Cytokinetics Announces Encouraging Results From Two Phase II Clinical Trials Evaluating CK-2017357 in Patients With Amyotrophic Lateral Sclerosis

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Safety and Tolerability of CK-2017357 in These Two Trials Support Progression to Registration Stage Program

SOUTH SAN FRANCISCO, CA, Apr 25, 2012 (MARKETWIRE via COMTEX) --Cytokinetics, Incorporated (NASDAQ: CYTK) announced today encouraging results from two Phase II clinical trials evaluating CK-2017357 in patients with amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's Disease. In these studies, CK-2017357 was determined to be safe and well-tolerated when dosed with riluzole, the only approved treatment for ALS. The clinical trials results were reported in an oral presentation and a poster at the American Academy of Neurology 64th Annual Meeting in New Orleans, Louisiana.

"The results of these two Phase II clinical trials which evaluated the multi-week safety and tolerability of different doses and dosing schedules of CK-2017357, with and without riluzole, are encouraging," stated Jeremy M. Shefner, MD, PhD, Professor and Chair of the Department of Neurology at the Upstate Medical University at the State University of New York. "I believe the novel mechanism of CK-2017357 may afford meaningful clinical benefit to ALS patients and I look forward to larger and longer studies with the goal of more conclusively demonstrating sustained functional improvements in patients with ALS."

"We are encouraged that the trends to increased function that were observed in the patients receiving CK-2017357 in these studies are consistent with results observed in prior clinical trials of CK-2017357 in patients with ALS," said Andrew A. Wolff, MD, Senior Vice President and Chief Medical Officer at Cytokinetics. "In these two clinical trials, the dizziness reported by patients receiving CK-2017357 was mostly mild and generally abated with continued dosing over the two and three week treatment periods we evaluated. Together with the results of our earlier studies of CK-2017357 in patients with ALS, these new data inform our registration strategy and support the progression of CK-2017357 into later-stage clinical development for the potential treatment of ALS."

In addition, company scientists presented encouraging results with CK-2017357 in a preclinical model of ALS in another poster presentation, also at the same meeting today.

Oral Presentation at the American Academy of Neurology 64th Annual Meeting

An oral presentation by Dr. Shefner titled "A Study to Evaluate Safety and Tolerability of Repeated Doses of CK-2017357 (CK-357) in Patients with Amyotrophic Lateral Sclerosis" included data from Part B of a two-part, randomized, double-blind, placebo-controlled, multiple dose, safety, tolerability, pharmacokinetic and pharmacodynamic clinical trial of CK-2017357 in patients with ALS (CY 4024). Results from Part A of this clinical trial were presented at the 22nd International Symposium on ALS and Motor Neurone Diseases in Sydney, Australia, in November 2011.

Dr. Shefner concluded that CK-2017357 appeared to be safe and well-tolerated dosed daily at 125 mg, 250 mg, and 375 for two weeks, and that encouraging trends were observed in the ALSFRS-R and MVV. As expected, plasma concentrations of CK-2017357 were unaffected by co-administration with riluzole, while riluzole levels increased during co-administration with CK-2017357. Adverse events and clinical assessments during treatment with CK-2017357 appeared similar, with or without co-administration of riluzole at the reduced dose of 50 mg daily. Dizziness, the most commonly reported adverse event, was mostly mild and generally began and resolved early after initiating treatment.

Design and Results

This clinical trial was designed to evaluate the safety and tolerability of two weeks of dosing with CK-2017357 in patients with ALS. In Part A, 24 ALS patients not taking riluzole were randomized to receive daily oral doses of placebo or 125 mg, 250 mg, or 375 mg of CK-2017357, respectively, for two weeks. Part B was identical in design to Part A of the study, except that all patients in Part B received riluzole at a reduced dose of 50 mg daily throughout the 14 days of treatment with CK-2017357 or matching placebo. In the complete study (i.e., both Parts A and B combined), a total of 49 patients were randomized to treatment with placebo (n = 13) or CK-2017357 at daily doses of 125 mg (n = 12), 250 mg (n = 12), or 500 mg (n = 12).

In Part B of this trial, CK-2017357 appeared to be as well-tolerated by those patients receiving riluzole as by those not receiving riluzole in Part A. As was observed in Part A of this study, dizziness was the most frequently reported adverse event. None of the 13 patients who received placebo reported dizziness, compared with 3 of 12 patients who received 125 mg of CK-2017357 daily (1 in Part A and 2 in Part B), 5 of 12 who received 250 mg daily (3 in Part A and 2 in Part B) and 6 of 12 who received 375 mg daily (4 in Part A and 2 in Part B). Again, as was observed in Part A of the study, dizziness was mostly mild, began early after the initiation of treatment, and resolved with continued dosing, usually within the first few days of continued treatment. No patients in Part B reported severe dizziness, and only one, on 250 mg of CK-2017357 dosed daily, reported moderate dizziness.

No patients in Part B discontinued the study prematurely; however, one patient in Part B experienced a change in mental status after receiving 375 mg of CK-2017357 dosed daily for 4 days that resulted in a hospital admission for observation and diagnostic testing, thereby defining her mental status change as a serious adverse event. Her symptoms responded to the administration of supplemental oxygen over a period during which study drug was withheld for one day. Because the patient tolerated the re-initiation of treatment with CK-2017357 while receiving oxygen without a recurrence of her mental status changes, and she completed the study, her symptoms were believed to be due to hypoxemia (which is not uncommon in patients with ALS) and not to treatment with CK-2017357.

While the trial was not designed or powered to evaluate statistically the effects of CK-2017357 on the various outcome measures that were assessed during the study, a combined analysis of patients from Parts A and B suggests encouraging trends that appear dose-related and potentially clinically meaningful in magnitude. Trends were observed in the ALS Functional Rating Scale in its revised form (ALSFRS-R) and in Maximum Voluntary Ventilation (MVV). There were no statistically significant differences in these outcomes measures between patients in Part A and those in Part B.

The ALSFRS-R is a clinically validated instrument designed to measure disease progression and changes in functional status in ALS patients; the average change in the ALSFRS-R score for patients with ALS is approximately -0.9 points per month. In this trial, the ALSFRS-R was evaluated twice, on Days 8 and 15. On Day 8, approximately 24 hours after the previous dose of double-blind study drug and before administration of the Day 8 dose,

the mean change from baseline in the ALSFRS-R was -0.4 points in patients receiving placebo, while the mean differences from placebo were -0.1, +0.4, and +0.9 points in patients receiving CK-2017357 at 125 mg, 250 mg, and 375 mg daily, respectively. On Day 15, approximately 24 hours after the final dose of double-blind study drug, the mean change from baseline in the ALSFRS-R was -0.4 points in patients who had received placebo, while the mean differences from placebo were -0.6, +0.4, and +0.4 points in patients who had received CK-2017357 at 125 mg, 250 mg, and 375 mg daily, respectively. In a post-hoc analysis, combining data from both Days 8 and 15, the mean change from baseline in the ALSFRS-R was -0.5 points on placebo and the mean differences from placebo were -0.3, +0.4, and +0.6 points on CK-2017357 at dose levels of 125 mg, 250 mg, and 375 mg daily, respectively; the p-value for this dose-response relationship was 0.10.

MVV is a clinical assessment of pulmonary function and endurance that measures the maximum volume of air that patients can inhale and exhale, expressed in units of L/min. In this trial, MVV was evaluated on Days 8 and 15. Four hours after dosing with double-blind study drug on Day 8, the mean change from baseline in MVV was +5.4 L/min in patients receiving placebo, while the mean differences from placebo were -2.8, +1.3, and +1.5 L/min in patients receiving doses of CK-2017357 at 125 mg, 250 mg, and 375 mg daily, respectively. On Day 15, approximately 24 hours after the final dose of double-blind study drug, the mean change from baseline was +1.6 L/min in patients who had received placebo, while the mean differences from placebo were -0.9, +4.7, and +4.5 L/min in patients who had received doses of CK-2017357 at 125 mg, 250 mg, and 375 mg daily, respectively.

Poster Presentation at the American Academy of Neurology 64th Annual Meeting

A poster titled "A Study to Evaluate Safety and Tolerability of CK-2017357 in Patients with Amyotrophic Lateral Sclerosis Using a Twice-Daily, Dose-Titration Regimen" was also presented by Dr. Shefner. The poster summarized data from a Phase II clinical trial evaluating CK-2017357 in patients with ALS (CY 4025). The authors concluded that the twice-daily dose-titration regimen evaluated in the trial was generally safe and well-tolerated, that the majority of patients could be titrated successfully to a CK-2017357 dose level of 250 mg twice daily, and that encouraging trends toward functional improvements were observed on CK-2017357 versus placebo.

Design and Results

This Phase II clinical trial was a randomized, double-blind, placebo-controlled study in which CK-2017357 was administered for 21 days using a twice-daily, dose titration regimen to patients with ALS taking riluzole at the reduced dose of 50 mg per day. Patients were randomized 3:1 to receive twice daily oral doses of CK-2017357 or placebo. After seven days of treatment with CK-2017357 at the starting dose of 125 mg twice daily, the dose was escalated to 125 mg in the morning and 250 mg in the evening, and after seven days at this dose, to 250 mg twice daily for the final seven days of dosing. Patients who did not tolerate a dose escalation returned to the previous tolerated dose level and remained at that dose level to complete the study. Placebo patients underwent a similar dummy dose titration to maintain the blind. The primary objective of CY 4025 was to assess the safety and tolerability of CK-2017357 when administered using this twice-daily dose titration regimen to patients with ALS and to determine if the total daily dose of CK-2017357 could be increased from the 375 mg once daily dose (that had been evaluated in earlier trials of CK-2017357 in patients with ALS) to a target of 250 mg dosed twice daily in patients enrolled in this trial.

Twenty-seven patients were treated in CY 4025. All six patients randomized to placebo completed three weeks of dosing. Of the 21 patients randomized to treatment with CK-2017357, 14 were escalated to the highest dose of 250 mg twice daily and completed three weeks of dosing; two others terminated the study prematurely while receiving 250 mg twice daily due to adverse events that required hospitalization. One of these patients was admitted for ataxia and confusion believed to be related to treatment with CK-2017357; the other was hospitalized for treatment of cellulitis believed to be unrelated to treatment with CK-2017357. Three other patients also withdrew from the study prematurely. One patient was hospitalized for an upper respiratory infection believed to be unrelated to treatment with CK-2017357 after receiving a week of treatment with CK-2017357 125 mg in the morning and 250 mg in the evening. Two patients withdrew from study for non-serious adverse events while receiving 125 mg of CK-2017357 twice daily, one for dysarthria and another for complaints of unsteadiness, decreased appetite, fatigue, dizziness, and nausea. Finally, two patients completed the study after a downward dose titration. As was observed in CY 4024, dizziness was the most frequently reported adverse event in CY 4025. None of the six patients who received placebo in CY 4025 reported dizziness, while 12 of 21 patients experienced dizziness during dose titration with CK-2017357. In 10 of these patients, dizziness was mild; the other two patients experienced moderate dizziness.

CY 4025 was not designed or powered to evaluate statistically the effects of CK-2017357 on the various outcome measures that were assessed during the study; nevertheless, increases in the ALSFRS-R and MVV were observed on CK-2017357 relative to placebo that were similar in direction and magnitude to those observed in CY 4024. For example, on Day 22, within 2 hours after the final dose of double-blind study drug, the mean change from baseline in the ALSFRS-R was -1.9 points in the six patients who had received placebo, while the mean difference from placebo was +0.3 points in the 16 patients who had competed three weeks of dosing with CK-2017357 (14 on 250 mg dosed twice daily, one on 125 mg dosed twice daily, and one on 125 mg dosed once daily. Similarly, the mean change from baseline to Day 22 in the MVV was -0.4 L/min on placebo, while the mean difference from placebo was +3.6 L/min on CK-2017357.

Additional Poster Presentation at the American Academy of Neurology 64th Annual Meeting

Cytokinetics' scientists presented a poster titled "The Fast Skeletal Troponin Activator, CK-2017357, Increases Muscle Function and Survival in SOD1 (G93A) Mice; a Model of ALS". The objective of this preclinical study was to examine the effects of CK-2017357 in SOD1G93A mutant transgenic mice, a model of ALS in humans. The authors concluded that mice treated with CK-2017357 maintained hindlimb grip strength during disease progression and that CK-2017357 increased muscle strength of a nerve-muscle pair in situ. In addition, there appeared to be a delay in the time to a pre-specified humane endpoint in the CK-2017357-treated mice compared to the age-matched control SOD1 mice. Overall, the authors concluded that the current preclinical findings support the hypothesis that CK-2017357 may benefit patients with ALS by increasing force generation in fast skeletal muscle fibers.

Background on Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that afflicts 20,000 to 30,000 people in the United States with an incidence rate in both the U.S. and Europe of approximately 1.5 new cases per 100,000 population per year. Approximately 5,600 new cases of ALS are diagnosed each year in the U.S. The average life expectancy of an ALS patient is approximately three to five years and only 10% 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. There is only one drug, riluzole, that has been approved for the treatment of ALS but it neither cures the disease nor addresses the functional deficits associated with ALS. As such, with few treatment options available for these patients, there is a high unmet need for new therapeutic options to address the symptoms and modify the disease progression of this grievous illness.

Development Status of CK-2017357 in ALS

Cytokinetics is developing CK-2017357, a selective fast-twitch skeletal muscle activator, as a potential treatment for diseases and conditions associated with aging, muscle wasting or neuromuscular dysfunction. CK-2017357 is currently the subject of a Phase II clinical development program and has been granted orphan drug designation by the U.S. Food and Drug Administration and orphan medicinal product designation from the European Medicines Agency for the potential treatment of ALS, a debilitating disease of neuromuscular impairment. In addition, CK-2017357 has received Fast Track designation from the U.S. Food and Drug Administration for the potential treatment of ALS.

Cytokinetics has met with the U.S. Food and Drug Administration's Division of Neurology Products and with the European Medicines Agency to discuss its progress in the development of CK-2017357 as a potential treatment for patients with ALS and the company's plans for its further development, including potential registration strategies. Cytokinetics is assessing options that may enable the initiation of a registration program for CK-2017357. Cytokinetics anticipates having additional interactions with U.S. and European regulatory authorities during 2012 to discuss the development of CK-2017357 as a potential treatment for patients with ALS, including potential registration strategies.

Background on Cytokinetics Skeletal Muscle Contractility Program

Skeletal muscle contractility is driven by the sarcomere, the fundamental unit of skeletal muscle contraction. The sarcomere is a highly ordered cytoskeletal structure composed of skeletal muscle myosin, the cytoskeletal motor that is directly responsible for converting chemical energy into mechanical force, as well as actin, and a set of regulatory proteins, troponins and tropomyosin, which make the actin-myosin interaction dependent on changes in intracellular calcium levels. Cytokinetics' skeletal muscle contractility program is focused to the discovery and development of small molecule skeletal sarcomere activators and leverages Cytokinetics' expertise developed in its ongoing discovery and development of cardiac sarcomere activators, including the cardiac myosin activator omecamtiv mecarbil, now in Phase II clinical development as a potential treatment for heart failure. CK-2017357, a fast skeletal muscle troponin activator, is the lead drug candidate from the company's skeletal muscle contractility program. CK-2017357 selectively activates the fast skeletal muscle troponin complex by increasing its sensitivity to calcium, leading to an increase in skeletal muscle force. This mechanism of action has demonstrated encouraging pharmacological activity in preclinical models that may relate to the potential treatment of diseases associated with aging, muscle wasting or neuromuscular dysfunction. In addition, CK-2017357 has shown pharmacological activity in healthy volunteers, in patients with ALS, and in patients with peripheral artery disease and claudication. The clinical effects of muscle 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 may potentially enhance physical performance and quality of life in patients suffering from diseases or medical conditions characterized or complicated by muscle weakness or wasting.

About Cytokinetics

Cytokinetics is a clinical-stage biopharmaceutical company focused on the discovery and development of novel small molecule therapeutics that modulate muscle function for the potential treatment of serious diseases and medical conditions. Cytokinetics' lead drug candidate from its cardiac muscle contractility program, omecamtiv mecarbil, is in Phase II clinical development for the potential treatment of heart failure. Amgen Inc. holds an exclusive license worldwide (excluding Japan) to develop and commercialize omecamtiv mecarbil and related compounds, subject to Cytokinetics' specified development and commercialization participation rights. Cytokinetics is independently developing CK-2017357, a skeletal muscle activator, as a potential treatment for diseases and conditions associated with aging, muscle wasting or neuromuscular dysfunction. CK-2017357 is currently the subject of a Phase II clinical trials program and has been granted orphan drug designation and fast track status by the U.S. Food and Drug Administration and orphan medicinal product designation by the European Medicines Agency for the potential treatment of amyotrophic lateral sclerosis, a debilitating disease of neuromuscular impairment in which CK-2017357 demonstrated potentially clinically relevant pharmacodynamic effects in a Phase IIa trial. Cytokinetics is also conducting research of compounds that inhibit smooth muscle contractility and which may be useful as potential treatments for diseases and conditions associated with excessive smooth muscle contraction, such as bronchoconstriction associated with asthma and chronic obstructive pulmonary disorder (COPD). All of these drug candidates and potential drug candidates have arisen from Cytokinetics' research activities and are directed towards the cytoskeleton. The cytoskeleton is a complex biological infrastructure that plays a fundamental role within every human cell. Additional information about Cytokinetics can be obtained at www.cytokinetics.com.

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, including plans for and the initiation, conduct, design and results of clinical trials for CK-2017357, the significance and utility of clinical trial results for CK-2017357, and anticipated interactions with regulatory authorities; the potential size of markets for CK-2017357, and the properties and potential benefits of CK-2017357 and Cytokinetics' other drug candidates and potential drug candidates, including CK-2017357's potential utility in the treatment of patients with ALS. 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, including risks that current and past results of clinical trials or preclinical studies may not be indicative of future clinical trials results, patient enrollment for or conduct of clinical trials may be difficult or delayed, Cytokinetics' drug candidates may have adverse side effects or inadequate therapeutic efficacy, the U.S. Food and Drug Administration (FDA) or foreign regulatory agencies may delay or limit Cytokinetics' or its partners' ability to conduct clinical trials, regulatory authorities may not grant CK-2017357 orphan drug exclusivity in ALS even if it is approved for marketing, and Cytokinetics may be unable to obtain or maintain patent or trade secret protection for its intellectual property; Amgen's decisions with respect to the design, initiation, conduct, timing and continuation of development activities for omecamtiv mecarbil; Cytokinetics will require significant additional funding to conduct the registration program for CK-2017357 for the potential treatment of ALS and may be unable to obtain such additional funding on acceptable terms, if at all; funding from the National Institute of Neurological Disorders and Stroke may not be available in future periods; Cytokinetics may incur unanticipated research and development and other costs; Cytokinetics may be unable to enter into future collaboration agreements for its drug candidates and programs on acceptable terms, if at all; 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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