



Cytokinetics Announces Results of FORTITUDE-ALS, a Phase 2 Clinical Trial of Reldesemtiv in Patients With ALS, Presented at American Academy of Neurology Annual Meeting

May 5, 2019 5:11 PM EDT

Trial Did Not Meet Statistical Significance for Primary Efficacy Analysis

Patients on All Doses of Reldesemtiv Declined Less Than Patients on Placebo for SVC and ALSFRS-R, With Clinically Meaningful Differences Emerging Over Time

Early Terminations and Serious Adverse Events Were Balanced Across Treatment Arms

Investor Event & Conference Call on May 6, 2019 at 7:30 a.m. Eastern Time

SOUTH SAN FRANCISCO, Calif., May 05, 2019 (GLOBE NEWSWIRE) -- Cytokinetics, Incorporated (Nasdaq: CYTK, "Cytokinetics") announced that results of FORTITUDE-ALS (Functional Outcomes in a Randomized Trial of Investigational Treatment with CK-2127107 to Understand Decline in Endpoints – in ALS) were presented today by Jeremy Shefner, M.D., Ph.D., Lead Investigator of FORTITUDE-ALS, Professor and Chair of Neurology at Barrow Neurological Institute, and Professor and Executive Chair of Neurology at the University of Arizona, Phoenix, at a podium presentation at the American Academy of Neurology Annual Meeting in Philadelphia.

FORTITUDE-ALS did not achieve statistical significance for a pre-specified dose-response relationship in its primary endpoint of change from baseline in slow vital capacity (SVC) after 12 weeks of dosing ($p=0.11$). Similar analyses of ALSFRS-R and slope of the Muscle Strength Mega-Score yielded p -values of 0.09 and 0.31, respectively. However, patients on all dose groups of *rel-desemtiv* declined less than patients on placebo for SVC and ALSFRS-R, with larger and clinically meaningful differences emerging over time.

While the dose-response analyses for the primary and secondary endpoints did not achieve statistical significance at the level of 0.05, in a post-hoc analysis pooling the doses together, patients who received *rel-desemtiv* in FORTITUDE-ALS declined less than patients who received placebo. The trial showed effects favoring *rel-desemtiv* across dose levels and timepoints with clinically meaningful magnitudes of effect observed at 12 weeks for the primary and secondary endpoints. The differences between *rel-desemtiv* and placebo in SVC and ALSFRS-R total score observed after 12 weeks of treatment were still evident at follow-up, four weeks after the last dose of study drug.

The incidence of early treatment discontinuations, serious adverse events and clinical adverse events in FORTITUDE-ALS were similar between placebo and active treatment arms. The most common clinical adverse effects in the trial included fatigue, nausea and headache. The leading cause for early termination from FORTITUDE-ALS for patients who received placebo was progressive disease; the leading cause for early termination for patients who received *rel-desemtiv* was a decline in cystatin C based estimated glomerular filtration rate (eGFR), a measure of renal function. Elevations in transaminases and declines in cystatin C eGFR were dose-related.

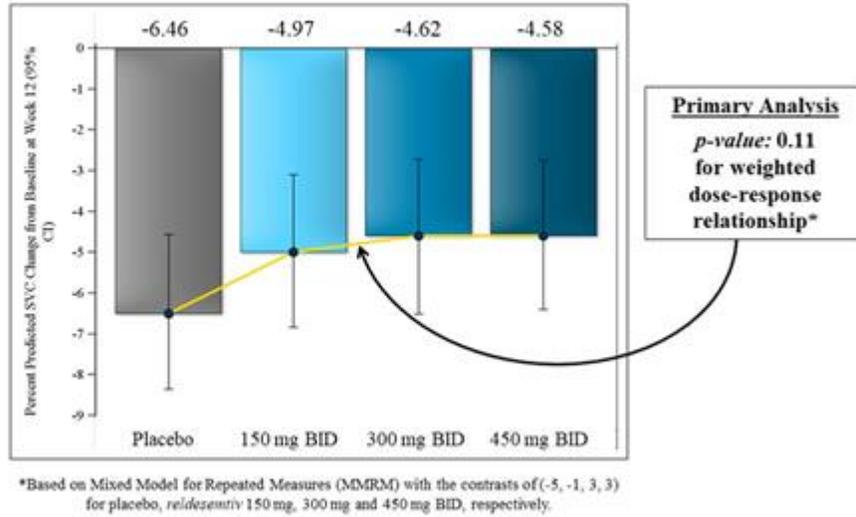
"Results from FORTITUDE-ALS are among the most impressive we have seen in a Phase 2 clinical trial in ALS," said Dr. Shefner. "Especially noteworthy are the consistency and durability of effects observed across treatment arms on clinically meaningful endpoints."

In collaboration with Astellas, Cytokinetics is developing *rel-desemtiv*, a next-generation fast skeletal muscle troponin activator (FSTA), as a potential treatment for people living with debilitating diseases and conditions associated with skeletal muscle weakness and/or fatigue.

Primary Efficacy Endpoint and Additional Analyses

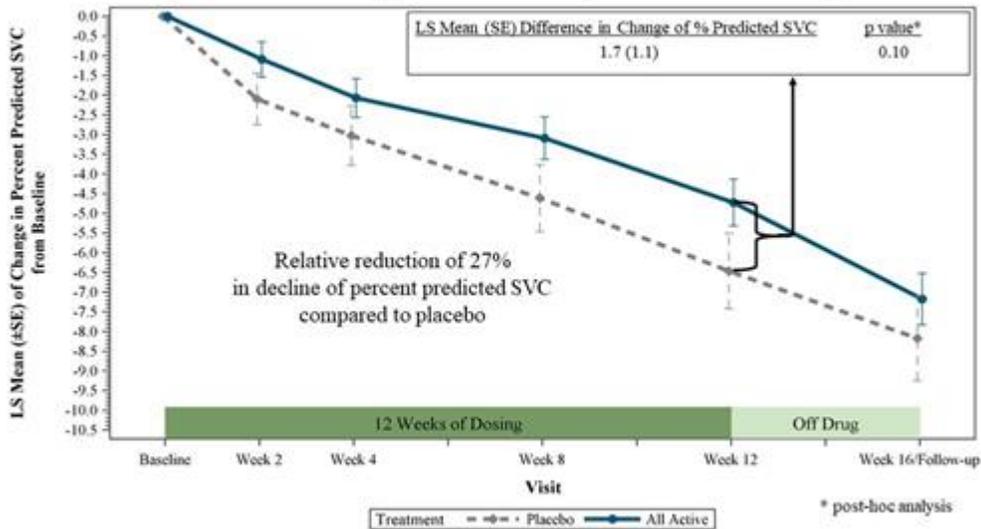
In FORTITUDE-ALS, the primary analysis of change from baseline to Week 12 in percent predicted SVC was analyzed using a mixed model for repeated measures (MMRM) with the contrast (-5, -1, 3, 3) to reflect the assumed weighted dose-response relationship for the placebo, 150 mg BID, 300 mg BID and 450 mg BID dose groups of *rel-desemtiv*, respectively. While all doses of *rel-desemtiv* demonstrated numerical reductions in SVC vs. placebo, the mixed model analysis was not statistically significant ($p=0.11$) (Figure 1). In a post-hoc analysis, when all active treatment groups were combined and compared to placebo, the trial showed a 27% reduction in the decline of SVC ($p=0.10$) (Figure 2).

Figure 1. Change from Baseline in Percent Predicted SVC at Week 12



Change from Baseline in Percent Predicted SVC at Week 12

Figure 2. SVC Change from Baseline (All Active vs Placebo)

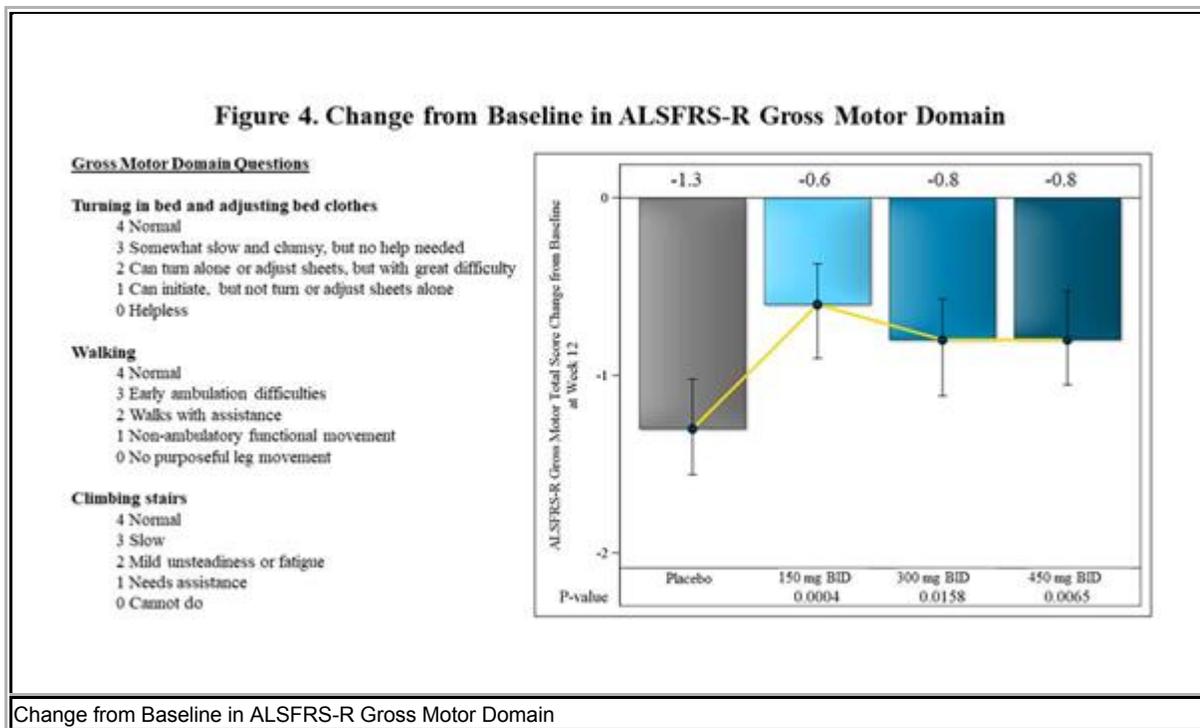
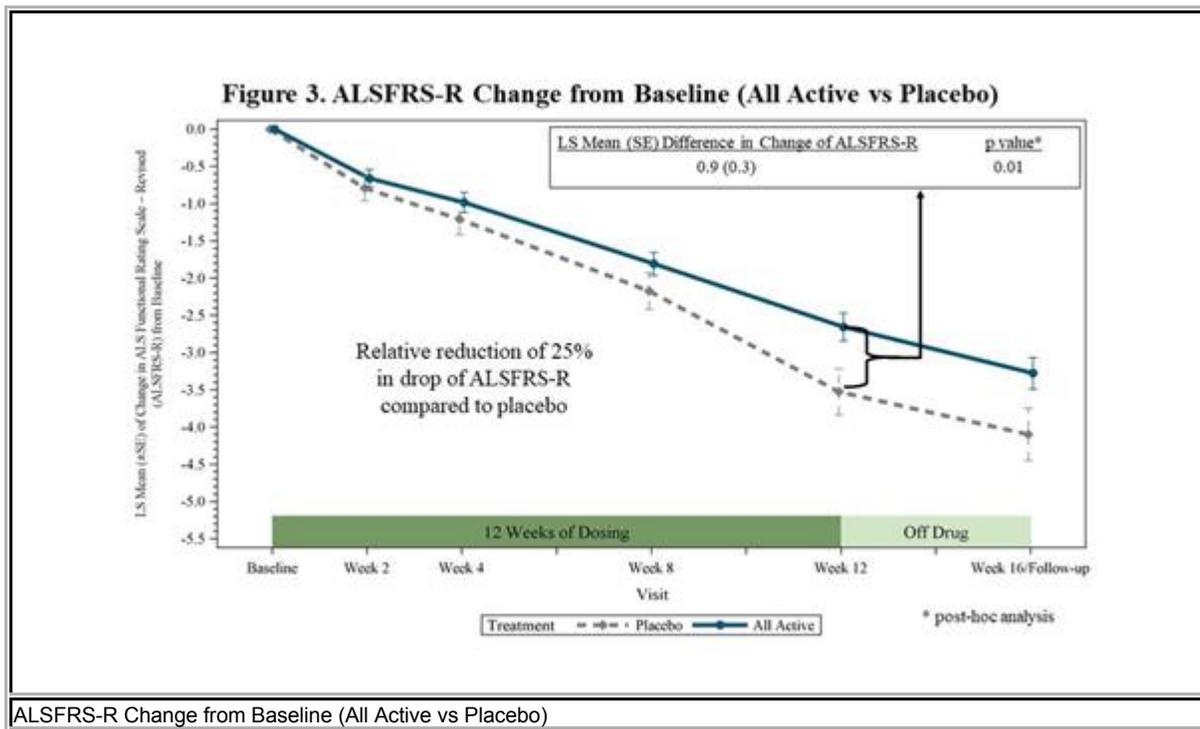


SVC Change from Baseline (All Active vs Placebo)

In FORTITUDE-ALS, the rate of decline in SVC in the placebo group was slower than has been observed in previous trials. FORTITUDE-ALS was powered with the expectation patients receiving placebo would decline approximately 8.0 percentage points during the 12-week trial. In FORTITUDE-ALS, patients receiving placebo declined 6.5 percentage points over 12 weeks.

Secondary Efficacy Endpoints: Additional Analyses

In a post-hoc analysis, FORTITUDE-ALS demonstrated a decrease in the decline of the ALSFRS-R from baseline to 12 weeks of 25% (*p*=0.01) when all active treatment groups combined were compared to placebo (Figure 3). The ALSFRS-R measures activities of daily living and has been deemed acceptable by regulatory authorities for approval and marketing authorization. According to a 2010 survey of ALS clinicians conducted by the Northeast ALS Consortium (NEALS), respondents deemed a therapy that resulted in a change of 20-25% or greater in the slope of decline of ALSFRS-R to be a clinically meaningful effect.¹



Within the ALSFRS-R domains, the largest effects observed at 12 weeks in FORTITUDE-ALS were in the Gross Motor Domain of the ALSFRS-R, which measures the ability of patients with ALS to turn in bed, walk and climb stairs. The effect of *reldesemtiv* for the Gross Motor Domain score was statistically significant at each dose vs. placebo ($p=0.0004$ for 150 mg BID, $p=0.0158$ for 300 mg BID, $p=0.0065$ for 450 mg BID) (Figure 4).

"While FORTITUDE-ALS did not meet the primary endpoint, we are encouraged by the results of the trial as they further validate the potential of skeletal muscle activation in treating patients battling ALS," said Fady I. Malik, M.D., Ph.D., Cytokinetics' Executive Vice President, Research and Development. "This Phase 2 trial of *reldesemtiv* demonstrated consistency of effect for doses, endpoints and timepoints and we believe the results support progression of *reldesemtiv* in further clinical trials toward potential registration."

Cytokinetics Event/Conference Call/Webcast

Cytokinetics will host an investor event and conference call on May 6, 2019 at 7:30 a.m. Eastern Time including members of management and members of the Steering Committee of FORTITUDE-ALS. The event will be held at the Loews Philadelphia Hotel in the Lescaze Room. The conference call will be simultaneously webcast and will be accessible in the Investors & Media section of Cytokinetics' website. The live audio of the

conference call is also accessible via telephone to investors, members of the news media and the general public by dialing either (866) 999-2985 (CYTK) (United States and Canada) or (706) 679-3078 (International) and typing in the passcode 4284768. An archived replay of the webcast will be available via Cytokinetics' website until June 3, 2019. The replay will also be available via telephone from May 6, 2019 at 11:00 a.m. Eastern Time until June 3, 2019 by dialing (855) 859-2056 (United States and Canada) or (404) 537-3406 (International) and typing in the passcode 4284768.

FORTITUDE-ALS: Clinical Trial Design

FORTITUDE-ALS is a Phase 2, double-blind, randomized, dose-ranging, placebo-controlled, parallel group study of *reldesemtiv* in patients with ALS. 458 eligible ALS patients from centers in the U.S., Canada, Europe and Australia were randomized (1:1:1:1) to receive either 150 mg, 300 mg or 450 mg of *reldesemtiv* or placebo dosed orally twice daily for 12 weeks. The primary efficacy endpoint was the change from baseline in the percent predicted SVC, a measure of respiratory function, at 12 weeks. Secondary endpoints included change from baseline in the ALS Functional Rating Scale – Revised (ALSFRS-R) and slope of the change from baseline in the mega-score of muscle strength measured by hand held dynamometry and handgrip dynamometry in patients on *reldesemtiv*; incidence and severity of treatment-emergent adverse events (TEAEs); and plasma concentrations of *reldesemtiv* at the sampled time points during the clinical trial.

In addition, exploratory endpoints were measured including the effect of *reldesemtiv* versus placebo on self-assessments of respiratory function made at home by the patient with assistance as needed by the caregiver; disease progression through quantitative measurement of speech production characteristics over time; disease progression through quantitative measurement of handwriting abilities over time; and change from baseline in quality of life (as measured by the ALSAQ-5) in patients on *reldesemtiv*.

About ALS

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that afflicts approximately 20,000 people in the United States and a comparable number of patients in Europe. Approximately 5,000 new cases of ALS are diagnosed each year in the United States. The average life expectancy of an ALS patient is approximately three to five years after diagnosis and only approximately 10 percent of patients survive for more than 10 years. Death is usually due to respiratory failure because of diminished strength in the skeletal muscles responsible for breathing. Few treatment options exist for these patients, resulting in a high unmet need for new therapies to address functional deficits and disease progression.

About Reldesemtiv

Skeletal muscle contractility is driven by the sarcomere, the fundamental unit of skeletal muscle contraction and a highly ordered cytoskeletal structure composed of several key proteins. Skeletal muscle myosin is the motor protein that converts chemical energy into mechanical force through its interaction with actin. A set of regulatory proteins, which includes tropomyosin and several types of troponin, make the actin-myosin interaction dependent on changes in intracellular calcium levels. *Reldesemtiv*, a next-generation FSTA arising from Cytokinetics' skeletal muscle contractility program, slows the rate of calcium release from the regulatory troponin complex of fast skeletal muscle fibers, which sensitizes the sarcomere to calcium, leading to an increase in skeletal muscle contractility. *Reldesemtiv* has demonstrated pharmacological activity that may lead to new therapeutic options for diseases associated with muscle weakness and fatigue. In non-clinical models of spinal muscular atrophy (SMA), a skeletal muscle activator has demonstrated increases in submaximal skeletal muscle force and power in response to neuronal input and delays in the onset and reductions in the degree of muscle fatigue. *Reldesemtiv* has been the subject of five completed Phase 1 clinical trials in healthy volunteers, which evaluated the safety, tolerability, bioavailability, pharmacokinetics and pharmacodynamics of the drug candidate. Mid-stage clinical trials in patients with SMA, COPD and elderly adults with limited mobility have been completed. In the Phase 2 clinical study in patients with SMA, patients treated with *reldesemtiv* demonstrated increases in measures of endurance and stamina consistent with the mechanism of action.

About Cytokinetics and Astellas Collaboration

In 2013, Cytokinetics and Astellas formed a partnership focused on the research, development, and potential commercialization of skeletal muscle activators. The primary objective of the collaboration is to advance novel therapies for diseases and medical conditions associated with muscle impairment and weakness. Cytokinetics initially exclusively licensed to Astellas rights to co-develop and potentially co-commercialize *reldesemtiv* and other FSTAs in non-neuromuscular indications and to develop and commercialize other novel mechanism skeletal muscle activators in all indications. Under the agreement as subsequently expanded and amended, Astellas also has exclusive rights to co-develop and commercialize *reldesemtiv* and other FSTAs in certain neuromuscular indications (including SMA and ALS). Cytokinetics has certain development and commercialization rights, including the right to co-promote FSTAs for neuromuscular indications in the U.S., Canada and Europe and to co-promote the other collaboration products in the U.S. and Canada.

About Cytokinetics

Cytokinetics is a late-stage biopharmaceutical company focused on discovering, developing and commercializing first-in-class muscle activators and best-in-class muscle inhibitors 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 impact muscle function and contractility. Cytokinetics is collaborating with Amgen Inc. (Amgen) to develop *omecamtiv mecarbil*, a novel cardiac muscle activator. *Omeclamtiv mecarbil* is the subject of an international clinical trials program in patients with heart failure including GALACTIC-HF and METEORIC-HF. Amgen holds an exclusive worldwide license to develop and commercialize *omecamtiv mecarbil* with a sublicense held by Servier for commercialization in Europe and certain other countries. Cytokinetics is collaborating with Astellas Pharma Inc. (Astellas) to develop *reldesemtiv*, a fast skeletal muscle troponin activator (FSTA). Astellas holds an exclusive worldwide license to develop and commercialize *reldesemtiv*. Licenses held by Amgen and Astellas are subject to specified co-development and co-commercialization rights of Cytokinetics. Cytokinetics is also developing CK-274, a novel cardiac myosin inhibitor that company scientists discovered independent of its collaborations, for the potential treatment of hypertrophic cardiomyopathies. Cytokinetics continues its over 20-year history of pioneering innovation in muscle biology and related pharmacology focused to diseases of muscle dysfunction and conditions of muscle weakness.

For additional information about Cytokinetics, visit www.cytokinetics.com and follow us on [Twitter](#), [LinkedIn](#), [Facebook](#) and [YouTube](#).

Forward-Looking Statements

This press release contains forward-looking statements for purposes of the Private Securities Litigation Reform Act of 1995 (the "Act"). Cytokinetics disclaims any intent or obligation to update these forward-looking statements and claims the protection of the Act's Safe Harbor for forward-looking statements. Examples of such statements include, but are not limited to, statements relating to Cytokinetics' and its partners' research and development activities; the Phase 2 clinical study of *reldesemtiv* in patients with ALS, including that such results may support progression of *reldesemtiv* into a potentially pivotal Phase 3 clinical trial; the potentially beneficial effects of *reldesemtiv*; and the properties and potential benefits of Cytokinetics' other drug candidates. Such statements are based on management's current expectations, but actual results may differ materially due to various risks and uncertainties, including, but not limited to, potential difficulties or delays in the development, testing, regulatory approvals for trial commencement, progression or product sale or manufacturing, or production of Cytokinetics' drug candidates that could slow or prevent clinical development or product approval; Astellas' decisions with respect to the design, initiation, conduct, timing and continuation of development activities

for *re/desemtiv*; Cytokinetics may incur unanticipated research and development and other costs or be unable to obtain additional financing necessary to conduct development of its products; standards of care may change, rendering Cytokinetics' drug candidates obsolete; competitive products or alternative therapies may be developed by others for the treatment of indications Cytokinetics' drug candidates and potential drug candidates may target; and risks and uncertainties relating to the timing and receipt of payments from its partners, including milestones and royalties on future potential product sales under Cytokinetics' collaboration agreements with such partners. For further information regarding these and other risks related to Cytokinetics' business, investors should consult Cytokinetics' filings with the Securities and Exchange Commission.

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¹ Castrillo-Viguera, et al. Clinical significance in the change of decline in ALSFRS-R. *Amyotrophic Lateral Sclerosis*. 2010; 11: 178-180



Source: Cytokinetics, Incorporated