Cytokinetics Announces Start of COURAGE-ALS, a Phase 3 Clinical Trial of Reldesemtiv in Patients With Amyotrophic Lateral Sclerosis

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Pivotal Trial Builds on Results from FORTITUDE-ALS which Demonstrated Slowing of Decline of SVC and ALSFRS-R in Patients on Reldesemtiv Compared to Placebo

Company Is Planning to Provide Continued Access to Patients Who Complete COURAGE-ALS and Patients Who Previously Participated in Cytokinetics Sponsored ALS Trials

SOUTH SAN FRANCISCO, Calif., Aug. 02, 2021 (GLOBE NEWSWIRE) -- Cytokinetics, Incorporated (Nasdaq: CYTK) today announced that COURAGE-ALS (**C**linical **O**utcomes **U**sing ***R**eldesemtiv* on **A**LSFRS-R in a **G**lobal **E**valuation in **ALS**), a Phase 3 clinical trial of *reldesemtiv* in patients with amyotrophic lateral sclerosis (ALS), is open to enrollment. *Reldesemtiv*, a next-generation fast skeletal muscle troponin activator (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. COURAGE-ALS follows FORTITUDE-ALS, a Phase 2 clinical trial of *reldesemtiv* that demonstrated encouraging results supportive of progression to a pivotal Phase 3 clinical trial.

"We recognize the profound urgency to deliver new treatments to people with ALS and are pleased to open COURAGE-ALS after gathering important input from patients, regulators, advocates and the clinical community," said Fady I. Malik, M.D., Ph.D., Cytokinetics' Executive Vice President of Research & Development. "As pioneers in muscle biology, we have been pursuing fast skeletal muscle activation for the potential treatment of ALS for over a decade and, based on the results from FORTITUDE-ALS, we believe there is a compelling rationale to advance *reldesemtiv* into this pivotal Phase 3 clinical trial, as it potentially may add to current standard of care and improve patients' functional status and overall quality of life. We are also working toward our goal to provide continued access to *reldesemtiv* for participants who complete dosing in COURAGE-ALS, as well as to make it available to participants from our previously completed ALS trials."

COURAGE-ALS: Clinical Trial Design Focused on Innovation and Accessibility

COURAGE-ALS, a Phase 3, multi-center, double-blind, randomized, placebo-controlled trial of *reldesemtiv* is expected to enroll approximately 555 patients with ALS. Patients will be randomized 2:1 to receive 300 mg of *reldesemtiv* or matching placebo dosed orally twice daily for 24 weeks, followed by a 24-week period in which all patients will receive 300 mg of *reldesemtiv* twice daily. Eligible patients will be within the first two years of their first symptom of muscle weakness, have a vital capacity of ≥65% predicted, and a screening ALS Functional Rating Scale – Revised (ALSFRS-R) ≤44. Patients currently taking stable doses of Radicava® (*edaravone*) and/or Rilutek® (*riluzole*) will be permitted and randomization stratified accordingly. The primary efficacy endpoint will be change from baseline to 24 weeks in ALSFRS-R. Secondary endpoints include combined assessment of ALSFRS-R total score, time to onset of respiratory insufficiency and survival time up to week 24 using a joint rank test; change from baseline to 24 weeks for vital capacity; ALSAQ-40; and bilateral handgrip strength. Two unblinded interim analyses by the Data Monitoring Committee are planned. The first interim analysis will assess for futility, 12 weeks after approximately one-third or more of the planned sample size is randomized. A second interim analysis will also assess for futility, and there will be an option for a fixed increase in total enrollment, if necessary, to augment the statistical power of the trial.

COURAGE-ALS: Elevating Patient Voice

Cytokinetics has established an ALS Patient and Caregiver Advisory Council (ALS-PAC) to elevate the voices of patients and caregivers into everything we do from planning and execution of clinical trial programs to educational materials related to the disease and our potential new therapies. Based on feedback from the ALS-PAC as well as a series of meetings with patients, caregivers, advocates, payors and healthcare professionals, the design of COURAGE-ALS incorporates elements designed to remove barriers to clinical trial participation including remote clinic visits, home nursing visits, and mobile-app based endpoint measurements. Additionally, at least one patient representative will serve on the steering committee of COURAGE-ALS to provide patient perspective on the continuing conduct of the trial and interpretation of results.

The company is planning to provide continued access to *reldesemtiv* for participants who complete COURAGE-ALS, as well as for those who participated in our prior ALS trials. The access program will be developed with the objective to ensure safe, ethical and equitable access to *reldesemtiv*.

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 ALS, 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 ALS, SMA, COPD and elderly adults with limited mobility have been completed.

FORTITUDE-ALS: Clinical Trial Design and Results

FORTITUDE-ALS was 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.

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 *reldesemtiv* 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 *reldesemtiv* in FORTITUDE-ALS declined less than patients who received placebo. The trial showed effects favoring *reldesemtiv* across dose levels and timepoints with clinically meaningful magnitudes of effect observed at 12 weeks for the primary and secondary endpoints. The differences between *reldesemtiv* 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.

About ALS

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that afflicts approximately 27,000 people in the United States and a comparable number of patients in Europe. Approximately 6,300 new cases of ALS are diagnosed each year in the United States. The average life expectancy of a person with ALS is approximately three to five years after diagnosis and only approximately 10 percent of people with ALS 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 Cytokinetics

Cytokinetics is a late-stage biopharmaceutical company focused on discovering, developing and commercializing first-in-class muscle activators and next-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 preparing a U.S. NDA submission of *omecamtiv mecarbil*, its novel cardiac muscle activator, following positive results from GALACTIC-HF, a large, international Phase 3 clinical trial in patients with heart failure. Cytokinetics is conducting METEORIC-HF, a second Phase 3 clinical trial of *omecamtiv mecarbil*. Cytokinetics is also developing CK-274, a next-generation cardiac myosin inhibitor, for the potential treatment of hypertrophic cardiomyopathies (HCM). The company has announced positive topline results from Cohorts 1 and 2 in REDWOOD-HCM, a Phase 2 clinical trial of CK-274 in patients with obstructive HCM. Cytokinetics expects to start a Phase 3 clinical trial of CK-274 in patients with obstructive HCM by year end. Cytokinetics is also developing *reldesemtiv*, a fast skeletal muscle troponin activator for the potential treatment of ALS following conduct of FORTITUDE-ALS and other Phase 2 clinical trials. The company is conducting COURAGE-ALS, a Phase 3 clinical trial of *reldesemtiv* in patients with ALS. 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 the timing, design and results of Cytokinetics’ Phase 1 clinical trial of CK-274; the potential benefits of CK-274; Cytokinetics’ and its partners’ research and development activities; the timing of enrollment of patients in Cytokinetics’ and its partners’ clinical trials; the design, timing, results, significance and utility of preclinical and clinical results; and the properties and potential benefits of Cytokinetics’ 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; 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 FDA or foreign regulatory agencies may delay or limit Cytokinetics’ or its partners’ ability to conduct clinical trials; Cytokinetics may be unable to obtain or maintain patent or trade secret protection for its intellectual property; Cytokinetics’ partners decisions with respect to research and development activities; 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, particularly under the caption “Risk Factors” in Cytokinetics’ latest Quarterly Report on Form 10-Q.

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