and market drugs that increase the levels of safety or efficacy that our drug candidates will need to show in order to obtain regulatory approval; or

introduce therapies or market drugs that render the market opportunity for our potential drugs obsolete.

We will compete for market share against large pharmaceutical and biotechnology companies and smaller companies that are collaborating with larger pharmaceutical companies, new companies, academic institutions, government agencies and other public and private research organizations. Many of these competitors, either alone or together with their partners, may develop new drug candidates that will compete with ours. Many of these competitors have larger research and development programs or substantially greater financial resources than we do. Our competitors may also have significantly greater experience in:

developing drug candidates;

undertaking preclinical testing and clinical trials;

building relationships with key customers and opinion-leading physicians;

obtaining and maintaining FDA and other regulatory approvals of drug candidates;

formulating and manufacturing drugs; and

launching, marketing and selling drugs.

If our competitors market drugs that are less expensive, safer or more efficacious than our potential drugs, or that reach the market sooner than our potential drugs, we may not achieve commercial success. In addition, the life sciences industry is characterized by rapid technological change. If we fail to stay at the forefront of technological change, we may be unable to compete effectively. Our competitors may render our technologies obsolete by improving existing technological approaches or developing new or different approaches, potentially eliminating the advantages in our drug discovery process that we believe we derive from our research approach and proprietary technologies.

***We have been granted orphan designations in the U.S. and in the E.U. for tirasemtiv; however, there can be no guarantee that we will receive orphan approval for tirasemtiv, nor that we will be able to prevent third parties from developing and commercializing products that are competitive to tirasemtiv.***

We have been granted orphan drug designation in the U.S. by the FDA and orphan medicinal product designation by the European Medicines Agency, in each case for tirasemtiv for the potential treatment of ALS. In the U.S., upon approval from the FDA of an NDA, products granted orphan drug approval are generally provided with seven years of marketing exclusivity in the U.S., meaning the FDA will generally not approve applications for other product candidates for the same orphan indication that contain the same active ingredient. Even if we are the first to obtain approval of an orphan product and are granted exclusivity in the U.S., there are limited circumstances under which a later competitor product may be approved for the same indication during the seven-



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year period of marketing exclusivity, such as if the later product is shown to be clinically superior to our product or due to an inability to assure a sufficient quantity of the orphan drug.

Orphan medicinal product status in Europe Union can provide up to 10 years of marketing exclusivity, meaning that another application for marketing authorization of a later similar medicinal product for the same therapeutic indication will generally not be approved in the European Union. Although we may have drug candidates that may obtain orphan drug exclusivity in Europe, the orphan approval and associated exclusivity period may be modified for several reasons, including a significant change to the orphan medicinal product designations or approval criteria after-market authorization of the orphan product (*e.g.*, product profitability exceeds the criteria for orphan drug designation), problems with the production or supply of the orphan drug or a competitor drug, although similar, is safer, more effective or otherwise clinically superior than the initial orphan drug.

We are not guaranteed to maintain orphan status for tirasemtiv or to receive orphan status for tirasemtiv for any other indication or for any of our other drug candidates for any indication. If our drug candidates that are granted orphan status were to lose their status as orphan drugs or the marketing exclusivity provided for them in the U.S. or the European Union, our business and results of operations could be materially adversely affected. While orphan status for any of our products, if granted or maintained, would provide market exclusivity in the U.S. and the European Union for the time periods specified above, we would not be able to exclude other companies from manufacturing and/or selling products using the same active ingredient for the same indication beyond the exclusivity period applicable to our product on the basis of orphan drug status. Moreover, we cannot guarantee that another company will not receive approval before we do of an orphan drug application in the U.S. or the European Union for a product candidate that has the same active ingredient or is a similar medicinal product for the same indication as any of our drug candidates for which we plan to file for orphan designation and status. If that were to happen, our orphan drug applications for our drug candidate for that indication may not be approved until the competing company's period of exclusivity has expired in the U.S. or the European Union, as applicable. Further, application of the orphan drug regulations in the U.S. and Europe is uncertain, and we cannot predict how the respective regulatory bodies will interpret and apply the regulations to our or our competitors' products.

***Our failure to attract and retain skilled personnel could impair our drug development and commercialization activities.***

Our business depends on the performance of our senior management and key scientific and technical personnel. The loss of the services of any member of our senior management or key scientific or technical staff may significantly delay or prevent the achievement of drug development and other business objectives by diverting management's attention to transition matters and identifying suitable replacements. We also rely on consultants and advisors to assist us in formulating our research and development strategy. All of our consultants and advisors are either self-employed or employed by other organizations, and they may have conflicts of interest or other commitments, such as consulting or advisory contracts with other organizations, that may affect their ability to contribute to us. In addition, if and as our business grows, we will need to recruit additional executive management and scientific and technical personnel. There is intense competition for skilled executives and employees with relevant scientific and technical expertise, and this competition is likely to continue. Our inability to attract and retain sufficient scientific, technical and managerial personnel could limit or delay our product development activities, which would adversely affect the development of our drug candidates and commercialization of our potential drugs and growth of our business.

***Any future workforce and expense reductions may have an adverse impact on our internal programs and our ability to hire and retain skilled personnel.***

Our future success will depend in large part upon our ability to attract and retain highly skilled personnel. In light of our continued need for funding and cost control, we may be required to implement future workforce and

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expense reductions, which could further limit our research and development activities. For example, in October 2011, we reduced our workforce by approximately 18% in order to reduce expenses and to focus resources primarily on our later-stage development programs for tirasemtiv and omecamtiv mecarbil and certain other research and development programs also directed to muscle biology. These headcount reductions and the cost control measures we have implemented may negatively affect our productivity and limit our research and development activities. We may have difficulty retaining and attracting such personnel as a result of a perceived risk of future workforce reductions. In addition, the implementation of any additional workforce or expense reduction programs may divert the efforts of our management team and other key employees, which could adversely affect our business.

***We may expand our development and clinical research capabilities and, as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.***

We may have growth in our expenditures, the number of our employees and the scope of our operations, in particular with respect to those drug candidates that we elect to develop or commercialize independently or together with a partner. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited resources, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The physical expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

***We currently have no sales or marketing capabilities and, if we are unable to enter into or maintain strategic alliances with marketing partners or to develop our own sales and marketing capabilities, we may not be successful in commercializing our potential drugs.***

We currently have no sales, marketing or distribution capabilities. We plan to commercialize drugs that can be effectively marketed and sold in concentrated markets that do not require a large sales force to be competitive. To achieve this goal, we will need to establish our own specialized sales force and marketing organization with technical expertise and supporting distribution capabilities. Developing such an organization is expensive and time-consuming and could delay a product launch. In addition, we may not be able to develop this capacity efficiently, cost-effectively or at all, which could make us unable to commercialize our drugs. If we determine not to market our drugs on our own, we will depend on strategic alliances with third parties, such as Amgen and Astellas, which have established distribution systems and direct sales forces to commercialize them. If we are unable to enter into such arrangements on acceptable terms, we may not be able to successfully commercialize these drugs. To the extent that we are not successful in commercializing any drugs ourselves or through a strategic alliance, our product revenues and business will suffer and our stock price would decrease.

***Our internal computer systems, or those of our CROs or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our drug development programs.***

Despite the implementation of security measures, our internal computer systems and those of our CROs and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. While we have not experienced any such system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our drug development programs. For example, the loss of clinical study data from completed or ongoing clinical studies for any of our drug candidates could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development of our product candidates could be delayed.

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**Risks Related To Our Industry**

*The regulatory approval process is expensive, time-consuming and uncertain and may prevent our partners or us from obtaining approvals to commercialize some or all of our drug candidates.*

The research, testing, manufacturing, selling and marketing of drugs are subject to extensive regulation by the FDA and other regulatory authorities in the United States and other countries, and regulations differ from country to country. Neither we nor our partners are permitted to market our potential drugs in the United States until we receive approval of a new drug application ( NDA ) from the FDA. Neither we nor our partners have received NDA or other marketing approval for any of our drug candidates.

Obtaining NDA approval is a lengthy, expensive and uncertain process. In addition, failure to comply with FDA and other applicable foreign and U.S. regulatory requirements may subject us to administrative or judicially imposed sanctions. These include warning letters, civil and criminal penalties, injunctions, product seizure or detention, product recalls, total or partial suspension of production, and refusal to approve pending NDAs or supplements to approved NDAs.

Regulatory approval of an NDA or NDA supplement is never guaranteed, and the approval process typically takes several years and is extremely expensive. The FDA and foreign regulatory agencies also have substantial discretion in the drug approval process, and the guidance and advice issued by such agencies is subject to change at any time. Despite the time and efforts exerted, failure can occur at any stage, and we may encounter problems that cause us to abandon clinical trials or to repeat or perform additional preclinical testing and clinical trials. The number and focus of preclinical studies and clinical trials that will be required for approval by the FDA and foreign regulatory agencies varies depending on the drug candidate, the disease or condition that the drug candidate is designed to address, and the regulations applicable to any particular drug candidate. In addition, the FDA may require that a proposed Risk Evaluation and Mitigation Strategy, also known as a REMS, be submitted as part of an NDA if the FDA determines that it is necessary to ensure that the benefits of the drug outweigh its risks. The FDA and foreign regulatory agencies can delay, limit or deny approval of a drug candidate for many reasons, including, but not limited to:

they might determine that a drug candidate is not safe or effective;

they might not find the data from nonclinical testing and clinical trials sufficient and could request that additional trials be performed;

they might not approve our, our partner s or the contract manufacturer s processes or facilities; or

they might change their approval policies or adopt new regulations.

Even if we receive regulatory approval to manufacture and sell a drug in a particular regulatory jurisdiction, other jurisdictions regulatory authorities may not approve that drug for manufacture and sale. If we or our partners fail to receive and maintain regulatory approval for the sale of any drugs resulting from our drug candidates, it would significantly harm our business and negatively affect our stock price.

*If we or our partners receive regulatory approval for our drug candidates, we or they will be subject to ongoing obligations to and continued regulatory review by the FDA and foreign regulatory agencies, and may be subject to additional post-marketing obligations, all of which may result in significant expense and limit commercialization of our potential drugs.*

Any regulatory approvals that we or our partners receive for our drug candidates may be subject to limitations on the indicated uses for which the drug may be marketed or require potentially costly post-marketing follow-up studies or compliance with a REMS. In addition, if the FDA or foreign regulatory agencies approves any of our drug candidates, the labeling, packaging, adverse event reporting, storage, advertising, promotion and record-keeping for the drug will be subject to extensive regulatory requirements. The subsequent discovery of previously unknown problems with the drug, including adverse events of unanticipated severity or frequency, or

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the discovery that adverse events or toxicities observed in preclinical research or clinical trials that were believed to be minor actually constitute much more serious problems, may result in restrictions on the marketing of the drug or withdrawal of the drug from the market.

The FDA and foreign regulatory agencies may change their policies and additional government regulations may be enacted that could prevent or delay regulatory approval of our drug candidates. We cannot predict the likelihood, nature or extent of adverse government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are not able to maintain regulatory compliance, we might not be permitted to market our drugs and our business would suffer.

***If physicians and patients do not accept our drugs, we may be unable to generate significant revenue, if any.***

Even if our drug candidates obtain regulatory approval, the resulting drugs, if any, may not gain market acceptance among physicians, healthcare payors, patients and the medical community. Even if the clinical safety and efficacy of drugs developed from our drug candidates are established for purposes of approval, physicians may elect not to recommend these drugs for a variety of reasons including, but not limited to:

introduction of competitive drugs to the market;

clinical safety and efficacy of alternative drugs or treatments;

cost-effectiveness;

availability of coverage and reimbursement from health maintenance organizations and other third-party payors;

convenience and ease of administration;

prevalence and severity of adverse events;

other potential disadvantages relative to alternative treatment methods; or

insufficient marketing and distribution support.

If our drugs fail to achieve market acceptance, we may not be able to generate significant revenue and our business would suffer.

***The coverage and reimbursement status of newly approved drugs is uncertain and failure to obtain adequate coverage and reimbursement could limit our ability to market any drugs we may develop and decrease our ability to generate revenue.***

Even if one or more of our drug candidates is approved for sale, the commercial success of our drugs in both domestic and international markets will be substantially dependent on whether third-party coverage and reimbursement is available for our drugs by the medical profession for use by their patients, which is highly uncertain. Medicare, Medicaid, health maintenance organizations and other third-party payors are increasingly attempting to contain healthcare costs by limiting both coverage and the level of reimbursement of new drugs. As a result, they may not cover or provide adequate payment for our drugs. They may not view our drugs as cost-effective and reimbursement may not be available to consumers or may be insufficient to allow our drugs to be marketed on a competitive basis. If we are unable to obtain adequate coverage and reimbursement for our drugs, our ability to generate revenue will be adversely affected. Likewise, current and future legislative or regulatory efforts to control or reduce healthcare costs or reform government healthcare programs, such as the Patient Protection Affordable Care Act and the Health Care and Education Reconciliation Act of 2010, could result in lower prices or rejection of coverage and reimbursement for our potential drugs. Changes in coverage and reimbursement policies or healthcare cost containment initiatives that limit or restrict reimbursement for any of our drug candidates that are approved could cause our potential future revenues to decline.



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***We may be subject to costly product liability or other liability claims and may not be able to obtain adequate insurance.***

The use of our drug candidates in clinical trials may result in adverse events. We cannot predict all the possible harms or adverse events that may result from our clinical trials. We currently maintain limited product liability insurance. We may not have sufficient resources to pay for any liabilities resulting from a personal injury or other claim excluded from, or beyond the limit of, our insurance coverage. Our insurance does not cover third parties' negligence or malpractice, and our clinical investigators and sites may have inadequate insurance or none at all. In addition, in order to conduct clinical trials or otherwise carry out our business, we may have to contractually assume liabilities for which we may not be insured. If we are unable to look to our own or a third party's insurance to pay claims against us, we may have to pay any arising costs and damages ourselves, which may be substantial.

In addition, if we commercially launch drugs based on our drug candidates, we will face even greater exposure to product liability claims. This risk exists even with respect to those drugs that are approved for commercial sale by the FDA and foreign regulatory agencies and manufactured in licensed and regulated facilities. We intend to secure additional limited product liability insurance coverage for drugs that we commercialize, but may not be able to obtain such insurance on acceptable terms with adequate coverage, or at reasonable costs. Even if we are ultimately successful in product liability litigation, the litigation would consume substantial amounts of our financial and managerial resources and may create adverse publicity, all of which would impair our ability to generate sales of the affected product and our other potential drugs. Moreover, product recalls may be issued at our discretion or at the direction of the FDA and foreign regulatory agencies, other governmental agencies or other companies having regulatory control for drug sales. Product recalls are generally expensive and often have an adverse effect on the reputation of the drugs being recalled and of the drug's developer or manufacturer.

We may be required to indemnify third parties against damages and other liabilities arising out of our development, commercialization and other business activities, which could be costly and time-consuming and distract management. If third parties that have agreed to indemnify us against damages and other liabilities arising from their activities do not fulfill their obligations, then we may be held responsible for those damages and other liabilities.

***Our relationships with customers, healthcare providers, clinical trial sites and professionals and third-party payors will be subject to applicable anti-kickback, fraud and abuse and other laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.***

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of any drug candidates for which we may obtain marketing approval. Our arrangements with customers, healthcare providers and professionals and third-party payors may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we develop, and may market, sell and distribute, our products for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations, include, but are not limited to, the following:

The federal healthcare anti-kickback statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under federally funded healthcare programs such as Medicare and Medicaid. This statute has been broadly interpreted to apply to manufacturer arrangements with prescribers, purchasers and formulary managers, among others. Several other countries, including the United Kingdom, have enacted similar anti-kickback, fraud and abuse, and healthcare laws and regulations.

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The federal False Claims Act imposes civil penalties, including civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government. The government and qui tam relators have brought False Claims Act actions against pharmaceutical companies on the theory that their practices have caused false claims to be submitted to the government. There is also a separate false claims provision imposing criminal penalties.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program. HIPAA also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information. HIPAA also imposes criminal liability for knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services.

The federal Physician Sunshine Act requirements under the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, referred to together as the Affordable Care Act, require manufacturers of drugs, devices, biologics and medical supplies to report to the Department of Health and Human Services information related to payments and other transfers of value made to or at the request of covered recipients, such as physicians and teaching hospitals, and physician ownership and investment interests in such manufacturers. Payments made to physicians and research institutions for clinical trials are included within the ambit of this law.

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

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. Exclusion, suspension and debarment from government funded healthcare programs would significantly impact our ability to commercialize, sell or distribute any drug. If any of the physicians or other providers or entities with whom we expect to do business are found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

In addition, health care providers in the United States, including research institutions from which we or our partners obtain patient information, are subject to privacy rules under HIPAA and state and local privacy laws. In the European Union, these entities are subject to the Directive 95/46-EC of the European Parliament on the protection of individuals with regard to the processing of personal data and individual European Union member states implementing additional legislation. Other countries have similar privacy legislation. We could face substantial penalties if we knowingly receive individually identifiable health information from a health care provider that has not satisfied the applicable privacy laws. In addition, certain privacy laws and genetic testing laws may apply directly to our operations and/or those of our partners and may impose restrictions on the use and dissemination of individuals' health information and use of biological samples.

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*Responding to any claims relating to improper handling, storage or disposal of the hazardous chemicals and radioactive and biological materials we use in our business could be time-consuming and costly.*

Our research and development processes involve the controlled use of hazardous materials, including chemicals and radioactive and biological materials. Our operations produce hazardous waste products. We cannot eliminate the risk of accidental contamination or discharge and any resultant injury from those materials. Federal, state and local laws and regulations govern the use, manufacture, storage, handling and disposal of hazardous materials. We may be sued for any injury or contamination that results from our or third parties' use of these materials. Compliance with environmental laws and regulations is expensive, and current or future environmental regulations may impair our research, development and production activities.

*Our facilities in California are located near an earthquake fault, and an earthquake or other types of natural disasters, catastrophic events or resource shortages could disrupt our operations and adversely affect our results.*

All of our facilities and our important documents and records, such as hard copies of our laboratory books and records for our drug candidates and compounds and our electronic business records, are located in our corporate headquarters at a single location in South San Francisco, California near active earthquake zones. If a natural disaster, such as an earthquake or flood, a catastrophic event such as a disease pandemic or terrorist attack, or a localized extended outage of critical utilities or transportation systems occurs, we could experience a significant business interruption. Our partners and other third parties on which we rely may also be subject to business interruptions from such events. In addition, California from time to time has experienced shortages of water, electric power and natural gas. Future shortages and conservation measures could disrupt our operations and cause expense, thus adversely affecting our business and financial results.

### **Risks Related To an Investment in Our Securities**

*We expect that our stock price will fluctuate significantly, and you may not be able to resell your shares at or at or above your investment price.*

The stock market, particularly in recent years, has experienced significant volatility, particularly with respect to pharmaceutical, biotechnology and other life sciences company stocks, which often does not relate to the operating performance of the companies represented by the stock. Factors that could cause volatility in the market price of our common stock include, but are not limited to:

announcements concerning any of the clinical trials for our drug candidates, such as tirasemtiv for the potential treatment of ALS, CK-2127107 for the potential treatment of SMA or other indications associated with muscle weakness and omecamtiv mecarbil for the potential treatment of heart failure (including, but not limited to, the timing of initiation or completion of such trials and the results of such trials, and delays or discontinuations of such trials, including delays resulting from slower than expected or suspended patient enrollment or discontinuations resulting from a failure to meet pre-defined clinical end points);

announcements concerning our strategic alliance with Amgen or Astellas or future strategic alliances;

failure or delays in entering additional drug candidates into clinical trials;

failure or discontinuation of any of our research programs;

issuance of new or changed securities analysts' reports or recommendations;

failure or delay in establishing new strategic alliances, or the terms of those alliances;



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market conditions in the pharmaceutical, biotechnology and other healthcare-related sectors;

actual or anticipated fluctuations in our quarterly financial and operating results;

developments or disputes concerning our intellectual property or other proprietary rights;

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introduction of technological innovations or new products by us or our competitors;

issues in manufacturing our drug candidates or drugs;

market acceptance of our drugs;

third-party healthcare coverage and reimbursement policies;

FDA or other U.S. or foreign regulatory actions affecting us or our industry;

litigation or public concern about the safety of our drug candidates or drugs;

additions or departures of key personnel;

substantial sales of our common stock by our existing stockholders, whether or not related to our performance;

automated trading activity by algorithmic and high-frequency trading programs; and

volatility in the stock prices of other companies in our industry or in the stock market generally.

These and other external factors may cause the market price and demand for our common stock to fluctuate substantially, which may limit or prevent investors from readily selling their shares of common stock and may otherwise negatively affect the liquidity of our common stock. In addition, when the market price of a stock has been volatile, holders of that stock have instituted securities class action litigation against the company that issued the stock. If any of our stockholders brought a lawsuit against us, we could incur substantial costs defending the lawsuit. Such a lawsuit could also divert our management's time and attention.

***If the ownership of our common stock continues to be highly concentrated, it may prevent you and other stockholders from influencing significant corporate decisions and may result in conflicts of interest that could cause our stock price to decline.***

As of February 26, 2016, our executive officers, directors and their affiliates beneficially owned or controlled approximately 10.2% of the outstanding shares of our common stock (after giving effect to the exercise of all outstanding vested and unvested options, restricted stock units and warrants). Accordingly, these executive officers, directors and their affiliates, acting as a group, will have substantial influence over the outcome of corporate actions requiring stockholder approval, including the election of directors, any merger, consolidation or sale of all or substantially all of our assets or any other significant corporate transactions. These stockholders may also delay or prevent a change of control of us, even if such a change of control would benefit our other stockholders. The significant concentration of stock ownership may adversely affect the trading price of our common stock due to investors' perception that conflicts of interest may exist or arise.

***Volatility in the stock prices of other companies may contribute to volatility in our stock price.***

The stock market in general, and the NASDAQ stock exchanges and the market for technology companies in particular, have experienced significant price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of those companies. Further, there has been particular volatility in the market prices of securities of early stage and clinical stage life sciences companies. These broad market and industry factors may seriously harm the market price of our common stock, regardless of our operating performance. In the past, following periods of volatility in the market price of a company's securities, securities class action litigation has often been instituted. A securities class action suit against us could result in substantial costs, potential liabilities and the diversion of management's attention and resources, and could harm our reputation and business.



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### ***Our common stock is thinly traded and there may not be an active, liquid trading market for our common stock.***

There is no guarantee that an active trading market for our common stock will be maintained on NASDAQ, or that the volume of trading will be sufficient to allow for timely trades. Investors may not be able to sell their shares quickly or at the latest market price if trading in our stock is not active or if trading volume is limited. In addition, if trading volume in our common stock is limited, trades of relatively small numbers of shares may have a disproportionate effect on the market price of our common stock.

### ***Our stockholders will experience substantial additional dilution if outstanding options or warrants are exercised for common stock.***

As of February 26, 2016, there were 5,709,522 shares of common stock issuable upon the exercise of warrants, having a weighted average exercise price of \$5.31 per share, and 4,827,005 shares of common stock issuable upon the exercise of stock options outstanding, having a weighted average exercise price of \$10.31 per share. The exercise of outstanding options or warrants for common stock would be substantially dilutive to the outstanding shares of common stock. Any dilution or potential dilution may cause our stockholders to sell their shares, which would contribute to a downward movement in the stock price of our common stock.

### ***Ownership changes may limit our ability to use our net operating losses and tax credits in the future.***

In general, under Section 382 of the Internal Revenue Code ( Section 382 ), a corporation that undergoes an ownership change is subject to limitations on its ability to utilize its pre-change net operating losses and tax credits to offset future taxable income. We have performed a Section 382 analysis and do not believe that we have experienced an ownership change since 2006. A portion of our existing net operating losses and tax credits are subject to limitations arising from previous ownership changes. Future changes in our stock ownership, some of which are outside of our control, could result in an ownership change under Section 382 and result in additional limitations. We intend to continue to monitor public filings made by third parties with the SEC to assess whether an ownership change under Section 382 has occurred. Our ability to accurately assess any such ownership change is limited by the timeliness and accuracy of these public filings.

### ***Evolving regulation of corporate governance and public disclosure may result in additional expenses, use of resources and continuing uncertainty.***

Changing laws, regulations and standards relating to corporate governance and public disclosure, including the Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act of 2010 and new SEC regulations and NASDAQ Stock Market LLC rules create uncertainty for public companies. We regularly evaluate and monitor developments with respect to new and proposed laws, regulations and standards. We cannot accurately predict or estimate the amount of the additional costs we may incur in connection with complying with such laws, regulations and standards or the timing of these costs. For example, compliance with the internal control requirements of Section 404 of the Sarbanes-Oxley Act has to date required us to commit significant resources to document and test the adequacy of our internal control over financial reporting. We can provide no assurance as to conclusions of management or by our independent registered public accounting firm with respect to the effectiveness of our internal control over financial reporting in the future. In addition, the SEC has adopted regulations that require us to file corporate financial statement information in an interactive data format known as XBRL. We may incur significant costs and need to invest considerable resources to remain in compliance with these regulations.

These new or changed laws, regulations and standards are subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

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We intend to maintain high standards of corporate governance and public disclosure. As a result, we intend to invest the resources necessary to comply with evolving laws, regulations and standards, and this investment may result in increased general and administrative expenses and a diversion of management time and attention from revenue-generating activities to compliance activities. If our efforts to comply with new or changed laws, regulations and standards differ from the activities intended by regulatory or governing bodies, due to ambiguities related to practice or otherwise, regulatory authorities may initiate legal proceedings against us, which could be costly and time-consuming, and our reputation and business may be harmed.

*We have never paid dividends on our capital stock, and we do not anticipate paying any cash dividends in the foreseeable future.*

We have paid no cash dividends on any of our classes of capital stock to date and we currently intend to retain our future earnings, if any, to fund the development and growth of our businesses. In addition, the terms of existing or any future debts may preclude us from paying these dividends.

### **Item 1B. *Unresolved Staff Comments***

None.

### **Item 2. *Properties***

Our facilities consist of approximately 81,587 square feet of research and office space. We lease 50,195 square feet located at 280 East Grand Avenue, and 31,392 square feet at 256 East Grand Avenue, in South San Francisco, California until 2018 with an option to renew the lease for an additional three years. We believe that these facilities are suitable and adequate for our current needs.

### **Item 3. *Legal Proceedings***

On November 28, 2014, Pharm-Olam International, Ltd. ( Pharm-Olam ) filed a lawsuit in the U.S. District Court for the Middle District of North Carolina, captioned Pharm-Olam International, Ltd. v. Cytokinetics, Inc. and Datatrak International, Inc., Civil Action No. 1:14-cv-01000 (the North Carolina Lawsuit ) in connection with its performance as the data management vendor for the BENEFIT-ALS clinical trial. Under the agreement between Pharm-Olam and us, Pharm-Olam was obligated to provide a variety of services, including building and maintaining the electronic system for BENEFIT-ALS that combined the electronic data capture ( EDC ) for clinical data and the interactive web response system ( IWRS ) used for patient randomization and treatment assignments to either tirasemtiv or placebo. Pharm-Olam 's failure to conduct these services in accordance with the agreement, regulatory requirements and industry standards resulted in programming errors in the IWRS which caused delay of the trial and additional expenses. Pharm-Olam entered into an agreement with Datatrak International Inc. ( Datatrak ) by which Datatrak provided the core EDC and IWRS system for BENEFIT-ALS. In the North Carolina lawsuit, Pharm-Olam sought declaratory judgment that (1) the limitation of liability provisions in the agreement between Pharm-Olam and us are enforceable and limit Pharm-Olam 's liability for the claims asserted by us to the direct services fees, and (2) Pharm-Olam 's subcontractor, Datatrak, must indemnify, defend and hold harmless Pharm-Olam for the claims asserted against it by Cytokinetics, pursuant to the indemnification provision in the agreement between Pharm-Olam and Datatrak. On December 17, 2014, we filed a motion to dismiss or transfer the North Carolina Lawsuit to the U.S. District Court for the Northern District of California based on lack of jurisdiction and improper venue. On September 16, 2015, the U.S. District Court for the Middle District of North Carolina dismissed the North Carolina lawsuit.

On December 1, 2014, we filed a lawsuit in the U.S. District Court for the Northern District of California, captioned Cytokinetics, Inc. v. Pharm-Olam International, Ltd., Case No. 3:14-cv-05256 (the California Lawsuit ). This lawsuit alleges fraudulent inducement, breach of contract and negligence by Pharm-Olam in connection with its performance as the data management vendor for the BENEFIT-ALS clinical trial. We are

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seeking monetary damages from Pharm-Olam. On January 23, 2015, Pharm-Olam filed a motion to dismiss the complaint, or in the alternative, to transfer the California Lawsuit to U.S. District Court for the Middle District of North Carolina. The motion to dismiss was denied in part and granted in part and the motion to transfer was denied on March 10, 2015. Pharm-Olam answered the complaint on March 24, 2015. Datatrak filed a motion to intervene on June 5, 2015, which the court granted on July 1, 2015. Datatrak seeks a declaratory judgment that the indemnification provision of the agreement between Pharm-Olam and Datatrak does not require Datatrak to indemnify Pharm-Olam for the claims asserted against Pharm-Olam by Cytokinetics. This is the only pending matter among the parties because the U.S. District Court for the Middle District of North Carolina dismissed the North Carolina lawsuit on September 16, 2015.

**Item 4. *Mine Safety Disclosures***

Not applicable.

**Table of Contents****PART II****Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities**

Prior to our initial public offering on April 29, 2004, there was no public market for our common stock. Our common stock was quoted under the symbol CYTK on the NASDAQ Global Market from the date of our initial public offering through December 19, 2012, and has since been quoted on the NASDAQ Capital Market. The following table sets forth the high and low closing sales price per share of our common stock as reported on the NASDAQ Global Market or NASDAQ Capital Market, as applicable, for the periods indicated.

	Closing Sale Price	
	High	Low
<b>2014:</b>		
First Quarter	\$ 10.55	\$ 6.72
Second Quarter	\$ 12.99	\$ 4.01
Third Quarter	\$ 4.90	\$ 3.52
Fourth Quarter	\$ 8.01	\$ 3.07
<b>2015:</b>		
First Quarter	\$ 8.17	\$ 6.25
Second Quarter	\$ 7.43	\$ 5.51
Third Quarter	\$ 7.79	\$ 6.01
Fourth Quarter	\$ 12.95	\$ 6.60

On February 26, 2016, the last reported sale price for our common stock on the NASDAQ Capital Market was \$6.85 per share. We currently expect to retain future earnings, if any, for use in the operation and expansion of our business and have not paid and do not in the foreseeable future anticipate paying any cash dividends. As of February 26, 2016, there were 63 holders of record of our common stock.

**Table of Contents****Equity Compensation Information**

Information regarding our equity compensation plans and the securities authorized for issuance thereunder is set forth in Part III, Item 12.

**Comparison of Historical Cumulative Total Return Among Cytokinetics, Incorporated, the NASDAQ Stock Market (U.S.) Index and the NASDAQ Biotechnology Index (\*)**

(\*) The above graph shows the cumulative total stockholder return of an investment of \$100 in cash from December 31, 2010 through December 31, 2015 for: (i) our common stock; (ii) the NASDAQ Stock Market (U.S.) Index; and (iii) the NASDAQ Biotechnology Index. All values assume reinvestment of the full amount of all dividends. Stockholder returns over the indicated period should not be considered indicative of future stockholder returns.

	12/31/10	12/31/11	12/31/12	12/31/13	12/31/14	12/31/15
Cytokinetics, Incorporated	\$ 100.00	\$ 45.93	\$ 31.58	\$ 51.84	\$ 63.88	\$ 83.42
NASDAQ Composite Index	\$ 100.00	\$ 98.20	\$ 113.82	\$ 157.44	\$ 178.53	\$ 188.75
NASDAQ Biotechnology Index	\$ 100.00	\$ 111.81	\$ 147.48	\$ 244.24	\$ 327.52	\$ 364.93

The information contained under this caption Comparison of Historical Cumulative Total Return Among Cytokinetics, Incorporated, the NASDAQ Stock Market (U.S.) Index and the NASDAQ Biotechnology Index shall not be deemed to be soliciting material or to be filed with the SEC, nor shall such information be incorporated by reference into any future filing under the Securities Act or the Exchange Act, except to the extent that we specifically incorporate it by reference into such filing.

**Sales of Unregistered Securities**

On December 26, 2014, we sold 2,040,816 shares of our common stock at a price per share of \$4.90 and an aggregate purchase price of \$10.0 million to Astellas.

We relied on the exemption from registration contained in Section 4(2) of the Securities Act, and Regulation D, Rule 506 thereunder, in connection with the issuance and sale of the common stock to Astellas.



**Table of Contents****Item 6. Selected Financial Data**

The following selected financial data should be read in conjunction with Item 7, Management's Discussion and Analysis of Financial Condition and Results of Operations and Item 8, Financial Statements and Supplemental Data of this report on Form 10-K.

	2015	Year Ended December 31,			2011
		2014	2013	2012	
		(In thousands, except per share amounts)			
<b>Statement of Operations Data:</b>					
Revenues:					
Research and development revenues from related parties(1)	\$ 14,665	\$ 19,538	\$ 2,019	\$ 4,177	\$ 2,054
Research and development, grant and other revenues	75	17,566	7,547	3,382	1,946
License revenues from related parties(1)	13,918		17,230		
License revenues		9,836	3,852		
<b>Total revenues</b>	<b>28,658</b>	<b>46,940</b>	<b>30,648</b>	<b>7,559</b>	<b>4,000</b>
Operating expenses:					
Research and development	46,398	44,426	49,450	35,643	37,182
General and administrative	19,667	17,268	15,092	12,429	13,590
Restructuring charges (reversals)				(56)	1,192
<b>Total operating expenses</b>	<b>66,065</b>	<b>61,694</b>	<b>64,542</b>	<b>48,016</b>	<b>51,964</b>
<b>Operating loss</b>	<b>(37,407)</b>	<b>(14,754)</b>	<b>(33,894)</b>	<b>(40,457)</b>	<b>(47,964)</b>
Interest and other income (expense), net	(94)	108	177	87	104
<b>Loss before income taxes</b>	<b>(37,501)</b>	<b>(14,646)</b>	<b>(33,717)</b>	<b>(40,370)</b>	<b>(47,860)</b>
Income tax provision (benefit)					
<b>Net loss</b>	<b>(37,501)</b>	<b>(14,646)</b>	<b>(33,717)</b>	<b>(40,370)</b>	<b>(47,860)</b>
Deemed dividend related to beneficial conversion feature of convertible preferred stock				(1,307)	(2,857)
<b>Net loss allocable to common stockholders:</b>	<b>\$ (37,501)</b>	<b>\$ (14,646)</b>	<b>\$ (33,717)</b>	<b>\$ (41,677)</b>	<b>\$ (50,717)</b>
Net loss per share allocable to common stockholders:(2)					
Basic and Diluted	\$ (0.97)	\$ (0.41)	\$ (1.24)	\$ (2.30)	\$ (4.30)
Weighted average shares used in computing net loss per share allocable to common stockholders:(3)					
Basic and Diluted	38,814	35,709	27,275	18,107	11,800

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	2015	2014	As of December 31, 2013 (In thousands)	2012	2011
<b>Balance Sheet Data:</b>					
Cash and cash equivalents, and investments	\$ 111,621	\$ 83,228	\$ 80,230	\$ 74,000	\$ 49,023
Restricted cash					196
Working capital	81,458	107,276	52,634	69,322	46,548
Total assets	115,237	132,968	83,188	77,551	52,773
Long-term debt	14,639				
Accumulated deficit	(534,744)	(497,243)	(482,597)	(448,880)	(408,510)
Total stockholders' equity(2)	68,590	92,064	54,442	70,085	48,178

- (1) Revenues from related parties consisted of revenues recognized under our research and development arrangements with related parties, including Amgen and Astellas. See Note 7, Related Parties and Related Party Transactions in the Notes to Consolidated Financial Statements for further details.
- (2) On June 24, 2013, we effected a one-for-six reverse stock split of our common stock through an amendment to our amended and restated certificate of incorporation (the COI Amendment). As of the effective time of the reverse stock split, every six shares of our issued and outstanding common stock were converted into one issued and outstanding share of common stock, without any change in par value per share. The reverse stock split affected all shares of our common stock outstanding immediately prior to the effective time of the reverse stock split, as well as the number of shares of common stock available for issuance under equity incentive plans. In addition, the reverse stock split effected a reduction in the number of shares of common stock issuable upon the conversion of shares of preferred stock or upon the exercise of stock options or warrants outstanding immediately prior to the effectiveness of the reverse stock split. No fractional shares were issued as a result of the reverse stock split. Stockholders who would otherwise have been entitled to receive a fractional share received cash payments in lieu thereof. In addition, the COI Amendment reduced the number of authorized shares of common stock to 81.5 million.

All references to shares of common stock and per share data for all periods presented in the accompanying selected financial data have been adjusted to reflect the reverse stock split on a retroactive basis.

- (3) In April 2011, we sold 883,333 shares of common stock, 8,070 shares of Series A convertible preferred stock and warrants to purchase 1,114,168 shares of common stock to Deerfield Private Design Fund II, L.P., Deerfield Private Design International II, L.P., Deerfield Special Situations Fund, L.P., and Deerfield Special Situations Fund International Limited for net proceeds of approximately \$19.9 million. In the fourth quarter of 2011, we sold 429,868 shares of common stock through McNicoll, Lewis & Vlak LLC (MLV) for net proceeds of \$2.4 million. In June 2012, we issued to various investors (i) 9,320,176 shares of common stock for a purchase price of \$4.56 per share, (ii) 23,026 shares of Series B convertible preferred stock for a purchase price of \$760.00 per share, and (iii) warrants to purchase 7,894,704 shares of common stock at an exercise price of \$5.28 per share, for aggregate gross proceeds of approximately \$60.0 million. In 2012, we sold 432,724 shares of common stock through MLV for net proceeds of \$2.8 million. In June 2013, we sold 1,404,100 shares of common stock to Amgen at a price per share of \$7.12 and an aggregate purchase price of \$10.0 million, pursuant to the Amgen Agreement Amendment. In 2013, we sold 1,170,583 shares of common stock through MLV for net proceeds of \$7.5 million. In January, 2014 we sold 364,103 shares of common stock through MLV for net proceeds of \$2.4 million. In February 2014, we sold 5,031,250 shares of common stock through an underwritten public offering at a price per share of \$8.00 and net proceeds of \$37.5 million. In December 2014, we sold 2,040,816 shares of common stock to Astellas at a price per share of \$4.90 and an aggregate purchase price of \$10.0 million. The 1,114,168 warrants issued in 2011 to Deerfield, expired unexercised on April 20, 2015. In 2015, we sold 808,193 shares of common stock through Cantor pursuant to the CE Offering Sales Agreement for net proceeds of \$8.7 million. See Note 12, Stockholders' Equity in the Notes to Consolidated Financial Statements for further details.

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

This discussion and analysis should be read in conjunction with our financial statements and accompanying notes included elsewhere in this report. Operating results are not necessarily indicative of results that may occur in future periods.

#### **Overview**

We were incorporated in Delaware in August 1997 as Cytokinetics, Incorporated. We are a late-stage biopharmaceutical company focused on the discovery and development of first-in-class muscle activators as potential treatments 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 drug candidates currently in clinical development are our skeletal muscle activators tirasemtiv and CK-2127107, and our cardiac muscle activator omecamtiv mecarbil. Cytokinetics retains exclusive rights to tirasemtiv, which is being evaluated for the potential treatment of amyotrophic lateral sclerosis ( ALS ). CK-2127107 is being evaluated for the potential treatment of spinal muscle atrophy ( SMA ) and for potential use in other indications associated with muscle weakness under a strategic alliance with Astellas Pharma Inc. ( Astellas ) established in June 2013 and expanded in December 2014. Omecamtiv mecarbil is being evaluated for the potential treatment of heart failure under a strategic alliance with Amgen established in 2006.

#### **Muscle Contractility Programs**

##### ***Skeletal Muscle Contractility Program***

###### **Tirasemtiv.**

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.

Further details regarding tirasemtiv and VITALITY-ALS can be found in Item 1 of this report under Research and Development Programs Skeletal Muscle Contractility Program Tirasemtiv.

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

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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.

The clinical trials program for tirasemtiv may proceed for several years, and we will not be in a position to generate any revenues or material net cash flows from sales of this drug candidate until the program is successfully completed, regulatory approval is achieved, and the drug is commercialized. Tirasemtiv is at too early a stage of development for us to predict if or when this may occur. Our expenditures will increase if and as we move tirasemtiv into later stage development.

**CK-2127107 and Other Skeletal Muscle Activators**

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 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 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.

During the years ended December 31, 2015, 2014 and 2013, the Company recorded license revenue of \$13.9 million, \$9.8 million and \$3.9 million, respectively, reimbursement of sponsored research and development activities of \$12.2 million, \$15.4 million and \$6.4 million, respectively, and milestone revenues of zero, \$17.0 million and zero, in connection with our strategic alliance with Astellas. See our consolidated financial statements for a further discussion of our revenue recognition policy under our agreement with Astellas.

The clinical trials programs for CK-2127107 may proceed for several years, and we will not be in a position to generate any revenues or material net cash flows from sales of this drug candidate until the program is successfully completed, regulatory approval is achieved, and the drug is commercialized. CK-2127107 is at too early a stage of development for us to predict if or when this may occur. Our expenditures will increase if Astellas terminates development of CK-2127107 or related compounds and we elect to develop them independently, or if we conduct early-stage development for certain agreed indications at our initial expense, subject to reimbursement if development continues under the collaboration.

**Ongoing Research in Skeletal Muscle Activators.**

Our research on the direct activation of skeletal muscle continues in two areas. We are conducting translational research in preclinical models of disease and muscle function with fast skeletal muscle troponin activators to explore the potential clinical applications of this novel mechanism in diseases or conditions associated with skeletal muscle dysfunction. We also intend to conduct preclinical research on other chemically and pharmacologically distinct mechanisms to activate the skeletal sarcomere. We are conducting a joint research program with Astellas directed to the discovery of next-generation skeletal muscle activators. Under the Amended Astellas Agreement, the joint research program will continue through 2016 and Astellas will reimburse us for certain research activities.

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**Research and Development Expenses.** We recorded research and development expenses for activities relating to our skeletal muscle contractility program of approximately \$36.3 million, \$32.9 million and \$40.8 million in the years ended December 31, 2015, 2014 and 2013, respectively. We recognized research and development revenue from Astellas of \$12.2 million, \$32.4 million, and \$6.4 million in the years ended December 31, 2015, 2014 and 2013, respectively, consisting of milestone payments, and reimbursements of full-time employee equivalents ( FTEs ) and other expenses. We anticipate that our expenditures relating to the research and development of compounds in our skeletal muscle contractility program will increase significantly if and as we advance tirasemtiv, CK-2127107 or other compounds from this program into and through development.

***Cardiac Muscle Contractility Program***

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. In June 2013, we expanded this collaboration to include Japan. As a result, 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 November 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 conducted 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 in Item 1 of this report under Research and Development Programs Cardiac Muscle Contractility Program Amgen Strategic Alliance.

During the years ended December 31, 2015, 2014 and 2013, we recorded \$2.5 million, \$4.5 million and \$2.0 million, respectively, in reimbursement of sponsored research and development activities relating to the Amgen Agreement. During the year ended December 31, 2013, we recorded \$17.2 million in license revenue under the Amgen Agreement, and no such revenue during the years ended December 31, 2015 and 2014, respectively. See our consolidated financial statements for a further discussion of our revenue recognition policy under our agreement with Amgen.

**Omecamtiv Mecarbil Clinical Development**

**COSMIC-HF.**

COSMIC-HF is a Phase 2, double-blind, randomized, placebo-controlled, multicenter, clinical trial designed to assess the pharmacokinetics and tolerability of omecamtiv mecarbil dosed orally in patients with heart failure and left ventricular systolic dysfunction as well as its effects on echocardiographic measures of cardiac function. COSMIC-HF was conducted by Amgen in collaboration with Cytokinetics. The study began with two dose escalation cohorts of 40 patients each, randomized 1:1:1:1 to placebo or one of three different modified release oral formulations of omecamtiv mecarbil for seven days. The omecamtiv mecarbil dose in the first of these two dose escalation cohorts was 25 mg twice daily; in the second, it was 50 mg twice daily. The purpose of the dose escalation cohorts was to select one of the three modified release oral formulations of omecamtiv mecarbil for further evaluation in a larger group of patients treated for a longer period of time.

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The expansion phase of COSMIC-HF was designed to evaluate the pharmacokinetics, pharmacodynamics, safety and tolerability of the modified release oral formulation omecamtiv mecarbil selected based on the results of the two dose escalation cohorts in 448 patients with chronic heart failure and left ventricular systolic dysfunction. Patients were randomized 1:1:1 to receive either placebo or treatment with omecamtiv mecarbil 25 mg twice daily or a dose titration group where 25 mg twice daily dosing could be increased to 50 mg twice daily depending on plasma concentrations of omecamtiv mecarbil after two weeks of treatment with the 25 mg dose. In November 2015, we announced the results from the expansion phase of COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) that were presented at American Heart Association.

Data from the expansion phase showed that dose titration controlled patient exposure to omecamtiv mecarbil. Approximately 60 percent of patients in the dose titration group escalated dosing to 50 mg twice daily.

Following 20 weeks of treatment, statistically significant improvements were observed in pre-specified secondary endpoint measures of cardiac function in the dose titration group, compared to placebo. Systolic ejection time increased by 25.0 msec ( $p < 0.001$ ), stroke volume increased by 3.63 mL ( $p = 0.022$ ) and heart rate decreased by 2.97 beats per min ( $p = 0.007$ ). Left ventricular end-systolic and end-diastolic dimensions decreased by 1.79 mm ( $p = 0.003$ ) and 1.29 mm ( $p = 0.013$ ), respectively, and were associated with statistically significant reductions in left ventricular end-systolic and end-diastolic volumes. N-terminal pro-brain natriuretic peptide (NT-proBNP) decreased by 970 pg/mL ( $p = 0.007$ ). Additionally, in the 25 mg twice daily group, there were statistically significant increases in systolic ejection time and stroke volume and a decrease in NT-proBNP. All changes are from baseline compared to placebo. The pharmacodynamic effects of omecamtiv mecarbil were generally dose dependent and larger in patients that received oral dosing with 50 mg twice daily.

Adverse events (AEs), including serious AEs, in patients on omecamtiv mecarbil were comparable to placebo. The incidence of adjudicated deaths (2.7 percent died on placebo, 1.4 percent died on omecamtiv mecarbil), myocardial infarction (1.34 percent on placebo, 0.34 percent on omecamtiv mecarbil) and unstable angina (0 percent on placebo, 0.34 percent on omecamtiv mecarbil) was similar. Other cardiac AEs were generally balanced between placebo and active treatment groups. In the omecamtiv mecarbil groups, compared to placebo, cardiac troponin increased by 0.001 ng/mL and 0.006 ng/mL (median change from baseline at week 20) in the 25 mg twice daily group and dose titration group, respectively. Events of increased troponin ( $n = 278$  across all treatment groups) were independently adjudicated and none were determined to be myocardial ischemia or infarction.

**ATOMIC-AHF.** ATOMIC-AHF (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure) was an international, randomized, double-blind, placebo-controlled, Phase 2b clinical trial of intravenous omecamtiv mecarbil in patients with left ventricular systolic dysfunction hospitalized with acutely decompensated heart failure, completed in 2013. ATOMIC-AHF was conducted by Amgen in collaboration with Cytokinetics. This clinical trial enrolled over 600 patients in three sequential, ascending-dose cohorts. In each cohort, patients were randomized to receive omecamtiv mecarbil or placebo. The primary efficacy objective of this trial was to evaluate the effect of 48 hours of intravenous omecamtiv mecarbil compared to placebo on dyspnea (shortness of breath). The secondary objectives were to assess the safety and tolerability of three dose levels of intravenous omecamtiv mecarbil compared with placebo and to evaluate the effects of 48 hours of treatment with intravenous omecamtiv mecarbil on additional measures of dyspnea, patients' global assessments, change in N-terminal pro brain-type natriuretic peptide (a biomarker associated with the severity of heart failure) and short-term clinical outcomes in these patients. In addition, the trial evaluated the relationship between plasma concentrations of omecamtiv mecarbil and echocardiographic parameters in patients with acute heart failure.

The primary efficacy endpoint of dyspnea symptom response was not met; however, the study demonstrated favorable trends between the dose and plasma concentration of *omecmtiv mecarbil* and dyspnea response. The incidence of worsening heart failure within seven days of initiating treatment appeared lower in each of the cohorts on omecamtiv mecarbil compared to the pooled placebo group of patients. Rates of adverse events (AEs), serious AEs, adjudicated deaths and hospitalizations were similar between omecamtiv mecarbil and placebo

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groups. Omecamtiv mecarbil was not associated with an increased incidence of tachyarrhythmias nor were heart rate or blood pressure adversely affected.

The clinical trials program for omecamtiv mecarbil may proceed for several years, and we will not be in a position to generate any revenues or material net cash flows from sales of this drug candidate until the program is successfully completed, regulatory approval is achieved, and the drug is commercialized. Omecamtiv mecarbil is at too early a stage of development for us to predict if or when this may occur.

**Ongoing Research in Cardiac Muscle Contractility.** We agreed with Amgen to additional research activities intended to be conducted through 2014 and 2015 under the research plan directed to next-generation compounds in our cardiac muscle contractility program. We expect to continue our joint research program with Amgen into 2016. Under the Amgen Agreement, Amgen will reimburse us for certain research activities we perform.

**Research and Development Expenses.** We recorded research and development expenses for activities relating to our cardiac muscle contractility program of approximately \$5.8 million, \$7.4 million and \$3.4 million in the years ended December 31, 2015, 2014 and 2013, respectively. We recognized research and development revenue from Amgen of \$2.5 million, \$4.5 million and \$2.0 million in the years ended December 31, 2015, 2014 and 2013, respectively, consisting of reimbursements of FTEs and other expenses. We anticipate that our expenditures relating to the research and development of compounds in our cardiac muscle contractility program will increase if we participate in the future advancement of omecamtiv mecarbil through clinical development. Our expenditures will also increase if Amgen terminates development of omecamtiv mecarbil or related compounds and we elect to develop them independently, or if we elect to co-fund later-stage development of omecamtiv mecarbil or other compounds in our cardiac muscle contractility program under our collaboration and option agreement with Amgen.

## **Beyond Muscle Contractility**

We have developed preclinical expertise in the mechanics of skeletal, cardiac and smooth muscle that extends from proteins to tissues to intact animal models. Our translational research in muscle contractility has enabled us to better understand the potential impact of small molecule compounds that increase skeletal or cardiac muscle contractility and to apply those findings to the further evaluation of our drug candidates in clinical populations. In addition to contractility, the other major functions of muscle include metabolism, growth and energetics, with each of these functions playing a role in certain diseases that could benefit from novel mechanism treatments. Accordingly, our knowledge of muscle contractility may serve as an entry point to the discovery of novel treatments for disorders involving muscle functions other than muscle contractility. We are leveraging our current understandings of muscle biology to investigate new ways of modulating these other aspects of muscle function for other potential therapeutic applications. For example, we are conducting research with compounds that affect muscle growth and that may have applications for serious diseases and medical conditions such as cachexia. Cachexia is a condition that can be associated with cancer, heart failure, chronic obstructive pulmonary disease or other conditions. This syndrome is characterized by the loss of muscle mass and may lead to weakness and disability. We are performing research on compounds that may increase muscle mass and which may impact patient functionality or potentially alter the course of diseases associated with muscle wasting.

## **Development Risks**

The successful development of any of our drug candidates is highly uncertain. We cannot estimate with certainty or know the exact nature, timing and costs of the activities necessary to complete the development of any of our drug candidates or the date of completion of these development activities due to numerous risks and uncertainties, including, but not limited to:

the results of clinical trials of our drug candidates conducted by us or our partners may not support the further clinical development of those drug candidates;

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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 FDA and/or other regulatory authorities may not accept effects on respiratory function, including SVC, as an appropriate clinical trial endpoint to support the registration of tirasemtiv for the treatment of ALS;

decisions made by Amgen with respect to the development of omeçantiv mecarbil and by Astellas with respect to the development of CK-2127107;

the uncertainty of the timing of the initiation and completion of patient enrollment and treatment in our or our partners' clinical trials;

the possibility of delays in the collection of clinical trial data and the uncertainty of the timing of the analyses of our clinical trial data after these trials have been initiated and completed;

our potential inability to obtain additional funding and resources for our development activities on acceptable terms, if at all, including, but not limited to, our potential inability to obtain or retain partners to assist in the design, management, conduct and funding of clinical trials;

failure by our clinical trial sites, clinical research organizations, clinical manufacturing organizations and other third parties supporting our or our partners' clinical trials to fulfill their obligations or otherwise perform as expected;

delays or additional costs in manufacturing of our drug candidates for clinical trial use, including developing appropriate formulations of our drug candidates;

the uncertainty of clinical trial results, including variability in patient response;

the uncertainty of obtaining FDA or other foreign regulatory agency approval required for the clinical investigation of our drug candidates;

the uncertainty related to the development of commercial scale manufacturing processes and qualification of a commercial scale manufacturing facility;

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

possible delays in the characterization, formulation and manufacture of drug candidates and other compounds.

If we fail to complete the development of any of our drug candidates in a timely manner, it could have a material adverse effect on our operations, financial position and liquidity. In addition, any failure by us or our partners to obtain, or any delay in obtaining, regulatory approvals for our drug candidates could have a material adverse effect on our results of operations. A further discussion of the risks and uncertainties associated with completing our programs as planned, or at all, and certain consequences of failing to do so are discussed further in the risk factors entitled "We will need substantial additional capital in the future to sufficiently fund our operations." We have never generated, and may never generate, revenues from commercial sales of our drugs and we may not have drugs to market for at least several years, if ever,



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Clinical trials may fail to demonstrate the desired safety and efficacy of our drug candidates, which could prevent or significantly delay completion of clinical development and regulatory approval and Clinical trials are expensive, time-consuming and subject to delay, and other risk factors.

### **Revenues**

Our current revenue sources are limited, and we do not expect to generate any revenue from product sales for several years, if at all. We have recognized revenues from our strategic alliances with Amgen, Astellas, and MyoKardia, Inc. ( MyoKardia ) and grant revenues from The ALS Association (the ALSA ) and the National Institute of Neurological Disorders and Strokes ( NINDS ).

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The following table summarizes the sources of our revenue for the years ended December 31, 2015, 2014 and 2013:

	Years Ended December 31,		
	2015	2014	2013
<b>Astellas</b>			
License revenues	\$ 13,918	\$ 9,836	\$ 3,852
Research and development revenues	12,184	32,391	6,415
Total Revenues from Astellas	26,102	42,227	10,267
<b>Amgen</b>			
License revenues			\$ 17,230
Research and development revenues	2,481	4,538	2,019
Total Revenues from Amgen	2,481	4,538	19,249
<b>MyoKardia</b>			
Research and development revenues		100	1,024
ALSA Grant Revenue	75		
NINDS Grant Revenue			69
Other Revenue		75	39
<b>Total revenues</b>	<b>\$ 28,658</b>	<b>\$ 46,940</b>	<b>\$ 30,648</b>

**Astellas**

In June 2013, we and Astellas executed a license and collaboration agreement (the "Original Astellas Agreement"), that was amended in December 2014 (the "Astellas Agreement Amendment").

Refer to Note 7, "Related Parties and Related Party Transactions" in the Notes to Consolidated Financial Statements for further details regarding this collaboration agreement.

In July 2013, we received an upfront payment of \$16.0 million in connection with the execution of the Original Astellas Agreement, establishing a collaboration directed to the research and development of skeletal muscle activators including CK-2127107 for potential application in non-neuromuscular indications associated with muscle weakness. This agreement provided for us to potentially receive over \$24.0 million in reimbursement of sponsored research and development activities during the initial two years of the collaboration and for research and early and late stage development milestone payments based on various research and clinical milestones. We determined the license and the research and development services relating to the Original Astellas Agreement are a single unit of accounting as the license was determined to not have stand-alone value. Accordingly, we are recognizing this revenue using the proportional performance model. During 2014, Revenue from reimbursement of research and development activities also includes \$2.0 million in research and development milestone fees and \$15.0 million in milestone fees in connection with the decision made by Astellas to advance CK-2127107 into Phase 2 clinical development.

In January 2015, we received an upfront license fee payment of \$30.0 million in connection with the execution of the Amended Astellas Agreement. Also, in conjunction with the execution of the Amended Astellas Agreement, we entered into a common stock purchase agreement pursuant to which we sold 2,040,816 shares of our common stock to Astellas at a price per share of \$4.90. The aggregate purchase price of \$10.0 million was received in December 2014. We determined the fair value of the stock issued to Astellas to be \$9.1 million. The \$0.9 million excess of cash received over fair value of was deferred and will be recognized as revenue as services are performed over approximately 24 months. Pursuant to this agreement, Astellas agreed to certain trading and other restrictions with respect to our common stock. We determined that the license and the research and development services relating to the Amended Astellas Agreement are a single unit of accounting as the license was determined to not have stand-alone value. Accordingly, we are recognizing this revenue using the proportional performance model over the initial research term of the Amended Astellas Agreement.

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Concurrently with the execution of the Amended Astellas Agreement and related common stock purchase agreement, Cytokinetics received \$15.0 million as a milestone payment relating to Astellas' decision to advance CK-2127107 into Phase 2 clinical development. Cytokinetics is also eligible to potentially receive over \$20.0 million in reimbursement of sponsored research and development activities during the two years of the collaboration following the execution of the Amended Astellas Agreement.

Under the Amended Astellas Agreement, additional research and early and late state development milestone payments which are based on various research and clinical milestones, including the initiation of certain clinical studies, the submission for approval of a drug candidate to certain regulatory authorities for marketing approval and the commercial launch of collaboration products could total over \$600.0 million, including up to \$95.0 million relating to CK-2127107 in non-neuromuscular indications, and over \$100.0 million related to CK-2127107 in each of SMA and other neuromuscular indications. Additionally, \$200.0 million in commercial milestones could be received under the Amended Astellas Agreement provided certain sales targets are met. Due to the nature of drug development, including the inherent risk of development and approval of drug candidates by regulatory authorities, it is not possible to estimate if and when these milestone payments could become due.

In the event Astellas commercializes any collaboration products, the Company will receive royalties on sales of such collaboration products, including royalties ranging from the high single digits to the high teens on sales of products containing CK-2127107. Cytokinetics also holds an option to co-fund certain development costs for CK-2127107 and other compounds in exchange for increased milestone payments and royalties; such royalties may increase under certain scenarios to exceed twenty percent. Under the Amended Astellas Agreement, Cytokinetics retains an option to co-promote collaboration products containing fast skeletal muscle activators for neuromuscular indications in the U.S., Canada and Europe, in addition to its option to co-promote other collaboration products in the U.S. and Canada as provided for in the Original Astellas Agreement. Astellas will reimburse Cytokinetics for certain expenses associated with its co-promotion activities. The Amended Astellas Agreement also provides for Cytokinetics to lead certain activities relating to the commercialization of collaboration products for neuromuscular indications in the U.S., Canada and Europe under particular scenarios.

**Amgen**

In June 2013, we and Amgen executed an amendment (the Amgen Agreement Amendment) to the Amgen Agreement to include Japan, resulting in a worldwide collaboration.

Refer to Note 7, Related Parties and Related Party Transactions in the Notes to Consolidated Financial Statements for further details regarding this collaboration agreement.

Under the terms of the Amgen Agreement Amendment, we received a non-refundable upfront license fee of \$15.0 million in June 2013. In conjunction with the Amgen Agreement Amendment, we also entered into a common stock purchase agreement which provided for the sale of 1,404,100 shares of our common stock to Amgen at a price per share of \$7.12 and an aggregate purchase price of \$10.0 million, which was received in June 2013. Pursuant to this agreement, Amgen agreed to certain trading and other restrictions with respect to our common stock. Under the Amgen Agreement Amendment, we conducted a Phase 1 pharmacokinetic study intended to support inclusion of Japan in a potential Phase 3 clinical development program and potential global registration dossier for omecamtiv mecarbil. Amgen reimbursed us for the costs of this study. In addition, we are eligible to receive additional pre-commercialization milestone payments relating to the development of omecamtiv mecarbil in Japan of up to \$50.0 million, and royalties on sales of omecamtiv mecarbil in Japan. In the fourth quarter of 2013, we determined that all conditions necessary for revenue recognition of the non-refundable upfront license fee under Financial Accounting Standards Board (FASB) Accounting Standards Codification (ASC) Topic 605-10 had been met and accordingly, in the fourth quarter of 2013, we recognized a total of \$17.2 million in license revenue attributable to the Amgen Agreement Amendment.

We have received reimbursements from Amgen for certain research and development activities during 2015, 2014 and 2013, which we recorded as revenue as the related expenses were incurred. We may be eligible to

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receive further reimbursements from Amgen for certain research and development activities, which we will record as revenue if and when the related expenses are incurred. We record amounts received in advance of performance as deferred revenue. Revenues related to the reimbursement of FTEs were based on negotiated rates intended to approximate the costs for our FTEs.

Under the Amgen Agreement, as amended, the Company is eligible to receive over \$350.0 million in development milestone payments which are based on various clinical milestones, including the initiation of certain clinical studies, the submission of a drug candidate to certain regulatory authorities for marketing approval and the receipt of such approvals. Additionally, the Company is eligible to receive up to \$300.0 million in commercial milestone payments provided certain sales targets are met. Due to the nature of drug development, including the inherent risk of development and approval of drug candidates by regulatory authorities, it is not possible to estimate if and when these milestone payments would become due. The achievement of each of these milestones is dependent solely upon the results of Amgen's development and commercialization activities and therefore none of these milestones was deemed to be substantive. During the years ended December 31, 2015, 2014 and 2013, the Company recognized no revenue for milestones achieved under the Amgen Agreement.

### **MyoKardia**

In August 2012, we entered into a collaboration agreement with MyoKardia. Under an agreed research plan, scientists from MyoKardia and our FTEs conducted research focused on small molecule therapeutics that inhibit cardiac sarcomere proteins. We provided MyoKardia access to certain research facilities, and provided FTEs and other resources at agreed reimbursement rates that approximated our costs. We were the primary obligor in the collaboration arrangement, and accordingly, we recorded expense reimbursements from MyoKardia as research and development revenue. The research plan ended as planned in August 2013.

### **NINDS Grant**

In July 2010 and in September 2012, the NINDS awarded us grants to support research and development of tirasemtiv directed to the potential treatment for myasthenia gravis for a period of up to three years. The grants were completed in June of 2013.

### **ALSA Grant**

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.

Because a substantial portion of our revenues for the foreseeable future will depend on achieving development and other pre-commercialization milestones under our strategic alliances with Amgen and Astellas, our results of operations may vary substantially from year to year.

If one or more of our drug candidates is approved for sale as a drug, we expect that our future revenues will most likely be derived from royalties on sales from drugs licensed to Amgen and Astellas under our respective

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strategic alliances and from those licensed to future partners, and from direct sales of our drugs. We retain a product-by-product option to co-fund certain Phase 3 development activities under the Amgen Agreement, thereby potentially increasing our royalties and affording us co-promotion rights in North America. If we exercise our co-promotion rights under the Amgen Agreement, we are entitled to receive reimbursement for certain sales force costs we incur in support of our commercial activities. Under the Amended Astellas Agreement, we retain an option to co-promote collaboration products containing fast skeletal muscle activators for neuromuscular indications in the U.S., Canada and Europe, in addition to our option to co-promote other collaboration products in the U.S. and Canada as provided for in the Original Astellas Agreement. Astellas will reimburse us for certain expenses associated with our co-promotion activities. The Amended Astellas Agreement also provides for us to lead certain activities relating to the commercialization of collaboration products for neuromuscular indications in the U.S., Canada and Europe under particular scenarios.

**Research and Development**

We incur research and development expenses associated with both partnered and our own research activities. We expect to incur research and development expenses for the clinical development of tirasemtiv. We expect to incur research and development expenses for CK-2127107 in accordance with agreed upon research and development plans with Astellas. We expect to incur research and development expenses for omecamtiv mecarbil and other next-generation compounds in our cardiac muscle contractility program in accordance with agreed upon research and development plans with Amgen.

Research and development expenses related to any development and commercialization activities we elect to fund consist primarily of employee compensation, supplies and materials, costs for consultants and contract research and manufacturing, facilities costs and depreciation of equipment.

**General and Administrative Expenses**

General and administrative expenses consist primarily of compensation for employees in executive and administrative functions, including, but not limited to, finance, human resources, legal, business and commercial development and strategic planning. Other significant costs include facilities costs, consulting costs and professional fees for accounting and legal services, including legal services associated with obtaining and maintaining patents and regulatory compliance.

**Stock Compensation**

The following table summarizes stock-based compensation related to stock options, restricted stock awards, restricted stock units, and employee stock purchases for 2015, 2014 and 2013 (in thousands):

	Years Ended December 31,		
	2015	2014	2013
Research and development	\$ 1,828	\$ 1,361	\$ 1,538
General and administrative	2,739	1,969	2,059
Stock-based compensation included in operating expenses	\$ 4,567	\$ 3,330	\$ 3,597

As of December 31, 2015, there was \$7.7 million of unrecognized compensation cost related to unvested stock options, which is expected to be recognized over a weighted-average period of 2.50 years and \$4.8 million of unrecognized compensation cost related to unvested restricted stock units, including the performance stock units (PSU s), which is expected to be recognized over a weighted-average period of 2.12 years.

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### **Income Taxes**

We account for income taxes under the asset and liability method. Under this method, deferred tax assets and liabilities are determined based on the difference between the financial statement and tax basis of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to affect taxable income. Valuation allowances are established when necessary to reduce the deferred tax assets to the amounts expected to be realized. We did not record an income tax provision in the years ended December 31, 2015, 2014 or 2013 because we had a net taxable loss in these periods.

Based upon the weight of available evidence, which includes our historical operating performance, reported cumulative net losses since inception, expected future losses, and difficulty in accurately forecasting our future results, we maintained a full valuation allowance on the net deferred tax assets as of December 31, 2015, 2014 and 2013. The valuation allowance was determined pursuant to the accounting guidance for income taxes, which requires an assessment of both positive and negative evidence when determining whether it is more likely than not that deferred tax assets are recoverable. We intend to maintain a full valuation allowance on the U.S. deferred tax assets until sufficient positive evidence exists to support reversal of the valuation allowance. The valuation allowance increased by \$13.9 million in 2015, \$1.0 million in 2014 and \$13.7 million in 2013.

We also follow the accounting guidance that defines the threshold for recognizing the benefits of tax return positions in the financial statements as more-likely-than-not to be sustained by the taxing authorities based solely on the technical merits of the position. If the recognition threshold is met, the tax benefit is measured and recognized as the largest amount of tax benefit that, in our judgment, is greater than 50% likely to be realized. Historically, we have filed income tax returns with the federal Internal Revenue Service ( IRS ) and the state of California. For jurisdictions in which tax filings are made, we are subject to income tax examination for all fiscal years since inception. In general, the statute of limitations for tax liabilities for these years remains open for the purpose of adjusting the amounts of the losses and credits carried forward from those years.

Interest accrued related to unrecognized tax benefits and penalties was zero for 2015, 2014 and 2013. We account for interest related to unrecognized tax benefits and penalties by classifying both as income tax expense in the financial statements in accordance with the accounting guidance for uncertainty in income taxes. We do not expect our unrecognized tax benefits to change materially over the next twelve months.

In general, under Section 382 of the Internal Revenue Code ( Section 382 ), a corporation that undergoes an ownership change is subject to limitations on its ability to utilize its pre-change net operating losses ( NOLs ) and tax credits to offset future taxable income. We have performed a Section 382 analysis and do not believe that we have experienced an ownership change since 2006. A portion of our existing NOLs and tax credits are subject to limitations arising from previous ownership changes. Future changes in our stock ownership, some of which are outside of our control, could result in an ownership change under Section 382 and result in additional limitations.

**Table of Contents****Results of Operations***Years ended December 31, 2015, 2014 and 2013**Revenues*

	Years Ended December 31,			Increase (Decrease)	
	2015	2014	2013	2015	2014
	(In millions)				
Research and development revenues from related parties	\$ 14.7	\$ 19.5	\$ 2.0	\$ (4.8)	\$ 17.5
Research and development, grant and other revenues	0.1	17.6	7.5	(17.5)	10.1
License revenues from related parties	13.9		17.2	13.9	(17.2)
License revenues		9.8	3.9	(9.8)	5.9
<b>Total revenues</b>	<b>\$ 28.7</b>	<b>\$ 46.9</b>	<b>\$ 30.6</b>	<b>\$ (18.2)</b>	<b>\$ 16.3</b>

Research and development revenues from related parties refers to research and development revenues from our strategic alliances with Astellas and Amgen. Revenues from Astellas, which became a related party in December 2014, were \$12.2 million and \$15.0 million for years ended December 31, 2015 and 2014, respectively, and consisted of reimbursements of internal costs for certain full-time employee equivalents, and other research and development expenses. Revenues from Astellas in 2014 consisted of \$15.0 million in milestone revenues. All research and development revenues from Astellas, prior to it becoming a related party are classified in research and development, grant and other revenues. Revenues from Amgen were \$2.5 million, \$4.5 million and \$2.0 million in 2015, 2014 and 2013, respectively. Revenues from Amgen in 2015, 2014 and 2013 consisted of reimbursement of internal costs of certain full-time employee equivalents, and recognition of allocated consideration relating to the Amgen Agreement Amendment.

Research and development, grant and other revenues in 2015 consisted of \$0.1 million of research and development revenues from our collaboration with ALSA. Research and development, grant and other revenues in 2015 and 2014 consisted primarily of revenues from our strategic alliance with Astellas, prior to becoming a related party in December 2014. Research and development, grant and other revenues in 2014 consisted primarily of \$15.4 million of research and development reimbursement revenues and \$2.0 million in milestone revenues from our collaboration with Astellas, and \$0.1 million in revenue from our collaboration with MyoKardia. Research and development, grant and other revenues in 2013 consisted primarily of \$6.4 million of research program reimbursement revenues from our collaboration with Astellas, and \$1.0 million in revenue from our collaboration with MyoKardia.

License revenues from related parties refers to license revenues from our strategic alliances with Astellas and Amgen. License revenues from Astellas, which became a related party in December 2014, were \$13.9 million in 2015 and consisted of the recognition of a portion of the \$16.0 million upfront license fee received from Astellas in July 2013, and the recognition of a portion of the \$30.0 million upfront license fee received from Astellas in January 2015. Both upfront license fees were recognized using the proportional performance model. License revenues from Amgen were \$17.2 million in 2013 and included the recognition of an upfront license fee of \$15.0 million, along with additional license revenues of \$2.2 million, resulting from the allocation of a portion of the excess of the cash received over the fair value of the common stock issued contemporaneously to Amgen upon execution of the license. Under the Amgen Agreement Amendment, we sold 1,404,100 shares of our common stock to Amgen for \$10.0 million. We determined the fair value of the stock issued to Amgen to be \$7.5 million. A portion of the excess of cash received over fair value of \$2.5 million was also allocated to the services performed and was deferred and was recognized as revenue as services were performed.

License revenues refers to license revenues from our collaboration with Astellas, prior to it becoming a related party in December 2014. License revenues from Astellas included \$9.8 and \$3.9 million in 2014 and

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2013, respectively, of the \$16.0 million upfront license fee received from Astellas in July 2013 in connection with the execution of the Original Astellas Agreement. We recognized this revenue over the term of the research and development services using the proportional performance model.

*Research and development expenses*

	<b>Years Ended December 31, 2015</b>	<b>Increase (Decrease)</b>
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